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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the seventeenth vol-

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

ume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrylonitrile (interim reports 19b, 21a, and 22), carbon tetrachloride (interim reports 13, 14, 18, and 22), cyanogen (interim report 19a), epichlorohydrin (interim reports 15, 19a, 20a, and 21a), ethylene chlorohydrin (interim reports 20a and 21a), toluene (interim reports 12, 18, and 22), trimethylacetyl chloride (interim reports 20a and 21a), hydrogen bromide (interim reports 16, 18, and 22), and boron tribromide (interim reports 19a and 22): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its re-

lease. The review of interim reports was overseen by David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr., (Howard University), and Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

National Research Council Committee Review of Acute Exposure Guideline Levels for Selected Airborne Chemicals

This report is the seventeenth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory 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/m^3) 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/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently SRC, Inc. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the committee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared sixteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014). This report is the seventeenth volume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

REFERENCES

NRC (National Research Council). 1968. Atmospheric Contaminants in Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1972. Atmospheric Contaminants in Manned Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984a. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1984b. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1984c. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 1984d. Toxicity Testing: Strategies to Determine Needs and Priorities. Washington, DC: National Academy Press.

NRC (National Research Council). 1985a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1985b. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1986a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council). 1986b. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 7. Washington, DC: National Academy Press.

NRC (National Research Council). 1988. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1996a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1996b. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 2000a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 2000b. Methods for Developing Spacecraft Water Exposure Guidelines. Washington, DC: National Academy Press.

NRC (National Research Council). 2001a. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2001b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 2002a. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: The National Academies Press.

NRC (National Research Council). 2002b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2003. Acute Exposure Guideline Levels for Selected Airborne Chemical, Vol. 3. Washington, DC: The National Academies Press.

NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 1. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 6. Washington, DC: The National Academies Press.

NRC (National Research Council). 2009. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 7. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 8. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.
NRC (National Research Council). 2011. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 10. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 11. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 12. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012c. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 13. Washington, DC: The National Academies Press.
NRC (National Research Council). 2013a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 14. Washington, DC: The National Academies Press.
NRC (National Research Council). 2013b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 15. Washington, DC: The National Academies Press.
NRC (National Research Council). 2014. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 16. Washington, DC: The National Academies Press.

Appendixes

1

Acrylonitrile[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could

[1]This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager Susan Ripple (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory 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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Acrylonitrile is a monomer used in the manufacture of acrylic fibers, synthetic rubber, resins, plastics, adhesives, and acrylamide. Acrylonitrile has a sharp onion-garlic odor. Worldwide production is estimated at 4-4.5 million metric tons. The odor threshold for acrylonitrile ranges from 1.6 to 36.3 ppm. A level of distinct odor awareness of 145 ppm was calculated for acrylonitrile.

Nonlethal effects of occupational exposure to acrylonitrile include headache, nasal and ocular irritation, thoracic discomfort, nervousness, and irritability. Information from occupational studies indicates that these effects have occurred at exposures of 16-100 ppm for 20-45 min. Workers routinely exposed to acrylonitrile at 5 ppm experienced initial conjunctival irritation followed by some degree of accommodation, and routine exposure at 5-20 ppm resulted in complaints of headache, fatigue, nausea, and insomnia. No signs or symptoms were reported by informed male volunteers after exposure to acrylonitrile at up to 4.6 ppm for 8 h. Lethality following acute inhalation exposure to acrylonitrile has been reported, but exposures were not defined.

Acute exposure data are available for several laboratory species (monkey, rat, dog, rabbit, guinea pig, and cat) and demonstrate qualitatively similar responses between species, ranging from mild irritation (redness of exposed skin, lacrimation, and nasal discharge) and mild effects on ventilation and cardiovas-

cular responses to severe respiratory effects, convulsions, and death. A 4-h exposure to acrylonitrile at 30-100 ppm produced little or no effect in most species tested, but dogs appeared to be notably more sensitive, exhibiting severe effects at the 100 ppm. Developmental toxicity studies conducted in rats found nonlethal effects on fetal development that included decrements in fetal body weight without fetal malformations (25-100 ppm) (Saillenfait et al. 1993a) and nonlethal fetal malformations (40 and 80 ppm) (Murray et al. 1978). Murray et al. (1978) found three malformations in two of 33 liters from dams exposed at 40 ppm and 11 malformations in six of 35 litters from dams exposed at 80 ppm. The most serious malformation was one omphalocele at 40 and 80 ppm. These malformations were not confirmed in the Saillenfait et al. (1993a) study at exposures up to 100 ppm. A two-generation study found weight decrements in F_1 offspring of the 90-ppm group, but no other evidence of exposure-related mortalities in adult animals, effects on reproduction or reproductive organs, or toxicity in developing offspring at exposures up to 90 ppm (Nemec et al. 2008). No effects on resorptions or live births were found in the single-generation or two-generation studies.

Lethality in rats appears to occur at cumulative exposure of 1,800-1,900 ppm-h for 30 min to 6 h, although for nose-only exposures it was notably higher (about 3,800 ppm-h). Analysis of exposure concentration-duration data suggest a near linear relationship ($C^n \times t = k$, where n = 1.1; ten Berge et al. 1986). Results of studies in animals showed that lethality may be delayed especially at the lower limits of lethal exposures. One study provided evidence of teratogenic effects in rats following gestational exposure of dams to acrylonitrile at 80 ppm but not at 40 ppm. Another study showed an exposure-related decrease in fetal weight following gestational exposure of dams at 25, 50, or 100 ppm; no other reproductive or developmental effects were detected. Acrylonitrile toxicity appears to be directly related to its metabolism. Two major metabolic pathways have been described: conjugation with glutathione and epoxidation by microsomal cytochrome P450 2E1, which forms 2-cyanoethylene oxide (CEO). Metabolites from both pathways are subject to additional biotransformation. The glutathione conjugate may form a mercapturic acid which is excreted in urine. CEO is further metabolized via conjugation with glutathione (catalysis with cytosolic glutathione S-transferase [GST] or nonenzymatically) resulting in additional conjugates and via hydrolysis by microsomal epoxide hydrolase (EH). The secondary metabolites of CEO may also be further metabolized. Cyanide may be generated via the EH pathway and by one of the glutathione (GSH) conjugation products. Cyanide, in turn, is detoxified to thiocyanate via rhodanese-mediated reactions with thiosulfate.

Results of genotoxicity studies are mixed, but provide evidence that acrylonitrile is genotoxic, with positive results in in vitro (DNA strand breaks, sister chromatid exchange [SCE], chromosomal aberrations, and cell transformations) and in vivo (DNA damage, SCE, chromosomal aberrations, and micronuclei) models. The overall weight of evidence supports the conclusion that acrylonitrile is genotoxic. Results of long-term inhalation exposure cancer bioassays

have shown that acrylonitrile is carcinogenic in rats, with brain, spinal cord, Zymbal's gland, tongue, small intestines and mammary glands identified as targets. Available data are sufficient for considering acrylonitrile to be carcinogenic in animals following chronic inhalation exposure.

The AEGL-1 values for acrylonitrile are based on the absence of effects in informed human volunteer (six males) exposed to acrylonitrile at 4.6 ppm for 8 h (Jakubowski et al. 1987), supported by observations of mild effects (initial conjunctival irritation, for which there was some accommodation) in workers routinely exposed at approximately 5 ppm (Sakurai et al. 1978). Therefore, the 8-h exposure at 4.6 ppm is considered a no-effect level for notable discomfort and a point-of-departure for deriving AEGL-1 values. That concentration is approximately 3-fold lower than concentrations reported by Wilson et al. (1948) to be associated with more severe effects in occupational settings (16-100 ppm for 20-45 min: headache, nasal and ocular irritation, discomfort of the chest, nervousness, and irritability). Pharmacokinetic variability is not likely to be significant for mild effects (ocular irritation) of low-level exposure. However, the point-of-departure is based on studies of healthy adults and, in the occupational studies, subjects who experienced repeated exposures to acrylonitrile, which may have resulted in some accommodation to the ocular irritation. Therefore, an intraspecies uncertainty factor of 3 was applied. No data are available on the relationship between exposure duration and severity of responses to acrylonitrile. Typically, in the absence of this information, AEGL-1 values based on an 8-h point-of-departure would be time scaled. However, in this case, the effect is ocular irritation, which would not be expected to have a response threshold that varies with exposure duration. Therefore, it is prudent to not time scale and the AEGL-1 values were held constant at 1.5 ppm for exposure durations of 10 and 30 min. However, 1.5 ppm exceeds AEGL-2 values for longer exposure durations; therefore, AEGL-1 values for 1 h, 4 h, and 8 h are not recommended.

The AEGL-2 values for acrylonitrile are based a developmental toxicity study conducted in rats, which showed that 12 ppm (6 h/day, gestation days 6-20) was a no-effect level for fetal toxicity, indicated by decrements in fetal body weight at higher concentrations (25-100 ppm). Support for the point-of-departure is provided from studies conducted in rats and monkeys. In monkeys, slight or modest reversible effects (transient skin flushing and elevation of respiration rates) were observed from 4-h exposures to acrylonitrile at 65 or 90 ppm (Dudley and Neal 1942). Slight transient effects were found in rats exposed to acrylonitrile at 305 ppm for 2 h (Dudley and Neal 1942). The effects resolved within 12 h postexposure. At higher concentrations or longer exposure durations, effects were more severe (rapid respiration, tremors, convulsions, and death). A threshold for these more severe effects in the rat appears to be above 305 ppm and below the threshold for lethality (the 2-h $BMCL_{05}$ [benchmark concentration, 95% lower confidence limit at the 5% response rate] is 491 ppm) in the rat. An interspecies uncertainty factor of 6 (3 × 2) was applied; a factor of 3 accounts for possible species differences in toxicodynamics of acrylonitrile and a factor of 2 accounts for interspecies differences in toxicokinetics. On the

basis of BPK modeling, Sweeney et al. (2003) predicted a 2-fold difference the concentrations of acrylonitrile and its metabolite, cyanoethylene oxide (the metabolic precursor to cyanide), in blood and brain during 8-h exposures at 2 ppm. Higher cyanoethylene oxide concentrations were predicted in human blood and brain than in rats. A PBPK model developed by Takano et al. (2010) used data on in vitro metabolism of acrylonitrile in rat and human liver microsomes to estimate hepatic clearance of cyanoethylene oxide. The model predicted that repeated oral exposures to acrylonitrile at 30 mg/kg/day for 14 days would result in peak blood acrylonitrile concentrations that were approximately 2-fold higher in rats than humans. Although the Takano et al. (2010) model was evaluated using oral exposure data, experimental data for metabolism were obtained from in vitro microsome studies. Taken together, the Sweeney et al. (2003) and Takano et al. (2010) PBPK models support application of an interspecies uncertainty factor of 2 to account for differences in toxicokinetics. An intraspecies uncertainty factor of 6 (3 × 2) was applied; a factor of 3 for possible variation in toxicodynamics of acrylonitrile in the human population and a factor of 2 for variability in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted that human variability in toxicokinetics of acrylonitrile would result in the 95th percentile individual having acrylonitrile or cyanoethylene oxide concentrations in blood 1.8-fold higher than the average (mean) individual. This suggests that an intraspecies uncertainty factor of 2 would account for toxicokinetics variability in the human population. The total uncertainty factor was 36 (6 × 6). Time scaling from the 6-h experimental point-of-departure to AEGL-specific exposure durations was performed using the equation $C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986). Analysis of occupational exposures and effects indicated that routine exposure to acrylonitrile at 5-20 ppm resulted in complaints of headache, fatigue, nausea, and insomnia, which were neither irreversible nor escape-impairing effects. The concentrations range is approximately 20-to-80 fold higher than the 8-h AEGL-2, which suggests that 8-h AEGL-2 is sufficiently protective.

The AEGL-3 values were derived using 30-min, 1-h, 4-h, and 8-h $BMCL_{05}$ estimates of lethality thresholds. Data for several AEGL-specific exposure periods were available from the reports by Appel et al. (1981a) and Dudley and Neal (1942). A 30-min $BMCL_{05}$ of 1,748 ppm was calculated from the Appel et al. (1981a) data. The 1-, 2-, 4-, and 8-h $BMCL_{05}$ values derived from rat lethality data published by Dudley and Neal (1942) are 1,024.4, 491.3, 179.5, and 185.8 ppm, respectively. With the exception of the 4-h value, the data show a consistent duration-dependent relationship; therefore, the 30-min, 1-h, and 8-h estimates were used to derive corresponding AEGL-3 values. Because the 4-h $BMCL_{05}$ was essentially equivalent to the 8-h $BMCL_{05}$, the 4-h AEGL-3 value was derived by time-scaling the 8-h $BMCL_{05}$. The 10-min AEGL-3 value was derived by time-scaling from the 30-min rat $BMCL_{05}$. Time scaling was performed using the equation $C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986). Although the dog appeared to be the most sensitive species, the overall database for

rats is more robust. The same uncertainty factors that were used to derive the AEGL-2 values were applied to the AEGL-3 values because the same toxicodynamic and toxicokinetic factors apply to both AEGl-2 and AEGL-3 dose-response relationships. An interspecies uncertainty factor of 6 (3 × 2) and an intraspecies uncertainty factor of 6 (3 × 2) were applied, for a total uncertainty factor of 36 (6 × 6).

The AEGL values for acrylonitrile are presented in Table 1-1.

1. INTRODUCTION

Acrylonitrile is a monomer used in the manufacture of acrylic fibers, synthetic rubber, resins, plastics, adhesives, and acrylamide. Acrylonitrile has a sharp onion-garlic odor. Worldwide production has been estimated at 4-4.5 million metric tons (Collins et al. 2003; NPI 2006). Production of acrylonitrile in the United States was 3.4 billion pounds in 1996 (NTP 2011). Chemical and physical data for acrylonitrile is presented in Table 1-2.

AIHA (1997) lists an odor threshold range of 1.6-21 ppm for acrylonitrile, and Ruth (1986) reported a range of 3.7-36.3 ppm. A level of distinct odor awareness of 145 ppm was calculated for acrylonitrile (see Appendix A).

TABLE 1-1 AEGL Values for Acrylonitrile

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR[a]	NR[a]	NR[a]	No-effect level for notable discomfort (ocular irritation) in human subjects, 4.6 ppm for 8 h (Sakurai et al. 1978; Jakubowski et al. 1987).
AEGL-2 (disabling)	8.6 ppm (19 mg/m^3)	3.2 ppm (6.9 mg/m^3)	1.7 ppm (3.7 mg/m^3)	0.48 ppm (1.0 mg/m^3)	0.26 ppm (0.56 mg/m^3)	No-effect level for fetal toxicity (fetal body weight) in rats, 12 ppm for 6 h (Saillenfait et al. 1993a).
AEGL-3 (lethal)	130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 ppm (11 mg/m^3)	No-effect level for lethality (30-min, 1-h, and 8-h $BMCL_{05}$) in rats (Dudley and Neal 1942; Appel et al. 1981a).

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure at concentrations below the AEGL-2 value is without effect.

TABLE 1-2 Chemical and Physical Data for Acrylonitrile

Parameter	Value	Reference
Synonyms	2-propenenitrile; vinyl cyanide; acrylonitrile monomer; cyanoethylene	HSDB 2013
CAS registry no.	107-13-1	HSDB 2013
Chemical formula	C_3H_3N	HSDB 2013
Molecular weight	53.06	HSDB 2013
Physical state	Liquid	HSDB 2013
Melting point	-82°C	HSDB 2013
Boiling point	77.3°C	HSDB 2013
Density/specific gravity	0.8 at 23°C/4°C	HSDB 2013
Solubility in water	74.5 g/L at 25°C	HSDB 2013
Vapor density	1.8 (air = 1)	HSDB 2013
Vapor pressure	109 mmHg at 25°C	HSDB 2013
Conversion factors in air	1ppm = 2.17 mg/m^3 1 mg/m^3 = 0.46 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

A child exposed overnight in a room fumigated with acrylonitrile died. Vomiting, lacrimation, convulsions, respiratory difficulty, cyanosis, and tachycardia were present. Five adults also in the room experienced little or no effect (see Section 2.2.) (Grunske 1949). No exposure concentration-duration information was reported. Another case study involved the death of a 10-year-old girl who had a delousing agent containing acrylonitrile applied to her scalp (Lorz 1950). Following dermal application of the delousing agent, the girl's head was wrapped in a cloth and she went to bed. Symptoms of nausea, headache, and dizziness were followed by repeated vomiting and coma. Cramps and increasing cyanosis were followed by death 4 h after application.

Loss of consciousness, convulsions, and respiratory arrest have been reported as outcomes of severe acute inhalation exposure to acrylonitrile (Buchter and Peter 1984). However, no exposure details were available.

The death of a worker cleaning an acrylonitrile-containing wagon at a train depot was attributed to exposure to the chemical (Bader and Wrbitzky 2006). No exposure data were available, although liquid acrylonitrile was present on the clothing of the individual. Cause of death was reportedly "blood circulation collapse".

2.2. Nonlethal Toxicity

Wilson et al. (1948) reported that exposure of workers handling "polymerizers" at concentrations of 16-100 ppm for 20-45 min experienced dull head-

aches, nasal and ocular irritation, discomfort in the chest, nervousness, and irritability. Workers with notable poisoning (exposures not reported) experienced nausea, vomiting, and weakness. Some developed mild jaundice, low-grade anemia, and leukocytosis. No exposure details were provided for the workers with these more serious effects, but all recovered upon removal from exposure.

Five adults who spent the night in the room in which a child died of acrylonitrile poisoning (see Section 2.1.) had no signs of poisoning and complained only of ocular irritation (Grunske 1949). No exposure concentration-duration information was reported.

Lacrimation and visual disturbance were reported in some nonfatal exposures to acrylonitrile (Davis et al. 1973). Although exposure concentrations were not reported, these effects were likely associated with very high acrylonitrile concentrations.

In an analysis of 144 case reports of acute acrylonitrile poisoning, Chen et al. (1999) estimated that 60 cases were exposed to concentrations in the range of 18-258 ppm (40-560 mg/m^3) and the remaining 84 cases were exposed at concentrations greater than 460 ppm (1000 mg/m^3). Air measurements were not made at the time of the accident and were estimated from accident simulations and postaccident measurements (5 h after the accident). Subjective symptoms reported for 92-100% of the cases included dizziness, headache, chest tightness, feebleness, and hyperactive knee jerk. Sore throat, dyspnea, vomiting, abdominal pain, fainting, and congestion of the pharynx were reported in 60-87% of cases. Other less frequently reported symptoms or effects (5-32% of cases) included numbness of limbs, convulsion, rapid heart rate, cough, hoarseness, rough breathing sound, coma, and abnormal liver function (Chen et al. 1999).

Subchronic (about 3 years) occupational exposure to acrylonitrile at concentrations ranging from 0.6 to 6.0 mg/m^3 (0.3 to 3 ppm) produced headaches, insomnia, general weakness, decreased working capacity, and irritability (Babanov et al. 1959).

In a report by Sakurai and Kusumoto (1972), the health records of 576 workers working in five acrylonitrile fiber plants over a 10-year period were examined. The report analyzed 4,439 examinations acquired over 10 years before 1970. Two cohorts, one exposed to concentrations of acrylonitrile below 11 mg/m^3 (5 ppm) and the other exposed to less than 45 mg/m^3 (20 ppm), were considered. Workers exposed to acrylonitrile at concentrations of 11 mg/m^3 (5 ppm) complained of headache, fatigue, nausea, and insomnia. There was a positive correlation with exposure duration but not with the exposure concentration or age of workers. In a later report, however, Sakurai et al. (1978) stated that the study lacked adequate epidemiologic design, the findings were based on routine health examinations, and the "exposure levels were not reliably reported" and may have been much higher. In this later appraisal it was noted that many of the symptoms reported in Sakurai and Kusumoto (1972) were associated with exposures well in excess of 5 ppm. Sakurai et al. (1978) examined health records for 608 acrylonitrile fiber factory workers. Subjects were grouped into three cohorts that had median air concentrations (from spot samples) of approximately

<1 ppm, 1 ppm, and 5 ppm. They reported that "many workers" complained of initial conjunctival irritation and respiratory irritation and for which there was some accommodation; however, these effects were not attributed to specific exposure cohorts. Sakurai et al. (1978) stated that their findings were not contradictory to those of Wilson et al. (1948), because they reflected the older and less controlled workplace environment where concentrations could have been up to 20 ppm. Taken together, the Sakurai and Kusumoto (1972) and Sakurai et al. (1978) studies suggest mild and transient ocular irritation in association with exposures at 5 ppm (or less), with more severe outcomes (headache, fatigue, nausea, and insomnia) in association with higher exposures (5-20 ppm).

In cross-sectional studies of acrylonitrile-exposed workers, subjective symptoms reported with increased prevalence compared with unexposed workers included dizziness, headache, chest tightness, poor memory, irritation, and neurologic effects. Average workplace air concentrations associated with increased prevalence of these subjective symptoms were 1.13 ppm (Muto et al. 1992), 1.8 ppm (Kaneko and Omae 1992), and 0.48 ppm (Chen et al. 2000). Rongzhu et al. (2005) reported statistically significant deficits in several neurobehavioral tests measured in exposed workers in a Chinese acrylic fiber manufacturing plant with mean workplace air concentrations of 0.11 ppm (0-1.70 ppm) and 0.91 ppm (range 0-8.34 ppm) in two different process areas. Deficits in exposed workers compared with nonexposed workers were noted in a profile of mood states test (20-68% higher for negative moods such as anger and confusion), a simple reaction time test of attention and response speed (10-16% deficits), and the backward sequence of the digit span test of auditory memory (21-24% deficits).

Ocular irritation was a primary effect in a 24-year old man whose face, eyes, and body were sprayed by acrylonitrile (no concentration data) explosively released from a defective valve (Vogel and Kirkendall 1984). Mild conjunctivitis with no corneal clouding was reported. Results of fundascopic examination were normal.

A study was conducted to evaluate the metabolism and excretion of acrylonitrile in informed volunteer subjects (Jakubowski et al. 1987). The six volunteers (including the investigators) were all males aged 28-45 years. Being toxicologists, they were all aware of the toxic properties of acrylonitrile. The subjects were exposed for 8 h to acrylonitrile vapors generated by a saturator immersed in a thermostat-controlled water bath and diluted with carrier air to produce the desired acrylonitrile concentrations (5 or 10 mg/m^3; equivalent to 2.3 and 4.6 ppm, respectively). Airflow in the 11.7-m^3 chamber was approximately 200 m^3/h. There were three 10-min breaks from the exposure at 2, 4, and 6 h. Gas chromatography was used to monitor the acrylonitrile concentration every 15 min. No symptoms were reported by any of the subjects. Limitations of the Jakubowski et al. (1987) study are that the objective of the study was to collect data on the toxicokinetics of acrylonitrile and not to evaluate health effects. All of the subjects were informed toxicologists who worked in the laboratory in

which the study was performed (stakeholders) and may have been more tolerant of mild irritant effects than less motivated individuals.

The World Health Organization (WHO 1983) summarized various workplace studies (Zotova 1975; Enikeeva et al. 1976; Delivanova et al.1978; Ivanov, State Medical Institute, Krasnoyarsk, USSR, personal commun. 1983). Blepharoconjunctivitis was reported following exposure to acrylonitrile at 5 ppm. Other nonocular symptoms were also reported.

Gincheva et al. (1977) reported no changes in the health status for a group of 23 men occupationally exposed to acrylonitrile at 1.9-3.3 ppm for 3-5 years.

2.3. Developmental and Reproductive Effects

Xu et al. (2003) reported that workers exposed to mean acrylonitrile concentration of 0.8 mg/m^3 (0.37 ppm) had a significant decrease (46%) in sperm density when compared with unexposed controls. In addition, DNA strand breakage and sex chromosome aneuploidy were significantly increased in the sperm cells of exposed workers. Xu et al. (2003) stated that aneuploidy transmitted via germ cells is a major contributor to infertility, spontaneous abortion, stillbirths, and infant death.

Reproductive outcomes in workers exposed to acrylonitrile were evaluated by Dong and Pan (1995) and Dong et al. (2000). Several inconsistencies were noted in the reports. The following incidence values correct for inconsistencies between tables and text in the original study reports. Dong and Pan (1995) reported statistically significantly increased incidences of adverse reproductive outcomes in acrylic fiber workers exposed to an average acrylonitrile concentration of 3.7 ppm for 3.2-10.2 years when compared with unexposed controls. These adverse outcomes included premature delivery (10.7% vs. 3.5%) and sterility (5.0% vs. 1.8%) in exposed males compared with controls and stillbirths (4.5% vs. 0%) in exposed females compared with controls.

Dong et al. (2000) reported statistically significantly increased incidences of adverse reproductive outcomes in female acrylic fiber workers exposed to an average acrylonitrile concentration of 3.7 ppm for 10.4 years. Adverse outcomes included increased stillbirths (2.66% vs. 0.68%), birth defects (1.93% vs. 0.45%), and premature deliveries (8.23% vs. 3.87%) compared with controls.

A reported decreased in testosterone in acrylonitrile factory workers (Ivanescu et al. 1990) was confounded by concurrent exposure to other chemicals. No adverse effect was detected for gynecological health of 410 women occupationally exposed to acrylonitrile (no exposure details) compared with 436 unexposed women (Dorodnova 1976). Czeizel et al. (1999) reported on the rate and type of congenital abnormalities in 46,326 infants born to mothers living within a 25-km radius of an acrylonitrile factory in Hungary. Significant clusters of pectus excavatum (depressed sternum), undescended testes, and clubfoot were noted. The authors, however, reported that the overall results supported the null hypothesis of no effects of acrylonitrile in people living in the vicinity of the acrylonitrile factory.

2.4. Genotoxicity

2.4.1. In Vitro Studies

In experiments with human lymphocytes, Perocco et al. (1982) showed that exposure of human lymphocytes to acrylonitrile at 0.5 mM (26.5 µg/mL) resulted in a significant increase in sister chromatid exchange (SCE). Obe et al. (1985), however, was unable to demonstrate SCE-induction by acrylonitrile in human lymphocytes exposed for 24 h to acrylonitrile at concentrations of 1 or 10 µg/mL in the absence of S9 and for 1 h in the presence of S9 from Arochlor-induced rat livers.

Rizzi et al. (1984) examined the incorporation of [^{3}H]TdR into DNA in HeLa cells. The test groups included a control and acrylonitrile-treated cells without hydroxyurea (-HU), and control and treated cells treated with hydroxyurea (+HU). The -HU/+HU relationship between treated and control cells and the value of +HU between treated and control cells were statistically significant at acrylonitrile concentrations of 0.18 ($p < 0.01$) and 0.036 mM ($p < 0.09$). It was concluded that acrylonitrile is mutagenic and genotoxic at very low concentrations. Contrary to this, Martin and Campbell (1985) failed to demonstrate unscheduled DNA repair in HeLa cells.

Acrylonitrile produced positive results in tests with human lymphoblasts (TK6, *TK* locus) both with and without metabolic activation (Crespi et al. 1985). Tests were conducted at acrylonitrile concentrations of 5-50 µg/mL for 3 h in the presence of S9 (from Arochlor-induced rat livers) or for 20 h without S9. There was a 3.5-fold increase in mutational frequency in the presence of S9 at 40 and 50 µg/mL. In the absence of S9, mutational frequency was increased 2-fold at 15 µg/mL and 1.3-fold at 20 µg/mL (compared with controls).

Crespi et al. (1985) also conducted tests using the AHH-1 cell line (HGPRT locus). Concentrations of acrylonitrile were 5-25 µg/mL for 28 h. Tests were conducted with metabolic activation and an expression period of 6 days. An approximate 4.5-fold increase in mutation frequency at 25 µg/mL was detected relative to controls which was similar to the response obtained with the benzo(a)pyrene (3.1 µg/mL, positive control).

The mutagenic potential of both acrylonitrile and its metabolite 2-cyanoethylene oxide (CEO) was examined using the TK human lymphoblast cell line (with and without S9) with heterozygous thymidine kinase (*tk*) locus as the marker (Recio et al. 1989). Cells were exposed for 2 h with an expression period of 6-8 days. Acrylonitrile was not mutagenic in the absence of S9 (less than a 2-fold increase in mutation frequency) over a concentration range of 0.4 to 1.5 mM (21 to 80 µg/mL). With S9, there was a statistically significant ($p < 0.05$) 4-fold mutagenic response at the highest concentration 1.5 mM (74 µg/mL). Survival was only 10% at 1.5 mM. The metabolite produced a 17-fold increase in mutation frequency without S9 at 100 µM. The results indicated acrylonitrile to be weakly mutagenic in mammalian cells, while the mutagenic response induced by CEO suggests that it may be the primary mutagenic metab-

olite of acrylonitrile. In a follow-up study (Recio et al. 1990), human TK6 lymphoblasts were treated with CEO (150 μM for 2 h). Base-pair substitution mutations and frameshift mutations were observed.

SCE and the induction of DNA single breaks were examined using adult human bronchial epithelial cells (Chang et al. 1990). The cultures were exposed for 20 h to acrylonitrile at 150, 300, 500, or 600 μg/mL and assessed for SCE and DNA strand breaks. Notable cytotoxicity was observed at 600 μg/mL, but not at the lower concentrations. SCEs were significantly increased ($p < 0.01$) at 150 and 300 μg/mL; incidence of SCE per cell was 6.6 and 10.7, respectively (3.7 in unexposed controls). The extent of DNA single strand breaks appeared to be positively correlated with acrylonitrile concentrations.

A human mammary epithelial cell (HMEC) DNA repair assay in secondary cultures of HMEC was reported by Butterworth et al. (1992). The cultures of normal HMEC were derived from mammoplasties of five healthy women. Although CEO was cytotoxic to HMEC at 1.0 mM, a positive unscheduled DNA synthesis response at 0.1 mM was produced thereby confirming its genotoxicity at subcytotoxic doses. Acrylonitrile exhibited considerable cytotoxicity but no genotoxicity was observed in the HMEC DNA repair assay.

2.4.2. In Vivo Studies

Beskid et al. (2006) noted moderate changes in chromosomal aberration patterns in chromosomes #1 and #4 as detected by the FISH assay in workers occupationally exposed to acrylonitrile compared with unexposed controls. In this study, smoking did not seem to have any effect on the pattern of aberrations detected.

Fan et al. (2006) detected increases in micronucleus formation in buccal mucosal cell and lymphocyte samples from both the low and intermediate exposure groups (concentrations not reported) of male workers in Shanghai, China when compared to matched unexposed males. They also noted a strong correlation between these findings and assays performed in the buccal mucosal cells and the circulating lymphocytes.

Xu et al. (2003) found that acrylonitrile had an effect on semen quality among exposed workers by inducing DNA strand breakage as detected by the Comet assay and sex chromosome nondisjunction in spermatogenesis as detected in the FISH assay. They also reported lower sperm counts in the exposed versus nonexposed subjects. The workers were employed by a recently opened plant (2.8 years exposure duration for all workers), which had a mean acrylonitrile concentration of 0.8 ± 0.25 mg/m^3.

Chromosomal damage in peripheral lymphocytes of 18 workers exposed to acrylonitrile for an average of 15.4 years was studied by Thiess and Fleig (1978). The workers were also exposed to styrene, ethylbenzene, butadiene, and butylacrylate. The actual acrylonitrile exposure was not reported. Air concentrations of acrylonitrile over approximately 10 years averaged 5 ppm and were

reportedly representative of normal operating conditions. During the actual conduct of the study, workplace concentrations of acrylonitrile were about 1.5 ppm. The frequency of chromosomal aberrations in peripheral lymphocytes of the workers was not increased compared with the unexposed controls.

Borba et al. (1996) reported chromosomal aberrations and SCEs in 14 workers employed in the polymerization area and in 12 maintenance workers of an acrylic fiber plant. A control group consisted of 20 unexposed workers in administration jobs. No acrylonitrile exposure concentration or exposure duration terms were provided. No difference in SCEs was detected when the exposed groups and the controls were compared.

2.5. Carcinogenicity

Several occupational studies have evaluated the potential carcinogenicity of acrylonitrile, with mixed results. Many earlier studies reporting a positive association between acrylonitrile exposure and increased cancer risk were limited by inadequate exposure data, small study populations, insufficient length of follow-up, and other confounding factors (e.g., concomitant exposure to other chemicals, smoking). More recent occupational studies generally examined larger cohorts and had longer follow-up periods. Although results of more recent studies are also mixed, Blair et al. (1998) reported an increased risk of lung cancer mortality in large cohort of workers exposed to high concentrations of acrylonitrile (additional study details provided below).

EPA's Integrated Risk Information System (IRIS) has an inhalation unit risk for acrylonitrile of 6.8×10^{-5} $(\mu g/m^3)^{-1}$, which is based on an excess incidence of respiratory cancer from an occupational study (O'Berg 1980). The inhalation unit risk was developed in 1983 (EPA 1984). However, a follow-up study (O'Berg et al. 1985) did not find an increased incidence of respiratory cancer in this cohort. The IRIS Program is currently reassessing this chemical. The availability of an inhalation unit risk requires that calculations of cancer risk from a single exposure to acrylonitrile be presented in an appendix to this document (NRC 2001). The calculations of cancer risk for a single exposure to acrylonitrile, based on the 1983 inhalation unit risk (EPA 1984), is presented in Appendix B. This calculation, however, may need to be revised following completion of the IRIS Program reevaluation.

Felter and Dollarhide (1997) concluded that the human weight of evidence for the carcinogenicity of acrylonitrile is insufficient. Their evaluation of the available human database showed no clear association between acrylonitrile exposure and human cancer; however, they stated that the studies did not have sufficient power to be able to rule out a small increase.

The International Agency for the Research on Cancer (IARC) modified their cancer classification for acrylonitrile from Group 2A (probably carcinogenic) to Group 2B (possibly carcinogenic to humans) (IARC 1999). This change was based on the lack of carcinogenic evidence from the more recent epidemio-

logic studies, with an overall conclusion that the potential carcinogenicity of acrylonitrile in humans is considered to be inadequate and no evidence of a causal association exists; however, they did note an increased risk of lung cancer was observed in individuals exposed at the highest concentrations of acrylonitrile in one of the largest studies conducted by the National Cancer Institute (Blair et al. 1998). They also found adequate evidence for carcinogenicity from studies with rats. Likewise, the National Toxicology Program (NTP 2011) concluded that acrylonitrile is "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals.

Blair et al. (1998) evaluated the relationship between occupational exposure to acrylonitrile and cancer mortality in a cohort of over 25,000 workers employed in acrylonitrile production or use from the 1950s through 1983. An elevated risk of lung cancer mortality was observed in the highest quintile of cumulative exposure. The investigators concluded that the increased risk of lung cancer may indicate carcinogenic risk at high levels of exposure. Exposure to acrylonitrile was not associated with an increased risk of cancers of the stomach, brain, breast, prostate gland, or the lymphatic or hematopoietic systems. More recently, Cole et al. (2008) reviewed a retrospective-cohort study and case-control studies on acrylonitrile. It was concluded that the results of the epidemiologic studies did not support a causal relationship between acrylonitrile and all cancers or any specific type of cancer.

2.6. Summary

A concentration range of 1.6-6.3 ppm has been reported as the odor threshold for acrylonitrile in humans. A level of distinct odor awareness of 145 ppm was calculated for acrylonitrile. Nonlethal effects of occupational exposure to acrylonitrile include headache, nasal and ocular irritation, thoracic discomfort, nervousness, and irritability, but definitive exposure-response data are lacking. Available information indicates that such effects resolve following removal from exposure. No signs or symptoms were reported in male volunteer subjects following exposures up to 4.6 ppm for 8 h. Lethality following acute inhalation exposure to acrylonitrile has been reported.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkey

Rhesus monkeys (two males and two females; 4.2-4.8 kg) were exposed to acrylonitrile at 65 or 90 ppm (two females) for 4 h (Dudley and Neal 1942). The test atmosphere was generated by bubbling air through acrylonitrile (purity determined through repeated fractional distillations free of cyanide and with a boil-

ing point of 76-77°C) and mixing the acrylonitrile-saturated air stream with a main air stream. Air flow through the exposure chamber was 260 L/min (± 2%). The concentration of acrylonitrile was varied by adjusting the volume of air passing through the bubbler. The concentration of acrylonitrile in the chamber was determined by the change in weight of the acrylonitrile in the bubbler, air flows, and start/stop times. Even at the highest concentration (90 ppm), all of the monkeys exhibited only slight redness of the face and genitals, and a slight increase in respiratory rate on initial exposure.

Dudley et al. (1942) exposed four rhesus monkeys to acrylonitrile at 56 ppm (average concentration) for 4 h/day, 5 days/week for 4 weeks. All four monkeys survived and showed no evidence of toxicity during the 4-week exposure period.

3.1.2. Dog

In their assessment of acrylonitrile lethality in multiple species, Dudley and Neal (1942) also exposed groups of two to four male and female dogs (5.5–12.0 kg; strain not specified) to various acrylonitrile concentrations for 4 h (see Table 1-3). The investigators found dogs to be more sensitive to acrylonitrile; exposures producing only minor effects in other species caused coma and death in the dogs.

Results of a 4-week repeat exposure experiment using two dogs exposed to an average concentration of acrylonitrile at 56 ppm for 4 h/day was reported by Dudley et al. (1942). After the first 4-h exposure, one dog died in convulsions while the second dog developed a transient paralysis of the hind legs after the fifth, thirteenth, and fourteenth exposure. Subsequent exposures were well tolerated.

3.1.3. Cat

In the study by Dudley and Neal (1942), groups of two to four cats (gender not specified; about 3.6 kg) were exposed to acrylonitrile for 4 h. Exposure at 100 ppm produced only salivation and slight transient effects (redness of the skin and mucosae) while exposure at 275 ppm resulted in more severe effects (marked salivation, signs of pain) but no deaths. At 600 ppm, 100% mortality (preceded by convulsions) occurred within 1.5 h of exposure.

Four cats were exposed to acrylonitrile at 56 ppm (average concentration) for 4 h/day, 5 days/week for 8 weeks (Dudley et al. 1942). The cats occasionally vomited, were lethargic, and lost weight. One cat developed a transitory weakness of the hind legs after the third exposure and died after the eleventh exposure. The remaining cats survived the entire exposure period with minimal effects.

TABLE 1-3 Toxicity of Acrylonitrile Vapor in Dogs Exposed for 4 Hours

Concentration (ppm)	Gender	Effects
30	Female	Slight salivation by end of exposure period; no other effects.
	Female	Slight salivation by end of exposure period; no other effects.
	Female	Slight salivation by end of exposure period; no other effects.
	Female	Slight salivation by end of exposure period; no other effects.
65	Female	Severe salivation; weak by end of exposure.
	Female	Coma by end of exposure; died at 8 h.
100	Male	Severe salivation during exposure; full recovery within 24 h.
	Female	Convulsions at 2.5 h; coma by end of exposure; partial paralysis of hind legs for 3 d.
	Female	Convulsions at 2.5 h; coma by end of exposure; full recovery within 48 h.
110	Female	Coma at end of exposure; dead at 4.5 h.
	Male	Coma at end of exposure; dead at 3 d.
	Female	Coma at end of exposure; food refusal for 10 d; slowly recovered.
165	Female	Convulsions at 2 h; dead at 3 h.
	Male	Coma from end of exposure to death at 4 h.

Source: Adapted from Dudley and Neal 1942.

3.1.4. Rat

Dudley and Neal (1942) conducted single exposure experiments in which groups of 16 Osborne-Mendel rats (about 295 g, sex not specified) were exposed for 0.5, 1, 2, 4, or 8 h to various concentrations of acrylonitrile (see Table 1-4). Details regarding generation of the test atmospheres are provided in Section 3.1.1. Responses included initial stimulation of respiration followed by rapid shallow respiration. At concentrations above 300 ppm, rats started exhibiting signs of ocular and nasal irritation. Rats exposed to any concentration of acrylonitrile exhibited flushing (reddening) of the skin, nose, ears, and feet. Prior to death, the rats were gasping and convulsing. Gross pathology findings of dead rats revealed bright red lungs of "normal consistency" and dark red blood. Rats which survived any acute exposure to acrylonitrile exhibited no residual effects. Results of the experiments are summarized in Table 1-4.

In another phase of the study by Dudley and Neal (1942), rats (16/group) were exposed for 4 h to acrylonitrile at 635, 315, 130, or 100 ppm (see Table 1-5). Exposure at 130 ppm produced slight transient effects and no lethality. Effects were similar to those described in the preceding paragraph. Exposure at 315 ppm resulted in 31% mortality and exposure at 635 ppm produced 100% mortality.

In a lethality study conducted at Haskell Laboratory (1968), groups of adult male ChR-CD rats (248-268 g) were exposed to acrylonitrile for 4 h. The test chamber atmosphere was analyzed at least every half hour by gas chromatography. Test animals were observed for 14 days. During exposure the rats exhibited irregular respiration, hyperemia, lacrimation, tremors, and convulsions. Deaths during exposure occurred within 2-4 h after the start of the exposure. Deaths after exposure occurred between 7 min and 18 h. A 4-h LC_{50} of 333 ppm (275-405 ppm, 95% confidence interval) was reported. Rats surviving the exposure exhibited mild to severe, dose-related weight loss the first day of observation followed by normal weight gain.

Appel et al. (1981a) provided lethality data for groups of three to six male Wistar rats exposed to acrylonitrile for 30-180 min at exposure concentration varying with exposure duration (see Table 1-6). In this study (designed to assess potential antidotes for acute acrylonitrile toxicity), acrylonitrile vapor was generated by evaporating acrylonitrile (99.5% purity) in a halothane vaporator and adjusting the acrylonitrile vapor concentration with clean filtered air. Vapor concentration was determined by gas chromatography.

In a rat study reported by Vernon et al. (1990), a group of 10 adult Sprague-Dawley rats (five/sex) was exposed for 1 h to acrylonitrile at 1,008 ppm. None of the rats died. Clinical signs reported included rapid shallow breathing, decreased activity, nasal discharge, salivation, lacrimation, and coma (three of 10 animals). The extremities of all animals were red 37 min into the exposure. All rats recovered within 5 min after exposure ended.

TABLE 1-4 Toxicity of Acrylonitrile Vapor in Rats Exposed for 0.5 to 8 Hours

Duration (h)	Concentration (ppm)	Mortality During Exposure (%)	Total Mortality (%)	Effects[a]
0.5	665	0	0	Moderate transitory effects.
	1,270	0	0	Marked; no residual effects in 24 h.
	1,490	0	0	Marked; no residual effects in 24 h.
	2,445	0	0	Marked; slight residual effects at 24 h.
1	665	0	0	Marked transitory effects.
	1,270	0	0	Marked effects; slight effects at 24 h; normal at 48 h.
	1,490	0	25	Deaths in 4 h; slight effects at 24 h in survivors.
	2,445	0	81	Deaths in 4 h; slight effects at 24 h in survivors.
2	305	0	0	Slight transitory effects.
	595	0	6	Marked transitory effects.
	1,260	0	100	Fatal; deaths within 4 h.
4	1,30	0	0	Slight transitory effects.
	315	25	31	Marked; no effects in survivors at 24 h.
	635	50	100	Fatal.
8	90	0	0	Slight discomfort.
	135	0	0	Moderate transitory effects.
	210	6	6	Marked transitory effects.
	270	44	44	Marked; no effects in survivors at 24 h.
	320	94	94	Fatal.

[a]Nonlethal effects included rapid respiration followed by rapid shallow breathing. Prior to death animals exhibited slow, gasping respiration, convulsions, and then coma.
Source: Adapted from Dudley and Neal 1942.

TABLE 1-5 Toxicity of Acrylonitrile Vapor in Rats Exposed for 4 Hours

Concentration (ppm)	Mortality During Exposure (%)	Total Mortality (%)	Effects
100	0	0	Slight transitory effects.
130	0	0	Slight transitory effects.
315	25	31	Marked effects; no residual effects in survivors.
635	50	100	Death occurred in 2-6 h.

Source: Adapted from Dudley and Neal 1942.

TABLE 1-6 Lethal Response of Rats Exposed to Acrylonitrile

Concentration (ppm)	Duration (min)	Mortality Ratio
650	180	1/3
950	120	1/3
1,100	120	3/3
1,600	30	0/3
2,600	30	1/3
3,000	30	6/6
2,400	10	0/3

Source: Adapted from Appel et al. 1981a.

A GLP-OECD guideline study sponsored by the Shanghai SECCO Petrochemical Company, Ltd., examined the acute toxicity of acrylonitrile in rats (WIL Research Laboratories 2005). In this study, groups of five male and five female Crl:CD/(SD) rats (8-12 weeks old; 242-297 g) were exposed to acrylonitrile (99.9% purity) for 4 h at 539, 775, 871, 1,006, or 1,181 ppm. The rats were acclimated for 7 days prior to exposure and observed for 14 days after exposure. Exposure was in a two-tiered conventional nose-only exposure system where exposure atmosphere conditions (temperature, oxygen, humidity) were monitored every 20-30 min. The acrylonitrile test atmosphere was generated by passing compressed nitrogen through the test material to create a vapor which was diluted with compressed air prior to being delivered to the exposure system. Actual acrylonitrile concentrations were determined by gas chromatography. Mortality data are summarized in Table 1-7. The report provided 4-h LC_{50} values of 964 ppm (857-1085 95% confidence interval) for males, 920 ppm (807-1050 95% confidence interval) for females, and 946 ppm (866-1,032 95% confidence interval) combined (determined by the method of Litchfield and Wilcoxon, 1949).

Clinical observations immediately following exposure included tremors, ataxia, labored respiration, hypoactivity, decreased defecation, and gasping, but there was no apparent exposure concentration-effect relationship. Necropsy findings in dead rats included the presence of a distended, gas-filled jejunum in one female of the 871-ppm group, distended gas-filled stomach in three females in the 871-ppm and 1,006-ppm groups, and dark, discoloration of the lungs in one male and one female in the 1,181-ppm group. No other findings were noted for rats that died. At scheduled sacrifice, the only finding was dark discoloration of the lungs in one male of the 871-ppm group.

3.1.5. Guinea Pig

Results of 4-h exposure experiments with guinea pigs (eight to 16 per group; about 695 g) are shown in Table 1-8 (Dudley and Neal 1942). Neither redness of the skin nor eyes was observed in guinea pigs, as it was in other species. Exposure

to acrylonitrile did cause watering of the eyes, nasal discharge, and coughing. As exposure increased, coughing was accompanied by moist breath sounds. Exposures that were lethal in dogs had very little effect on guinea pigs. Delayed death (3-6 days post exposure) was attributed to pulmonary edema.

3.1.6. Rabbit

In the Dudley and Neal (1942) report, groups of two to three albino rabbits (sex not specified; about 4.5 kg) were exposed to acrylonitrile for 4 h. Signs of exposure were similar to those observed for rats but the rabbits appeared to be more susceptible to acrylonitrile-induced lethality. Exposure at 100 or 135 ppm produced slight to marked transitory effects. Exposure at 260 ppm resulted in the mortality of one of two rabbits during exposure, and the second died within 4-5 h. Exposure at 580 ppm resulted in a similar response with the second rabbit dead within 3-4 h.

TABLE 1-7 Lethality in Rats Following Nose-only Inhalation Exposure to Acrylonitrile for 4 Hours

	Mortality During Exposure		Total Mortality		
Concentration (ppm)	Male	Female	Male	Female	Comments
539	0	0	0	0	
775	0	0	0	0	
871	0	0	1	3	Deaths at 0-1 d postexposure.
1,006	1	1	3	4	2 males, 3 females at 0-1 d postexposure.
1,181	4	3	5	4	1 male, 1 female at 0-1 d postexposure.

Source: Adapted from WIL Research Laboratories 2005.

TABLE 1-8 Toxicity of Acrylonitrile Vapor in Guinea Pigs Exposed for 4 Hours

Exposure Concentration (ppm)	Mortality (%) During Exposure	Total Mortality (%)	Effects
100	0	0	Slight to no effect.
265	0	0	Slight transitory effect; reduced feed consumption for 4 d.
575	25	63	Ocular and nasal irritation during exposure; delayed death (3-6 d) probably from pulmonary edema.
1,160	13	100	Five dead within 1.5 h postexposure; 2 dead at 18 h.

Source: Dudley and Neal 1942.

In an 8-week repeat exposure study, three rabbits were exposed to acrylonitrile at 100 ppm (average concentration) for 4 h/day, 5 days/week (Dudley et al. 1942). The rabbits survived for the full exposure duration, but were drowsy and listless during exposure and gained no weight gain. No additional effects were observed.

3.2. Nonlethal Toxicity

3.2.1. Monkey

No evidence of toxicity was observed in rhesus monkeys (four per group; sex not specified) exposed to acrylonitrile at 56 ppm (126 mg/m^3) for 4 h/day, 5 days/week for 4 weeks (Dudley et al. 1942). A slight increase in respiration on initial exposure was the only effect reported for two male and two female monkeys exposed for 4 h at 65 ppm (Dudley and Neal 1942). In the same study, two female monkeys exposed to acrylonitrile at 90 ppm for 4 h exhibited slight weakness, redness of the face and genitals, and a slight increase in respiratory rate. The effects resolved within 12-h postexposure. Details regarding generation of the test atmospheres are provided in Section 3.1.1.

3.2.2. Dog

In a preliminary investigation into the toxicity of acrylonitrile (Haskell Laboratory 1942), three dogs (strain, sex, age, and weight not specified) exposed to acrylonitrile a 25 ppm for 6 h had a rise in body temperature of at least 2°F. Exposure at 50 ppm resulted in a drop in body temperature of as much as 1.6°F. Three dogs were exposed for 1.75 h to acrylonitrile at 225 ppm. Two of the dogs exhibited an initial marked increase in pulse rate followed by a decrease. Blood pressure increased in two of three dogs and decreased in a third dog. Overt signs of exposure included ocular and nasal irritation, vomiting, incoordination, and "noisy" respiration. All dogs recovered within 24 h.

Four dogs exposed to acrylonitrile at 30 ppm for 4 h exhibited only slight salivation (Dudley and Neal 1942). Severity of effects increased with increasing concentration. Exposure at 65 ppm produced weakness in one dog and coma in another while exposure at 100 ppm resulted in convulsions in two of three dogs (see Table 1-3, Section 3.1.2). All of the dogs in these exposure groups fully recovered within 48 h or less. Details regarding generation of the test atmospheres for these experiments are described in Section 3.1.1.

3.2.3. Cat

In the study by Dudley and Neal (1942), groups of two to four cats (sex not specified; about 3.6 kg) were exposed to acrylonitrile at 100 ppm for 4 h and exhibited only salivation and slight transient effects (redness of the skin and

mucosae) whereas exposure at 275 ppm resulted in more severe effects (marked salivation, signs of pain) but no deaths.

3.2.4. Rat

Dudley et al. (1942) exposed 16 rats to acrylonitrile at an average concentration of 100 ppm for 5 days/week for 8 weeks. Slight lethargy during exposure was the only adverse effect observed. During the test period, three of the seven females gave birth and raised normal litters.

Results of a study by Bhooma et al. (1992) demonstrated fibrin-network formation in the lungs of six male Wistar rats exposed to acrylonitrile at 100 ppm for 5 h/day for 5 days and observed for 28 days. Alveolar macrophage activity was elevated from postexposure day 1 to day 14 and returned to normal by day 28. Procoagulant activity in lavage fluid was unaltered for the first 5 days, but was elevated when assessed at days 14 and 28.

Quast et al. (1980) exposed rats to acrylonitrile at 20 and 80 ppm for 6 h/day, 5 days/week. The rats exhibited "minimal changes microscopically in the respiratory epithelium of the nasal turbinates of 80 ppm rats suggestive of slight degree of irritation" at the 6-month interim sacrifice interval. There was no mention of adverse effects associated with the 20-ppm exposure.

In the study by WIL Research Laboratories (2005), vocalization by rats when handled was reported in animals exposed (nose only) to acrylonitrile at 539 ppm for 4 h. Some rats exposed at 775 ppm exhibited ataxia, labored breathing, hyperactivity, and decreased urination and defecation during or after exposure. The rats in both groups were normal within 2 days (539-ppm group) or 8 days (775-ppm group) after exposure.

3.2.5. Rabbit

In the Dudley and Neal (1942) study, groups of two to three albino rabbits (sex not specified; about 4.5 kg) exposed to acrylonitrile at 100 or 135 ppm for 4 h had slight to marked transitory effects in respiratory pattern and signs of irritation.

3.2.6. Guinea Pig

Dudley et al. (1942) exposed 16 guinea pigs to an average concentration of acrylonitrile of 100 ppm for 4 h/day, 5 days/week for 8 weeks. The guinea pigs gained weight moderately and exhibited slight lethargy during the exposure but no other adverse signs were observed.

3.3. Developmental and Reproductive Effects

Acrylonitrile has been shown to produce fetal anomalies in rats following oral gavage dosing (Murray et al. 1976; Saillenfait and Sabate 2000) and hamsters following intraperitoneal injection (Willhite et al. 1981a,b). Dose-response

data for inhalation exposures is limited to two studies conducted in rats (Murray et al. 1978; Saillenfait et al. 1993a).

In a developmental toxicity study conducted by Murray et al. (1978), groups of 30 pregnant Sprague-Dawley rats were exposed to acrylonitrile (>99 purity) at 0, 40, or 80 ppm for 6 h/day on gestation days 6-15. The concentrations were selected on the basis of the threshold limit value of 20 ppm and preliminary results of a long-term inhalation toxicity study. Clinical signs (made daily), maternal body weight, and feed consumption were monitored and gross necropsies were performed. Standard developmental parameters were assessed. Sex, body weight, external abnormalities, and skeletal and soft-tissue anomalies of fetuses were evaluated. The rats were exposed in stainless steel and glass Rochester-type chambers (4.3 m^3) with dynamic airflow conditions. Acrylonitrile vapor was generated by metering it into an airstream. The test atmosphere was analyzed by gas-liquid chromatography three times per day. Time-weighted mean concentrations of acrylonitrile were 40 ± 2 and 77 ± 8 ppm (mean ± standard deviation).

Results of the Murray et al. (1978) study are summarized in Tables 1-9, 1-10, and 1-11. Mean body weight and maternal body weight gain was significantly decreased during treatment in both dose groups. Relative to controls, food consumption was decreased during gestation days 15-17 but increased on days 18-20. Maternal liver weight was unaffected by acrylonitrile exposure. Pregnancy incidence, mean litter size, incidence of resorptions, and average fetal body measurements were unaffected by exposure to acrylonitrile. A significant ($p < 0.06$) increased incidence of total malformations was detected in litters of the 80-ppm group. Specific malformations included short tail, short trunk, missing ribs, delayed ossification of skull bones, omphalocele, and hemivertebrae, and were observed only in the 80-ppm treatment group. These high-dose effects were considered to be exposure related, because of similar findings in a gavage study by Murray et al. (1976). The investigators concluded that the data suggested a teratogenic effect of acrylonitrile at 80 ppm but that there was no evidence of teratogenicity or embryotoxicity in rats exposed at 40 ppm.

In contrast to the Murray et al. (1976) study, Saillenfait et al. (1993a) did not observe fetal malformations in rats exposed to acrylonitrile at concentrations up to 100 ppm. Groups of 20-23 pregnant Sprague-Dawley rats were exposed by inhalation to acrylonitrile (>99% purity) at 0, 12, 25, 50, or 100 ppm for 6 h/day on gestation days 6-20, and euthanized on day 21. Clinical signs of toxicity, maternal body weight, and feed consumption were monitored, and gross necropsies were performed. Fetal examinations included gender ratio, body weight, external abnormalities, and skeletal and soft-tissue anomalies. The rats were exposed in 200-L stainless steel chambers (23°C, 50% relative humidity) with dynamic and adjustable laminar air flow (10-20 m^3/h). Acrylonitrile vapor was generated by bubbling air through a flask containing acrylonitrile, and the concentration in the chamber was calculated from the ratio of the amount of acrylonitrile vaporized to the total chamber air flow during the test period. Concentration of acrylonitrile was determined analytically by hourly sampling and gas-liquid chromatography.

TABLE 1-9 Maternal Toxicity in Rats Exposed by Inhalation to Acrylonitrile[a]

	Exposure Concentration		
Parameter	0 ppm	40 ppm	80 ppm
No. deaths/no. females	0/40	0/38	0/40
Percentage pregnant (no.)	88 (35)	97 (37)	90 (36)
Additional pregnancies (detected by stain)	0	0	3
Body weight gain of dams			
Gestation days 6-9	19 ± 5	1 ± 6[b]	-5 ± 10[b]
Gestation days 10-15	43 ± 8	32 ± 14[b]	31 ± 17[b]
Gestation days 16-20	82 ± 12	84 ± 22	92 ± 15
Liver weight (gestation day 21)			
Absolute (g)	16.0 ± 1.8	15.9 ± 1.8	15.3 ± 1.6
Relative to body weight (g/kg)	38.6 ± 2.9	41.3 ± 3.1	40.3 ± 4.3

[a]Rats were exposed for 6 h/day on gestations days 6-15.
[b]$p < 0.05$
Source: Adapted from Murray et al. 1978.

TABLE 1-10 Litter Data for Pregnant Rats Exposed to Acrylonitrile Vapor[a]

	Exposure Concentration		
Parameter	0 ppm	40 ppm	80 ppm
No. of litters	33	36	35
Implantations/dam	13 ± 2	13 ± 2	12 ± 3
Live fetuses/litter	13 ± 2	12 ± 2	12 ± 3
Resorptions/litter	0.6 ± 0.7	0.7 ± 1.1	0.5 ± 0.6
Fetal body weight (g)	5.79 ± 0.33	5.72 ± 0.42	5.90 ± 0.25
Fetal crown-rump length (mm)	43.9 ± 2.1	43.5 ± 2.2	43.7 ± 2.2

[a]Rats were exposed for 6 h/day on gestation days 6-15.
Source: Adapted from Murray et al. 1978.

There were no maternal deaths, but a concentration-dependent decrease in absolute body weight gain was observed; the decrease was significant ($p < 0.01$) in the three highest exposure groups (-0.1, -7.8, and -24.3 g at 25, 50, and 100 ppm, respectively). No adverse effect on pregnancy rate, average number of implantations or number of live fetuses, incidences of nonsurviving implants and resorptions, or fetal sex ratio were found (see Table 1-12). A statistically significant ($p < 0.01$ to 0.005; see Table 1-12) exposure-related reduction in fetal weights was observed at 25 ppm and higher concentrations (13% to 15% decreases at 100 ppm). Evaluation of external, visceral, and skeletal variations in the fetuses revealed no acrylonitrile-related effects. The no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity was 12 ppm on the basis of fetal body weight.

TABLE 1-11 Incidence of Fetal Malformations in Litters of Rats Exposed to Acrylonitrile Vapor

	Exposure Concentration		
Parameter	0 ppm	40 ppm	80 ppm
No. fetuses/no. litters examined			
External and skeletal malformations	421/33	441/36	406/35
Visceral malformations	140/33	148/36	136/35
No. fetuses (litters) affected			
External malformations			
Short tail	0 (0)	0 (0)	2 (2)
Short trunk	0 (0)	0 (0)	1 (1)
Imperforate anus	0 (0)	0 (0)	0 (0)
Omphalocele	0 (0)	1 (1)	1 (1)
Visceral malformations			
Right-sided aortic arch	0 (0)	0 (0)	0 (0)
Missing kidney, unilateral	0 (0)	0 (0)	0 (0)
Anteriorly-displaced ovaries	0 (0)	0 (0)	1 (1)
Skeletal malformations			
Missing vertebrae (associated with short tail)	0 (0)	2 (1)	2 (2)
Missing two vertebrae and a pair of ribs	8 (1)	2 (1)	7 (2)
Hemivertebra	0 (0)	0 (0)	1 (1)
Total malformed	8 (1)	3 (2)	11 (6)[a]

[a]Rats were exposed for 6 h/day on gestation days 6-15.
[b] $p < 0.06$
Source: Adapted from Murray et al. 1978.

TABLE 1-12 Reproductive Parameters in Rats Exposed to Acrylonitrile Vapor on Gestation Days 6-20

Parameter	0 ppm	12 pm	25 ppm	50 ppm	100 ppm
No. deaths of treated females	0/20	0/21	0/21	0/20	0/21
Pregnant at euthanization (%)	100.0	95.2	95.2	90.0	90.5
No. examined litters	20	20	20	18	19
Implantations sites[a]	13.65 ± 2.81	14.80 ± 1.99	14.40 ± 3.38	15.11 ± 2.00	14.37 ± 2.17
Live fetuses/litter[a]	12.30 ± 4.09	14.00 ± 2.18	13.85 ± 3.26	14.50 ± 1.89	13.63 ± 2.22
Non-surviving implants/litter (%)[a]	10.40 ± 22.75	5.44 ± 7.38	3.49 ± 6.10	3.89 ± 5.37	4.94 ± 8.33
Resorption sites/litter (%)[a]	10.40 ± 22.75	5.11 ± 6.46	3.49 ± 6.10	3.89 ± 5.37	4.94 ± 8.33
Fetal sex ratio (male:female) (%)	1.05	0.96	1.23	1.10	0.96
Fetal body weight					
Male	5.95 ± 0.28	5.79 ± 0.28	5.64 ± 0.36[b]	5.54 ± 0.24[b]	5.04 ± 0.36[b]
Female	5.66 ± 0.36	5.51 ± 0.27	5.37 ± 0.28[c]	5.18 ± 0.25[b]	4.90 ± 0.49[b]

[a]Mean ± standard deviation.
[b] $p < 0.05$
[c] $p < 0.01$
Source: Adapted from Saillenfait et al. 1993a.

Nemec et al. (2008) conducted a two-generation reproductive toxicity study of acrylonitrile in Sprague-Dawley rats (25/sex/group) exposed (whole-body) at concentrations of 0, 5, 15, and 45 ppm (two offspring generations), and at 90 ppm (one offspring generation). Exposure were for 6 h/day, and were conducted on one litter per generation through F_2 weanlings on postnatal day 28. After approximately 3 weeks of exposure following weaning, exposure of the 90-ppm F_1 rats was terminated because of excessive systemic toxicity in the males. There were no exposure-related mortalities in adult animals, no functional effects on reproduction, no effects on reproductive organs, and no evidence of cumulative toxicity. There was no evidence of toxicity in pregnant and lactating dams or in developing animals. Adult systemic toxicity was limited to body weight and/or food consumption deficits in both sexes and generations (greater in males) at 45 and 90 ppm, and increased liver weights occurred in the 90-ppm F_0 males and females and 45-ppm F_1 males. Neonatal toxicity was limited to weight decrements in the 90-ppm F_1 offspring. Signs of local irritation during and immediately following exposure were observed at 90 ppm. Microscopic lesions of the rostral nasal epithelium (site-of-contact irritation) were observed in some animals at 5-45 ppm. The NOAEL for reproductive toxicity over two generations and neonatal toxicity of acrylonitrile administered to rats via whole-body inhalation was 45 ppm. The NOAEL was 90 ppm for reproductive toxicity for the first generation, and 15 ppm for parental systemic toxicity.

3.4. Genotoxicity

Acrylonitrile has been extensively tested for genotoxic potential. Acrylonitrile has been shown to be mutagenic in *Salmonella typhimurium*, usually with metabolic activation (S9) (e.g., Milvy and Wolff 1977; de Meester et al. 1978; Lijinsky and Andrews 1980). Acrylonitrile produced both positive and negative outcomes in *Escherichia coli* and fungi (*Saccharomyces cerevisiae*); metabolic activation in these systems was not required for a positive response. Positive results for somatic cell mutation and aneuploidy were obtained in several studies with *Drosophila melanogaster* (reviewed by IARC 1999).

In in vitro assays with mammalian cells, acrylonitrile induced DNA strand breaks, gene mutations, sister-chromatid exchange and chromosomal aberrations; a positive genotoxic response was not obtained for aneuploidy or unscheduled DNA synthesis in rat hepatocytes. In several test systems, acrylonitrile induced cell transformations in mouse or Syrian hamster ovary cells (reviewed by IARC 1999).

Results from most in vivo mammalian cell assays (unscheduled DNA synthesis in rat hepatocytes or spermatocytes, chromosome aberrations in mouse and rat bone marrow or mouse spermatogonia, micronuclei in mouse bone marrow, and dominant lethal mutations in rat and mouse) were negative (reviewed by IARC 1999). Acrylonitrile induced sister-chromatid exchanges and chromosomal aberrations in mouse bone marrow (Fahmy 1999) and micronuclei in the bone marrow of rats (Wakata et al. 1998). Comet assays found DNA damage in

the forestomach, colon, bladder, lungs, and brain of mice following a single intraperitoneal injection of acrylonitrile, and in the forestomach, colon, kidneys, bladder, and lungs of rats injected with acrylonitrile (Sekihashi et al. 2002).

In studies with mammalian DNA, Solomon et al. (1984) identified and Yates et al. (1993) characterized the nature of adducts formed in interactions of mammalian DNA with CEO, the reactive metabolite of acrylonitrile.

In conclusion, results of in vitro and in vivo studies provide evidence that acrylonitrile is genotoxic. In in vitro models, acrylonitrile induced DNA strand breaks, sister-chromatid exchanges, chromosomal aberrations, and cell transformations. Following in vivo exposure, acrylonitrile induced DNA damage, sister-chromatid exchanges, chromosomal aberrations, and micronuclei. Although negative results have also been reported, the overall weight of evidence supports the conclusion that acrylonitrile has genotoxic activity.

3.5. Carcinogenicity

A cancer bioassay was conducted by Maltoni et al. (1977). In this study groups of 30 male and 30 female rats were exposed by inhalation to acrylonitrile at 5, 10, 20, or 40 ppm for 4 h/day, 5 days/week for 12 months. A group of rats exposed to clean air served as the control group. The rats were observed until death. Body weight was unaffected by the acrylonitrile exposure. There was a statistically significant increase in the percentage of animals with benign and malignant tumors ($p < 0.01$) and malignant tumors alone ($p < 0.01$). The total malignant tumors per 100 animals was noted for several treated groups, but lacked a definitive dose-response relationship. There was no increase in Zymbal's gland tumors, extrahepatic angiosarcomas, or hepatomas. Encephalic glioma incidence was increased in rats exposed at 20 ppm (3.3%; 2/60) and 40 ppm (5%; 3/60). Although not statistically significant, the response was considered by the investigators to be of possible biologic relevance because the brain was shown to be a target organ in the oral administration part of the study.

Maltoni et al. (1988) also conducted experiments in which groups of 54 breeder female rats (Group I) were exposed to acrylonitrile at 60 ppm for 4 h/day, 5 days/week for 7 weeks followed by 7 h/day, 5 days/week for 97 weeks. A group of 60 female rats served as controls (Group II). Following transplacental exposure of the pregnant rats in Group I, inhalation exposure of offspring continued; exposures were for 4 h/day, 7 days/week for 7 weeks followed by 7 h/day, 5 days/week for 97 weeks (Group Ia), or 4 h/day, 5 days/week for 7 weeks followed by 7 h/day, 5 days/week for 8 weeks (Group Ib). Offspring group size was 67 males and 54 females in Group Ia and 60 of each gender in Group Ib. The control offspring group (Group IIa) included 158 males and 149 females. The percentage of animals with malignant tumors in the parental groups was 37% (20/54) in Group I and 16.7% (10/60) in the Group II (control). For the offspring in Group Ia, the percentage of animals (males and females) was 54.5% (66/121) and for Group Ib was 33.3% (40/120). For control offspring (Group IIa), the percentage of animals with malignant tumors was 17.9% (55/307).

In the long-term inhalation study by Quast et al. (1980), Sprague-Dawley (Spartan substrain) rats (100/sex/concentration) were exposed by inhalation to acrylonitrile at 0 (control), 20, and 80 ppm for 6 h/day, 5 days/week for 2 years (analytic concentrations were 20.1 ± 2.1 and 79.5 ± 7.3 ppm, respectively, at the 6-month sacrifice). A control group was exposed to clean air. The groups also included animals for interim sacrifices at 6 months (7/sex/concentration) and 12 months (13/sex/concentration). Hematology, urinalysis, and clinical chemistry assessments were performed at specific intervals. Clinical observations were made of body weight, mortality, clinical appearance, onset of tumors, and frequency of observed palpable tumors. All rats, regardless of time of death, were subjected to gross pathology examinations.

Alterations in the aforementioned clinical observations occurred earliest and with the highest frequency in the 80-ppm group. Mortality rate was significantly increased ($p < 0.05$) during the first year in both male and female rats of the 80-ppm group and for females of the 20-ppm group during the last 10 weeks of the study. Non-neoplastic effects for both exposure groups included concentration-related inflammation and degeneration of tissue in the nasal turbinates (mucosa suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium, with hyperplasia of the mucous secreting cells). Although these tumors are known to occur spontaneously and at a high rate in Sprague-Dawley rats, they were observed earlier and at a higher frequency in acrylonitrile-exposed animals. Focal perivascular cuffing and gliosis were found in the brain of male rats at 20 ppm (2/99; $p < 0.05$) and 80 ppm (7/99; $p < 0.05$). They were also found in female rats at 20 ppm (2/100; $p < 0.05$) and 80 ppm (8/100; $p < 0.05$). There was an increased incidence of brain tumors ($p < 0.05$) in both sexes at 80 ppm compared with the controls, identified histopathologically as focal or multifocal glial-cell tumors (astrocytomas). Proliferative glial-cell lesion incidence was significantly increased in the 80-ppm males only.

Deaths of rats in the Quast et al. (1980) study were often attributable to severe ulceration of the Zymbal's gland or mammary-tissue tumors, and suppurative pneumonia (80-ppm group only) resulting from acrylonitrile-induced pulmonary irritation. The frequency of Zymbal's gland tumors was significantly increased in males (11/100; $p < 0.05$) and in females (10/100; $p < 0.05$) in the 80-ppm group; in females the highest incidence occurred during the 13- to 18-month interval. An incidence of 3/100 was observed in males exposed at 20 ppm (1/100 in controls). No Zymbal's gland tumors were found in 20-ppm females. Tumor type and incidence data are presented in Table 1-13.

Felter and Dollarhide (1997) developed a concentration-response analysis of the astrocytoma incidence data reported by Quast et al. (1980). A polynomial dose-response model was applied to the data to estimate the EC_{10} and lower confidence limit on the EC_{10} (LEC_{10}). The calculated unit risks for lifetime continuous exposure ranged from 8.2×10^{-6} per 1 μg/m^3 (based on the EC_{10}) to 1.1×10^{-5} per 1 μg/m^3 (based on the LEC_{10}). The unit risk based on the LEC_{10} corresponds to a lifetime 1×10^{-4} risk-specific exposure concentration of 9 μg/m^3 (4.1×10^3 ppm).

TABLE 1-13 Tumor Type and Incidence Data for Rats Exposed to Acrylonitrile Vapor

Concentration (ppm)	Zymbal's Gland Carcinoma	Tongue Papilloma/ Carcinoma	Mammary Gland Fibroadenoma	Small Intestine Cystadeno-carcinoma	Brain Astrocytoma
Males					
0	1/100	1/96	–	2/99	0/100
20	3/100	0/14	–	2/20	4/99
80	11/100[a]	7/89[a]	–	14/98[a]	15/99[a]
Females					
0	0/100	–	79/100	–	0/100
20	0/100	–	95/100[a]	–	4/100[a]
80	10/100[a]	–	75/100	–	17/100[a]

[a]Significantly different from control group ($p < 0.05$).
Source: Quast et al. 1980.

3.6. Summary

Acute exposure data from tests with various laboratory species (monkey, rat, dog, rabbit, guinea pig, and cat) revealed qualitatively similar responses ranging from mild irritation (redness of exposed skin, lacrimation, and nasal discharge) and mild effects on ventilation and cardiovascular responses to severe respiratory effects, convulsions, and death. Four-hour exposure to acrylonitrile at concentrations ranging from 30 to 100 ppm produced little or no effect in all species except dogs, which exhibited severe effects at 100 ppm. Results of a recent nose-only exposure study in rats showed that concentrations up to 50 ppm for 6 h or 225 ppm for 1.75 h produced only minor transient effects on blood pressure. Lethality in rats appears to occur at cumulative exposure of 1,800-1,900 ppm-h for 30-min to 6-h durations, although for nose-only exposures it is notably higher (about 3,800 ppm-h). Lethality data for various exposure durations and concentrations suggest a near linear relationship ($C^n \times t = k$, where $n = 1.1$). Death may be delayed especially at the lower limits of lethal exposures. One study provided evidence for teratogenic effects in rats following gestational exposure of dams to acrylonitrile at 80 ppm but not at 40 ppm. Another study showed an exposure-related decrease in fetal weight following gestational exposure of dams to 25, 50, or 100 ppm acrylonitrile; no other reproductive or developmental effects were detected. Results of genotoxicity studies provide evidence that acrylonitrile is genotoxic, with positive results in in vitro (DNA strand breaks, sister-chromatid exchanges, chromosomal aberrations, and cell transformations) and in vivo (DNA damage, sister-chromatid exchanges, chromosomal aberrations, and micronuclei) models. The overall weight of evidence supports that acrylonitrile is genotoxic. Results of cancer bioassays have shown that acrylonitrile is carcinogenic in rats. The brain, spinal cord, Zymbal's gland, tongue, small intestines, and mammary glands have all been identified as targets.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Following inhalation exposure, acrylonitrile undergoes rapid absorption by passive diffusion. Data from six male volunteers exposed to acrylonitrile (5 or 22 ppm) for 8 h indicated that about 52% of the inhaled acrylonitrile was retained (Jakubowski et al. 1987). Approximately 91.5% retention was reported in rats exposed at 1,800 ppm (3,900 mg/m^3) (Peter and Bolt 1984). These investigators also reported that rhesus monkeys absorbed nearly all acrylonitrile after 6 h.

Absorbed acrylonitrile is readily distributed throughout the body. Kedderis et al. (1996) reported detection of acrylonitrile and CEO in the blood, brain, and liver of Fisher F-344 rat 3 h after exposure at 186, 254, or 291 ppm. Concentrations of acrylonitrile and CEO tended to be greatest in the brain than in liver, and decreased rapidly following cessation of exposure. GSH depletion was shown to enhance tissue uptake of acrylonitrile into the brain, stomach, liver, kidneys, and blood of GSH-depleted (phorone/buthionine sulfoximine treatment) F-344 rats (Pilon et al. 1988). GSH depletion, however, resulted in a decrease in total radioactivity recovered in the brain, stomach, liver, kidneys, and blood and a decrease in the nondialyzable radioactivity (acrylonitrile-derived) in the same organs. Control rats showed an accumulation of radiolabel which was greatest in brain RNA; no radioactivity was detected in the DNA of any organ examined. In the GSH-depleted rats, radiolabel was greater in brain RNA than in that of the liver or stomach, but was only about half that observed in brain RNA of control rats.

Acrylonitrile is eliminated rapidly (half-time <1 h), primarily through metabolism and excretion of metabolites (Peter and Bolt, 1984; Kedderis et al. 1996). Excretion of acrylonitrile and its metabolites is primarily via the urine, with feces and exhaled air being minor routes of excretion. Acrylonitrile and its metabolites have been detected in the urine of exposed workers. Perbellini et al. (1998) reported that concentrations of acrylonitrile in urine of pre- and post-shift workers were greater than in nonexposed controls.

At 24 h after inhalation exposure of male Sprague-Dawley rats to acrylonitrile at 0, 4, 20, or 100 ppm for 6 h, 2-cyanoethylmercapturic acid, 2-hydroxyethylmercapturic acid, and thiocyanate were measured in the urine (Tardif et al. 1987). The relationship between total urinary metabolites and exposure appeared to be linear. A dose-dependent excretion profile was reported for male Wistar rats following inhalation exposure to acrylonitrile at 1, 5, 10, 50, or 100 ppm for 8 h (Müller et al. 1987). Cyanoethyl mercapturic acid, S-carboxymethyl cysteine, hydroxyethyl mercapturic acid, and thioglycolic acid were detected as urinary metabolites. The investigators concluded that urinary metabolite profiles may be useful for biologic monitoring of industrial exposure. Specifically, unmetabolized acrylonitrile and the metabolites, cyanoethyl mercapturic acid and thioglycolic acid, were considered important.

Acrylonitrile toxicity appears to be directly related to its metabolism. Two major metabolism pathways have been described (Dahl and Waruszewski 1989; Fennell et al. 1991; Kedderis et al. 1993; Burka et al. 1994; Gargas et al. 1995; Sumner et al. 1999). One pathway is conjugation with glutathione and the second is epoxidation by microsomal cytochrome P450 2E1 which forms CEO. Metabolites from both pathways are subject to additional biotransformation. The glutathione conjugate may form a mercapturic acid which is excreted in urine. CEO is further metabolized via conjugation with glutathione (catalysis with cytosolic GST or nonenzymatically) resulting in additional conjugates and via hydrolysis by microsomal epoxide hydrolase (EH). The secondary metabolites of CEO may also be further metabolized. Cyanide may be generated via the EH pathway and by one of the GSH conjugation products. Cyanide, in turn, is detoxified to thiocyanate via rhodanese-mediated reactions with thiosulfate. Thiocyanate has been detected in the blood and urine of volunteer subjects following exposure to acrylonitrile (21-51 ppm for 30 min) (Wilson and McCormick 1949).

Vodiĉka et al. (1990) provided data showing that rats exposed for 6 h to acrylonitrile at 75, 150, or 300 mg/m^3 (equivalent to 35, 69, and 138 ppm, respectively) excreted thioethers at 35.0, 22.7, and 18.1%, respectively, of the dose within 24 h. About one-third to one-half of the excretion occurred during the 6-h exposure.

Benz and Nerland (2005) reported on the effect of cytochrome P450 inhibitors and anticonvulsants on the toxicity of acrylonitrile in male Sprague-Dawley rats. Treatment of rats with 1-benzylimidazole and ethanol effectively reduced blood cyanide concentrations and early seizures in rats given an LD_{90} subcutaneous dose of acrylonitrile but did not affect the clonic convulsions that precede death or acrylonitrile-induced mortality, thereby suggesting that acrylonitrile is acutely toxic even in the absence of cyanide.

4.2. Mechanism of Toxicity

The mechanism by which acrylonitrile causes irritation is unknown. Nasal tissue damage in rats may be related to metabolism of acrylonitrile by this tissue (Dahl and Waruszewski 1989). Hematologic effects may be due to acrylonitrile and CEO hemoglobin adducts (Bergmark 1997; Fennell et al. 2000), whereas GSH depletion in erythrocytes may result in the oxidation of hemoglobin to methemoglobin (Farooqui and Ahmed 1983).

Generally, the toxic effects following acute inhalation exposure to acrylonitrile appear to be irritation of the respiratory tract and the metabolism of acrylonitrile to cyanide. Acrylonitrile-induced neurologic effects in laboratory animals appear to involve the parent compound and the cyanide metabolite. The pivotal role cyanide in the acute toxicity of a series of aliphatic nitriles has been clearly demonstrated (Willhite and Smith 1981). Acrylonitrile-induced convulsions are likely the result of cyanide resulting from acrylonitrile metabolism (Nerland et al. 1989; Ghanayem et al. 1991), although results of metabolism studies by Benz and Nerland (2005) suggest that only the early seizures are cya-

nide-mediated and that severe clonic convulsions preceding death may be due to parent compound as previously described in Section 4.1. Other possible modes of action include inhibition of glyceraldehyde-3-phosphate dehydrogenase, by binding to critical cysteine residues (Campian et al. 2002), and ATP production by cyanide with respect to central nervous system effects. Additionally, it has been hypothesized that acrylonitrile-induced oxidative stress may be related to some neurologic effects (Fechter et al. 2003). Fechter et al. (2003) found that subcutaneously administered acrylonitrile depleted cochlear glutathione concentrations and potentiated noise-induced hearing loss in rats.

Cyanide formation by dams may be responsible, in part, for the developmental toxicity of acrylonitrile in animals. Saillenfait and Sabate (2000) reported that a series of aliphatic nitriles produced embryotoxicity similar to that observed for sodium cyanide. Saillenfait et al. (1993b) suggested that glutathione depletion may be involved in the embryotoxicity of inhaled acrylonitrile in rats.

4.3. Structure-Activity Relationships

Willhite and Smith (1981) demonstrated the importance of the acrylonitrile metabolite, cyanide, in the lethal response of CD-1 mice following intraperitoneal injections of acetonitrile, proprionitrile, acrylonitrile, *n*-butyronitrile, malonitrile, or succinonitrile. In studies on the effects of P450 inhibitors and anticonvulsants, Benz and Nerland (2005) reported that acrylonitrile appears to have inherent acute toxicity even in the absence of cyanide. With the data available for acrylonitrile and considering the apparent complexity of acrylonitrile acute toxicity compared with other nitriles, structure-activity relationships were not used in the derivation of AEGL values.

4.4. Species Variability

The effects of acute inhalation exposure to acrylonitrile are qualitatively similar among several animal species (monkey, dog, cat, rat, rabbit, and guinea pig). Nerland et al. (1989) categorized the clinical signs of acute inhalation exposure to acrylonitrile into four stages: (1) an excitatory phase characterized by lacrimation and agitation; (2) a tranquil phase in which cholinergic responses (salivation, lacrimation, urination, and defecation) occur; (3) a convulsive stage characterized by clonic seizures; and (4) a terminal stage characterized by paralysis and death. At least some of the variability in the toxic response to acrylonitrile may be a function of the cyanide metabolite and activity levels of rhodanese. Drawbaugh and Marrs (1987) reported that dogs have relatively lower concentrations of rhodanese and that rats had relatively high concentrations; overall species variability was about 3-fold. Results of experiments by Dudley and Neal (1942) also indicated that the dog was the most sensitive species.

Species differences in metabolism of acrylonitrile are notable. Both rats and mice appear to form CEO at a greater rate (1.5-fold and 4-fold, respectively)

than humans (Roberts et al. 1991). Although the rate of CEO formation was greater in mice, concentrations of CEO were only a third of that found in rats (Roberts et al. 1991) suggesting difference between these rodent species. The conjugation rate for CEO with GSH is reportedly faster in humans (1.5-fold) than in mice or rats (Kedderis et al. 1995). The hydrolysis of CEO by EH is notably higher in humans and virtually absent in mice and rats (Kedderis et al. 1995). On the basis of spectral analysis of acrylonitrile interaction with microsomal preparations from rats, mice, and humans, Appel et al. (1981b) conclude that rats resemble humans more closely than do mice.

4.5. Susceptible Populations

Due to the pivotal role of oxidative metabolism of acrylonitrile in the formation of cyanide, alterations in oxidative metabolism capacity (e.g., induction or inhibition of CYP2E1) may affect cyanide production rate (induction resulting in greater cyanide formation). Because cyanide detoxification may be affected by variances in sulfane sulfur as a source for thiocyanate formation via rodanese, individuals with lower circulating levels of sulfane sulfur (e.g., low cysteine content diets) may have lower capacity for cyanide detoxification. It is the net difference between the capacities of these processes that will ultimately determine the overall cyanide-induced toxicity.

Results of a study examining the relationship between cigarette smoking, acrylonitrile-derived hemoglobin adducts (*N*-(2-cyanoethyl)valine), and null genotypes for glutathione transferase (GSTM1 and GSTT1) were reported by Fennell et al. (2000). Analysis of the GST genotypes (by blood analysis) from 16 nonsmokers and 32 smokers (one to two packs/day) showed that hemoglobin adduct levels increased with increased cigarette smoking. Because the GSTM1 and GSTT1 genotypes had little effect on adduct concentrations, the results suggest that GST polymorphism may not be relevant to assessing susceptibility to acrylonitrile toxicity.

4.6. Concurrent Exposure Issues

Concurrent exposure to agents capable of altering CYP2E1 function or glutathione concentrations may affect the biotransformation of acrylonitrile and, therefore, its potential toxicity. Data are unavailable to allow for a quantitative adjustment of AEGL values due to potential concurrent exposure issues.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Occupational exposure to acrylonitrile at 16-100 ppm for 20-45 min produced headache, nasal and ocular irritation, discomfort of the chest, nervous-

ness, and irritability (Wilson et al. 1948). Occupational exposure at 0.3-3 ppm for approximately 3 years produced similar effects (Babanov et al. 1959). Sakurai et al. (1978) reported that workers routinely exposed to acrylonitrile at approximately 5 ppm in an acrylic fiber factory experienced initial conjunctival irritation, followed by some degree of accommodation. Occupational exposures to acrylonitrile at 5-20 ppm resulted in complaints of headache, fatigue, nausea, and insomnia (Sakurai and Kusumoto 1972; Sakurai et al. 1978). Six informed male volunteer subjects (including the investigators) exposed to acrylonitrile at 2.3 and 4.6 ppm for 8 h reported no symptoms of exposure (Jakubowski et al. 1987).

5.2. Animal Data Relevant to AEGL-1

Dudley et al. (1942) reported that rhesus monkeys exposed to acrylonitrile at 65 ppm for 4 h exhibited no adverse effects. Nonlethal responses in rats included slight to marked transitory effects from exposure to acrylonitrile at 665 ppm for 30 min or 1 h, 305 ppm for 2 h, 130 ppm for 4 h, and 90 ppm for 8 h. Four-hour exposure of dogs to acrylonitrile at 30 ppm, and guinea pigs, cats, and rabbits at 100 ppm resulted in slight to moderate transitory effects. WIL Research Laboratories (2005) reported only vocalization upon handling of rats exposed (nose-only) to acrylonitrile at 539 ppm for 4 h. Some rats exposed at 775 ppm exhibited ataxia, hyperactivity, and decreased urination and defecation. Other lethality bioassay reports simply indicated some exposures as nonlethal with no details regarding the presence or absence of nonlethal effects.

5.3. Derivation of AEGL-1 Values

The most relevant data for AEGL-1 derivation is the human response data reported by Jakubowski et al. (1987). No effects were observed in volunteer subjects exposed to acrylonitrile at 4.6 ppm for 8 h. Limitations of the study include that the objective of the study was to collect data on the toxicokinetics of acrylonitrile and not to evaluate health effects. All of the subjects were informed toxicologists who worked in the laboratory in which the study was performed (stakeholders) and may have been more tolerant of mild irritant effects than less motivated individuals. However, the outcome of the Jakubowski et al. (1987) study is supported by the report by Sakurai et al. (1978), in which workers routinely exposed to acrylonitrile at approximately 5 ppm experienced mild effects (initial conjunctival irritation, for which there was some accommodation). Therefore, the 8-h exposure at 4.6 ppm is considered a no-effect level for notable discomfort and a point-of-departure for deriving AEGL-1 values. That concentration is approximately 3-fold lower than concentrations reported by Wilson et al. (1948) to be associated with more severe effects in occupational settings (16-100 ppm for 20-45 min: headache, nasal and ocular irritation, discomfort of the chest, nervousness, and irritability). Therefore, 4.6 ppm was considered an

appropriate point-of-departure for AEGL-1 derivation. Pharmacokinetic variability is not likely to be significant for mild effects (ocular irritation) of low-level exposure. However, the point-of-departure is based on studies of healthy adults and, in the occupational studies, subjects who experienced repeated exposures to acrylonitrile, which may have resulted in some accommodation to the ocular irritation. Therefore, an intraspecies uncertainty factor of 3 was applied. No data are available on the relationship between exposure duration and severity of responses to acrylonitrile. Typically, in the absence of this information, AEGL-1 values based on an 8-h point-of-departure would be time scaled. However, in this case, the effect is ocular irritation, which would not be expected to have a response threshold that varies with exposure duration. Therefore, it is prudent to not time scale and the AEGL-1 values were held constant at 1.5 ppm for the 10- and 30-min durations. However, 1.5 ppm exceeds AEGL-2 values for longer exposure durations; therefore, AEGL-1 values for 1 h, 4 h, and 8 h are not recommended. AEGL-1 values for acrylonitrile are presented in Table 1-14, and their derivation is presented in Appendix C.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are no quantitative acute exposure-response data regarding AEGL-2-type effects in humans. Numerous case reports of acute accidental exposure indicate that acrylonitrile produces symptoms consistent with neurotoxicity, including headache, dizziness, feebleness, hyperactive knee jerk reflex, numbness of extremities, and convulsions (Chen et al. 1999). However, exposure data are not adequate to provide a basis for AEGL-2 values (exposures were estimated from accident simulations and post-accident measurements and ranged from 18 to over 460 ppm). Studies of workers exposed for approximately 3 years also show effects of acrylonitrile-induced neurotoxicity, including headache, insomnia, general weakness, decreased working capacity, and irritability (Babanov et al. 1959). Due to the long exposure duration, the data are not suitable as the basis of AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

AEGL-2 type effects observed in laboratory animals include changes in respiratory patterns, tremors, and convulsions, the severity of which appear to increase immediately prior to death. The onset of the more severe effects was usually preceded by varying signs of irritation (salivation, redness of skin, and lacrimation). Post-exposure observation in multiple species showed qualitatively similar effects; effects, even severe ones, were often reversible when exposure ended.

TABLE 1-14 AEGL-1 Values for Acrylonitrile

10 min	30 min	1 h	4 h	8 h
1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR[a]	NR[a]	NR[a]

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 valued is without adverse effect.

The report by Dudley and Neal (1942) provides data for six species (monkey, rat, dog, guinea pig, rabbit, and cat). For rats, 0.5-, 1-, 2-, 4-, or 8-h exposure to acrylonitrile at 2,445, 1,270, 305, or 135 ppm, respectively, produced reversible effects. Appel et al. (1981a) reported data for rats showing that 10-min exposure to acrylonitrile at 2,400 ppm or 30-min exposure at 1,600 ppm was not lethal. Dogs were more sensitive to the effects of acrylonitrile, as demonstrated by convulsions and coma at exposures as low as 65 ppm for 4 h (Dudley and Neal 1942). Results of a nose-only experiment with rats showed that 4-h exposure to acrylonitrile at 775 ppm was not lethal, but details were lacking regarding the attribution of observed effects (tremors, ataxia, labored breathing, hypoactivity, and gasping) to these exposures. For rabbits, 4-h exposure to acrylonitrile at up to 135 ppm produced slight to marked, but reversible, effects (Dudley and Neal 1942). Monkeys exposed to acrylonitrile at 65 or 90 ppm for 4 h exhibited transient skin flushing and transient elevation of respiration rate (Dudley and Neal 1942).

A developmental toxicity study conducted in rats found dose-related decrements in fetal body weight that became statistically significant at 25 ppm (6 h/day, gestation days 6-20) (Saillenfait et al. 1993a). The no-effect level was 12 ppm. Although evidence of fetal toxicity (e.g., decrements in fetal body weight or fetal crown-rump length) were not observed at 40 or 80 ppm (6 h/day, gestation days 6-15) (Murray et al. 1978), the Saillenfait et al. (1993a) study suggests that 12 ppm (6 h/day) is a no-effect level for nonlethal fetal toxicity.

6.3. Derivation of AEGL-2 Values

The AEGL-2 values are based a developmental toxicity study conducted in rats which showed that 12 ppm (6 h/day, gestation days 6-20) was a no-effect level for fetal toxicity, indicated by decrements in fetal body weight at higher concentrations (25-100 ppm). Support for the point-of-departure is provided from studies conducted in rats and monkeys. In monkeys, slight or modest reversible effects (transient skin flushing and elevation of respiration rates) were observed after 4-h exposures at 65 or 90 ppm (Dudley and Neal 1942). Slight transient effects (ocular and nasal irritation, redness of skin) were observed in rats following a 2-h exposure at 305 ppm (Dudley and Neal 1942). All effects resolved within 12 h postexposure. At higher concentrations or at longer exposure durations, effects were more severe (rapid respiration, tremors, convulsions, and death). A threshold for these more severe effects in the rat appears to be

above 305 ppm and below the threshold for lethality (the 2-h $BMCL_{05}$ is 491 ppm in the rat [see Section 7, Data Analysis for AEGL-3]). An interspecies uncertainty factor of 6 (3 × 2) was applied; a factor of 3 to account for possible species differences in toxicodynamics of acrylonitrile and a factor of 2 to account for interspecies differences in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted a 2-fold difference in the concentrations of acrylonitrile and its metabolite, cyanoethylene oxide (the metabolic precursor to cyanide), in blood and brain during 8-h exposures to acrylonitrile at 2 ppm. Higher cyanoethylene oxide concentrations were predicted in human blood and brain than in rats. A PBPK model developed by Takano et al. (2010) used data on in vitro metabolism of acrylonitrile in rat and human liver microsomes to estimate hepatic clearance of cyanoethylene oxide. The model predicted that repeated oral exposures to acrylonitrile at 30 mg/kg/day for 14 days would result in peak blood acrylonitrile concentrations that were approximately 2-fold higher in rats than humans. Although the Takano et al. (2010) model was evaluated using oral exposure data, experimental data for metabolism were obtained from in vitro microsome studies. Taken together, the Sweeney et al. (2003) and Takano et al. (2010) PBPK models support application of an interspecies uncertainty factor of 2 to account for differences in toxicokinetics. An intraspecies uncertainty factor of 6 (3 × 2) was also applied; a factor of 3 to account for possible variation in toxicodynamics of acrylonitrile in the human population and a factor of 2 to account for variability in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted that human variability in toxicokinetics of acrylonitrile will result in the 95th percentile individual having acrylonitrile or cyanoethylene oxide concentrations in blood 1.8-fold higher than the average (mean) individual. That suggests that an intraspecies uncertainty factor of 2 would account for toxicokinetic variability in the human population. The total uncertainty factor was 36 (6 × 6). Time scaling for AEGL-2 specific durations from the 6-h experimental point-of-departure was performed using the equation $C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986). Data from occupational studies suggest that the AEGL-2 values are sufficiently protective. Occupational exposure data showed that routine exposure to acrylonitrile at 5-20 ppm (approximately 20-to-80-fold higher than the 8-h AEGL-2) resulted in complaints of headache, fatigue, nausea, and insomnia, which are neither irreversible nor escape-impairing effects (Sakurai and Kusumoto 1972; Sakurai et al. 1978). The 1-h and 4-h AEGL-2 values are also below the lower end of the range of exposures estimated for occupational accidents (over18 ppm) (Chen et al. 1999). The AEGL-2 values for acrylonitrile are presented in Table 1-15, and their derivation is summarized in Appendix C.

TABLE 1-15 AEGL-2 Values for Acrylonitrile

10 min	30 min	1 h	4 h	8 h
8.6 ppm (19 mg/m^3)	3.2 ppm (6.9 mg/m^3)	1.7 ppm (3.7 mg/m^3)	0.48 ppm (1.0 mg/m^3)	0.26 ppm (0.56 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Quantitative exposure-response data in humans regarding the lethality of acrylonitrile were not available.

7.2. Animal Data Relevant to AEGL-3

Lethality data in multiple laboratory species (monkey, rat, dog, rabbit, guinea pig, and cat) are available. Lethality in rats appears to occur at cumulative exposures of 1,800-1,900 ppm-h for 30-min to 6-h exposure durations, although for nose-only exposures it is notably higher (about 3,800 ppm-h). Lethal response data for monkeys were not available. Dogs were the most sensitive species, with lethality in 1 of 2 dogs observed following a 4-h exposure to acrylonitrile at 65 ppm. However, a 4-h exposure of four dogs to acrylonitrile at 100 ppm resulted in no deaths, whereas exposure at 110 ppm killed two of three dogs. Data from studies of rats were the most extensive. Dudley and Neal (1942) provided response data in rats exposed for 0.5, 1, 2, 4, or 8 h. Thirty-minute exposure of rats to acrylonitrile concentrations as high as 2,445 ppm were without lethal effect. Exposure at 1,270 ppm for 1 h, 305 ppm for 2 h, 130 ppm for 4 h, or 135 ppm for 8 h did not result in deaths of any rats (16/group). A 4-h LC_{50} of 333 ppm was reported for rats (Haskell 1968). At higher concentrations, rats died within 2-4 h into the exposure period while deaths following exposure occurred between 7 min and 18 h; there was a 14-day observation period. There were no deaths among 10 rats exposed to acrylonitrile at 1,008 ppm for 1 h (Vernon et al. 1990). A mortality rate of 33% (1 of 3 rats) was reported in rats exposed at 650 ppm for 180 min, 950 ppm for 120 min, and 2,600 ppm for 30 min, but no deaths occurred at exposures of 1,600 ppm for 30 min or 2,400 ppm for 10 min (Appel et al. 1981a). Developmental toxicity studies conducted in rats found nonlethal effects on fetal development that included decrements in fetal body weight without fetal malformations (25-100 ppm) (Saillenfait et al. 1993a) and nonlethal fetal malformations (40 and 80 ppm) (Murray et al. 1978). Murray et al. (1978) found three malformations in two of 33 liters from dams exposed to acrylonitrile at 40 ppm and 11 malformations in six of 35 litters at 80 ppm, the most serious of which was one omphalocele at 40 and 80 ppm. These malformations were not confirmed in the Saillenfait et al. (1993a) study at concentrations up to 100 ppm. A two-generation study found weight decrements in the F_1 offspring of the 90-ppm group, but no other evidence of exposure-related mortalities in adult animals, functional effects on reproduction or effects on reproductive organs, or toxicity in developing offspring at exposures up to 90 ppm (Nemec et al. 2008). No effects on resorptions or live births were found in the single-generation or two-generation studies.

7.3. Derivation of AEGL-3 Values

The AEGL-3 values were derived using $BMCL_{05}$ as estimates of lethality thresholds. Data for 30-min, 1-h, 4-h, and 8-h AEGL-specific exposure periods are available from the reports by Appel et al. (1981a) and Dudley and Neal (1942). A 30-min $BMCL_{05}$ of 1,784 ppm was calculated from the Appel et al. (1981a) data. The 1-, 2-, 4-, and 8-h $BMCL_{05}$ values derived from lethality data published by Dudley and Neal (1942) were 1,024.4, 491.3, 179.5, and 185.8 ppm, respectively, for rats exposed to acrylonitrile at various concentrations for 1, 2, 4, or 8 h. With the exception of the 4-h value, the resulting $BMCL_{05}$ values show a consistent duration-dependent relationship; therefore, the 30-min, 1-h, and 8-h estimates were used to derive corresponding AEGL-3 values. Because the 4-h $BMCL_{05}$ was essentially equivalent to the 8-h $BMCL_{05}$, the 4-h AEGL-3 was time-scaled using the 8-h $BMCL_{05}$ of 185.9 ppm. The 10-min AEGL-3 value was derived by time-scaling from the 30-min rat $BMCL_{05}$. Time scaling was performed using the equation $C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986). Although the dog appeared to be the most sensitive species, the overall database for rats is more robust. An interspecies uncertainty factor of 6 (3 × 2) was applied; a factor of 3 was applied to account for possible species differences in toxicodynamics of acrylonitrile and a factor of 2 to account for interspecies differences in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted a 2-fold difference the concentrations of acrylonitrile and the acrylonitrile metabolite, cyanoethylene oxide (the metabolic precursor to cyanide), in blood and brain during 8-h exposures to acrylonitrile at 2 ppm. Higher cyanoethylene oxide concentrations were predicted in human blood and brain than in rats. A PBPK model developed by Takano et al. (2010) used data on in vitro metabolism of acrylonitrile in rat and human liver microsomes to estimate hepatic clearance of cyanoethylene oxide in rats and humans. The model predicted that repeated oral exposures to acrylonitrile at 30 mg/kg/day for 14 days would result in peak blood acrylonitrile concentrations that were approximately 2-fold higher in rats than humans. Although the Takano et al. (2010) model was evaluated using oral exposure data, experimental data on metabolism were obtained from in vitro microsome studies. Taken together, the Sweeney et al. (2003) and Takano et al. (2010) PBPK models support application of an interspecies uncertainty factor of 2 to account for differences in toxicokinetics. An intraspecies uncertainty factor of 6 (3 × 2) was also applied; a factor of 3 was applied to account for possible variation in toxicodynamics of acrylonitrile in the human population and a factor of 2 to account for variability in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted that human variability in toxicokinetics of acrylonitrile would result in the 95th percentile individual having acrylonitrile or cyanoethylene oxide concentrations in blood 1.8-fold higher than the average (mean) individual. This suggests that an intraspecies uncertainty factor of 2 would account for toxicokinetic variability in the human population. The total uncertainty factor was 36 (6 × 6). The resulting AEGL-3 values are presented in Table 1-16, and their derivation is summarized in Appendix C.

TABLE 1-16 AEGL-3 Values for Acrylonitrile

10 min	30 min	1 h	4 h	8h
130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 ppm (11 mg/m^3)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for acrylonitrile are presented in Table 1-17. The AEGL-1 values are based on the absence of effects in male volunteer subjects exposed to acrylonitrile in a controlled-exposure study (Jakubowski et al. 1987) and occupational exposure data showing ocular irritation and headache at 16-20 ppm. The AEGL-2 values are based on a no-effect level for fetal toxicity (decreased fetal body weight) in rats exposed to acrylonitrile at 12 ppm for 6 h/day on gestation days 6-20 (Saillenfait et al. 1993a). The AEGL-3 values were derived on the basis of estimated lethality thresholds ($BMCL_{05}$s) in rats (Dudley and Neal 1942; Appel et al. 1981a), the species for which the most lethality data are available.

8.2. Comparisons with Other Standards and Guidelines

The AEGL values and existing standards and guidelines for acrylonitrile are presented in Table 1-18. The 30-min AEGL-2 value is consistent with the immediately dangerous to life or health (IDLH) value and is approximately 26 times higher than the 30-min AEGL-2. The difference reflects different end points used to derive the values. The IDLH is based on human toxicity data and the 30-min AEGL-2 is based on fetal toxicity in rats. The emergency response planning guidline-2 (ERPG-2) is approximately 20 times higher than the 1-h AEGL-2 value. The ERPG-2 is based on reversible effects observed in dogs (salivation observed at 35 ppm for 4 h), whereas the 1-h AEGL-2 value is based on a no-effect level for fetal toxicity in rats (12 ppm, 6 h, gestation days 6-20). The ERPG-3 is approximately 3 times higher than the 1-h AEGL-3 value. The ERPG-3 is based on severe effects and lethality in dogs (65-200 ppm), whereas the 1-h AEGL-3 value is based on estimates of the duration-specific $BMCL_{05}$ for lethality in rats.

8.3. Data Adequacy and Research Needs

Data were adequate for the development of AEGL values for acrylonitrile. Human data were used for deriving AEGL-1 values for 10 min and 30 min durations; however, values for 1 h, 4 h and 8 h are not recommended because they

would be higher than AEGL-2 values for the same durations. Data on developmental toxicity in rats, supported with more limited data in monkeys, were used for developing AEGL-2 values. A robust data set in rats allowed for derivation of AEGL-3 values.

TABLE 1-17 AEGL Values for Acrylonitrile

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)[a]	1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	8.6 ppm (19 mg/m^3)	3.2 ppm (6.9 mg/m^3)	1.7 ppm (3.7 mg/m^3)	0.48 ppm (1.0 mg/m^3)	0.26 ppm (0.56 mg/m^3)
AEGL-3 (lethal)	130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 ppm (11 mg/m^3)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effect.

TABLE 1-18 Standards and Guidelines for Acrylonitrile

	Exposure Duration				
Guideline	1 min	30 min	1 h	4 h	8 h
AEGL-1	1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR[a]	NR[a]	NR[a]
AEGL-2	8.6 ppm 19 mg/m^3	3.2 ppm 6.9 mg/m^3	1.7 ppm 3.7 mg/m^3	0.48 ppm 1.0 mg/m^3	0.26 ppm 0.56 mg/m^3
AEGL-3	130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 ppm (11 mg/m^3)
ERPG-1 (AIHA)[a]	–	–	10 ppm	–	–
ERPG-2 (AIHA)	–	–	35 ppm	–	–
ERPG-3 (AIHA)	–	–	75 ppm	–	–
IDLH (NIOSH)[b]	–	85 ppm	–	–	–
TLV-TWA (ACGIH)[c]	–	–	–	–	2 ppm (skin)
PEL-TWA (OSHA)[d]	–	–	–	–	2 ppm
REL-TWA (NIOSH)[e]	–	–	–	–	1 ppm
PEL-STEL/C (OSHA)[f]	10 ppm (15 min)	–		–	–

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effect.
[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013).
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversi-

ble or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.
[b]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[c]TLV-TWA (threshold limit value-time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Acrylonitrile is categorized as a confirmed animal carcinogen with unknown relevance to humans.
[d]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[e]REL-TWA (recommended exposure limits – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.
[f]PEL-STEL/C (permissible exposure limit – short-term exposure limit and ceiling, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is a 15-min time-weighted average that should not be exceeded at any time during the workday. A ceiling value should not be exceeded at any time.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. TLVs and BEIs Based on the Documentation of the Threshold Limit values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 1997. Emergency Response Planning Guidelines: Acrylonitrile. American Industrial Hygiene Association, Fairfax, VA.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013 ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Appel, K.E., H. Peter, and H.M. Bolt. 1981a. Effect of potential antidotes on the acute toxicity of acrylonitrile. Int. Arch. Occup. Environ. Health 49(2):157-163.

Appel, K.E., H. Peter, M. Bolt, and H.M. Bolt. 1981b. Interaction of acrylonitrile with hepatic microsomes of rats and men. Toxicol. Lett. 7(4-5):335-340.

Babanov, G.P., V.N. Kljuchikov, N.I. Karajeva, and Z.V. Lileeva. 1959. Clinical symptoms of chronic poisoning by acrylonitrile [in Russian]. Vrach. Delo. 8:833-836 (as cited in WHO 1983).

Bader, M., and R. Wrbitzky. 2006. Follow-up biomonitoring after accidental exposure to acrylonitrile- Implications for protein adducts as a dose monitor for short-term exposure. Toxicol. Lett. 162(2-3):125-131.

Benz, F.W., and D.E. Nerland. 2005. Effect of cytochrome P450 inhibitors and anticonvulsants on the acute toxicity of acrylonitrile. Arch. Toxicol. 79(10):610-614.

Bergmark, E. 1997. Hemoglobin adducts of acrylamide and acrylonitrile in laboratory workers, smokers and nonsmokers. Chem. Res. Toxicol. 10(1):78-84.

Beskid, O., Z. Dusek, I. Solansky, and R.J. Sram. 2006. The effects of exposure to different clastogens on the pattern of chromosomal aberrations detected by FISH whole chromosome painting in occupationally exposed individuals. Mutat. Res. 594(1-2):20-29.

Bhooma, T., B. Padmavathi, and S.N. Devaraj. 1992. Effect of acrylonitrile on the procoagulant activity of rat lung. Bull. Environ. Contam. Toxicol. 48(2):321-326.

Blair, A., P.A. Stewart, D.D. Zaebst, L. Pottern, J.N. Zey, T.F. Bloom, B. Miller, E. Ward, and J. Lubin. 1998. Mortality of industrial workers exposed to acrylonitrile. Scand. J. Work Environ. Health 24(suppl. 2):25-41.

Borba, H., M. Monteiro, M.J. Proenca, T. Chaveca, V. Pereira, N. Lynce, and J. Rueff. 1996. Evaluation of some biomonitoring markers in occupationally exposed populations to acrylonitrile. Teratog. Carcinog. Mutagen. 16(4):205-218.

Buchter, A., and H. Peter. 1984. Clinical toxicology of acrylonitrile. G. Ital. Med. Lav. 6(3-4):83-86.

Burka, L.T., I.M. Sanchez, E.A. Ahmed, and B.I. Ghanayem. 1994. Comparative metabolism and deposition of acrylonitrile and methacrylonitrile in rats. Arch. Toxicol. 68(10):611-618.

Butterworth, B.E., S.R. Eldridge, C.S. Sprankle, P.K. Working, K.S. Bentley, and M.E. Hurtt. 1992. Tissue-specific genotoxic effects of acrylamide and acrylonitrile. Environ. Mol. Mutagen. 20(3): 148-155.

Campian, E.C., J. Cai, and F.W. Benz. 2002. Acrylonitrile irreversibly inactivates glyceraldehyde-3-phosphate dehydrogenase by alkylating the catalytically active cysteine 149. Chem. Biol. Interact. 140(3):279-291.

Chang, C.M., M.T. Hsia, G.D. Stoner, and I.C. Hsu. 1990. Acrylonitrile-induced sister-chromatid exchanges and DNA single-strand breaks in adult human bronchial epithelial cells. Mutat. Res. 241(4):355-360.

Chen, Y., C. Chen, S. Jin, and L. Zhou. 1999. The diagnosis and treatment of acute acrylonitrile poisoning: A clinical study of 144 cases. J. Occup. Health 41(3):172-176.

Chen, Y., C. Chen, and P. Zhu. 2000. Study on the effects of occupational exposure to acrylonitrile in workers. China Occup. Med. J. 18(3).

Cole, P., J.S. Mandel, and J.J. Collins. 2008. Acrylonitrile and cancer: A review of the epidemiology. Regul. Toxicol. Pharmacol. 52(3):342-351.

Collins, J.J., R. Cheng, G.M. Buck, J. Zhang, M. Klebanoff, E.F. Schisterman, T. Scheffers, H. Ohta, K. Takaya, H. Miyauchi, M. Markowitz, B. Divine, and S. Tsai. 2003. The feasibility of conducting a reproductive outcome study of Chinese acrylonitrile worker. J. Environ. Occup. Med. 1:29-32.

Crespi, C.L., C.G. Ryan, G.M. Seixas, T.R. Turner, and B.W. Penman. 1985. Tests for mutagenic activity using mutation assays at two loci in the human lymphoblast cell lines TK6 and AHH-1. Pp. 497-516 in Evaluation of Short-Term Tests for Carcinogens, J. Ashby, F.J. de Serres, M. Draper, M. Ishidate, Jr., B.H. Margolin, B.E. Matter, and M.D. Shelby, eds. Progress in Mutation Research Vol. 5. New York: Elsevier.

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4(3):163-176.

Czeizel, A.E., S. Hegedus, and L. Timar. 1999. Congenital abnormalities and indicators of germinal mutations in the vicinity of an acrylonitrile producing factory. Mutat. Res. 427(2):105-123.

Dahl, A.R., and B.A. Waruszewski. 1989. Metabolism of organonitriles and cyanide by rat nasal tissue enzymes. Xenobiotica 19(11):1201-1205.

Davis, J.H., J.E. Davies, A. Rafonnelli, and G. Reich. 1973. Investigation of fatal acrylonitrile intoxications. Pp. 547-556 in Pesticides and the Environment: A Continuing Controversy, W.B. Deichmann, ed. New York: Intercontinental Medical Book Corporation.

Delivanova, S., P. Popovski, and T. Orusev. 1978. Blepharoconjunctivitis in workers in the manufacture of synthetic polyacrylonitrile fibers [in Serbian]. God. Zb. Med. Fak. Skopje 24:279-282.

de Meester, C., F. Poncelet, M. Roberfroid, and M. Mercier. 1978. Mutagenicity of acrylonitrile. Toxicology 11(1):19-27.

Dong, D., and J. Pan. 1995. Acrylonitrile effect on worker's reproductive system. Petrochem. Safe. Technol. Mag. 5:30-31.

Dong, D., D. Wang, X. Ai, and H. Zhang. 2000. Study of Acrylonitrile Hazardous Effects on Workers' Reproductive System. Submitted to EPA by acrylonitrile Group, Inc., Washington, DC with cover letter dated September 15, 2000. EPA Document No. 89000000313. Microfiche No. OTS0559911.

Dorodnova, N.S. 1976. Gynecological morbidity and the specific functions of the female body in the chemical manufacture of "nitron" [in Russian]. Gig. Tr. Prof. Zabol. 8:45-46.

Drawbaugh, R.B., and T.C. Marrs. 1987. Interspecies differences in rhodanese (thiosulfate sulfurtransferase, EC 2.8.1.1) activity in liver, kidney and plasma. Comp. Biochem. Physiol. 86(2): 307-310.

Dudley, H.C., and P.A. Neal. 1942. Toxicology of acrylonitrile (vinyl cyanide). I. Study of the acute toxicity. J. Ind. Hyg. Toxicol. 24(2):27-36.

Dudley, H.C., T.R. Sweeney, and J.W. Miller. 1942. Toxicology of acrylonitrile. II. Studies of effects of daily inhalation. J. Ind. Hyg. Toxicol. 24(9):255-258.

Enikeeva, N.A., R.S. Ostrovskaja, L.V. Syso, Z.G. Podrez, L.L. Braginskaja, N.P. Gvozdev, N.E. Nesterova, A.N. Musserskaja, N.A. Suzdaltreva, and A.M. Efremov. 1976. Industrial hygiene and health status of workers involved in the manufacture of the synthetic fibre Nitron [in Russian]. Gig. Tr. Ohr. Zdor. Rab. Nef. Negtehim. Prom-sti. 9:22-25 (as cited in WHO 1983).

EPA (U.S. Environmental Protection Agency). 1984. Health Assessment Document for Acrylonitrile. EPA-600/8-82-007F. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, NC.

EPA (U.S. Environmental. Protection Agency). 1991. Acrylonitrile (CAS No. 107-13-01). Integrated Risk information System, U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/ncea/iris/subst/0206.htm [accessed Mar. 24, 2014].

Fahmy, M.A. 1999. Evaluation of the genotoxicity of acrylonitrile in different tissues of male mice. Cytologia 64(1):1-9.

Fan, W., W.L. Wang, S. Ding, Y.L. Zhou, and F.S. Jin. 2006. Application of micronucleus test of buccal mucosal cells in assessing the genetic damage of workers exposed to acrylonitrile [in Chinese]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 24(2):106-108.

Farooqui, M.Y., and A.E. Ahmed. 1983. In vivo interactions of acrylonitrile with macromolecules in rats. Chem. Biol. Interact. 47(3):363-371.

Fechter, L.D., S.F. Klis, N.A. Shirwany, T.G. Moore, and D.B. Rao. 2003. Acrylonitrile produces transient cochlear function loss and potentiates permanent noise-induced hearing loss. Toxicol. Sci. 75(1):117-123.

Felter, S.P., and J.S. Dollarhide. 1997. Acrylonitrile: A reevaluation of the database to support an inhalation cancer risk assessment. Regul. Toxicol. Pharmacol. 26(3):281-287.

Fennell, T.R., G.L. Kedderis, and S.C. Sumner. 1991. Urinary metabolites of [1,2,3-13C]acrylonitrile in rats and mice detected by 13C nuclear magnetic resonance spectroscopy. Chem. Res. Toxicol. 4(6):678-687.

Fennell, T.R., J.P. MacNeela, R.W. Morris, M. Watson, C.L. Thompson, and D.A. Bell. 2000. Hemoglobin adducts from acrylonitrile and ethylene oxide in cigarette smokers: Effects of glutathione S-transferase T1-null and M1-null genotypes. Cancer Epidemiol. Biomarkers Prev. 9(7):705-712.

Gargas, M.L., M.E. Anderson, S.K. Teo, R. Batra, T.R. Fennell, and G.L. Kedderis. 1995. A physiologically-based dosimetry description of acrylonitrile and cyanoethylene oxide in the rat. Toxicol. Appl. Pharmacol. 134(2):185-194.

Ghanayem, B.I., M.Y. Farooqui, O. Elshabrawy, M.M. Mumtaz, and A.E. Ahmed. 1991. Assessment of the acute acrylonitrile-induced neurotoxicity in rats. Neurotoxicol. Teratol. 13(5):499-502.

Gincheva, N., N. Stamova, L. Hinkova, and S. Kyurktchiev, M. Spasovski, A. Bainova, M. Muhtarova, and V. Hristeva. 1977. Study of the health status of workers from the acrylonitrile department. P. 41 in Proceedings of the International Symposium on Occupational Health in the Production of Artificial Fibres-Abstracts, June 6-10, 1977, Finland (as cited in WHO 1983).

Grunske, F. 1949. Ventox and Ventox intoxication [in German]. Dtsch. Med. Wochenschr. 74(35/36):1081-1083.

Haber, F.R. 1924. On the history of the gas war. Pp. 76-92 in Five Lectures from the Years 1920-1923[in German]. Berlin, Germany: Verlag von Julius Springer.

Haskell Laboratory. 1942. Toxicity of Vinyl Cyanide. Medical Research Project No. M-97. Haskell Laboratory of Industrial Toxicology, Wilmington, DE. March 25, 1942.

Haskell Laboratory. 1968. Acute Inhalation Toxicity in Rats with Acrylonitrile (Inhibited): Methacrylonitrile (Inhibited); and Acetonitrile, October 21, 1968. Submitted to EPA by DuPont, Wilmington, DE, with cover letter dated October 15, 1992. EPA Document No. 88-920009947. Microfiche No. OTS0571605.

HSDB (Hazardous Substances Data Bank). 2013. Acrylonitrile. TOXNET Toxicology Data Network, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/ [accessed Jan. 13, 2014].

IARC (International Agency for the Research on Cancer). 1999. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 71. Lyon, France: IARC Press [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol71/mono71.pdf [accessed March 20, 2014].

Ivanescu, M., M. Berinde, and L. Simionescu. 1990. Testosterone in sera of workers exposed to acrylonitrile. Endocrinologie 28(3-4):187-192.

Jakubowski, M., I. Linhart, G. Pielas, and J. Kopecky. 1987. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br. J. Ind. Med. 44(12):834-840.

Kaneko, Y., and K. Omae. 1992. Effect of chronic exposure to acrylonitrile on subjective symptoms. Keio J. Med. 41(1):25-32.

Kedderis, G.L., R. Batra, and D.R. Koop. 1993. Epoxidation of acrylonitrile by rat and human cytochromes P450. Chem. Res. Toxicol. 6(6):866-871.

Kedderis, G.L., R. Batra, and M.J. Turner, Jr. 1995. Conjugation of acrylonitrile and 2-cyanoethylene oxide with hepatic glutathione. Toxicol. Appl. Pharmacol. 135(1): 9-17.

Kedderis, G.L., S.K. Teo, R. Batra, S.D. Held, and M.L. Gargas. 1996. Refinement and verification of the physiologically-based dosimetry description for acrylonitrile in rats. Toxicol. Appl. Pharmacol. 140(2):422-435.

Lijinsky, W., and A.W. Andrews. 1980. Mutagenicity of vinyl compounds in *Salmonella typhimurium*. Teratog. Carcinog. Mutagen. 1(3):259-267.

Litchfield, J.T., and F. Wilcoxon. 1949. Simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96(2):99-113.

Lorz, H. 1950. Percutaneous poisoning with acrylonitrile [in German]. Dtsch. Med. Wochenschr. 75(33-34):1087-1088.

Maltoni, C., A. Cilberti, and V. Di Maio. 1977. Carcinogenicity bioassays on rats of acrylonitrile administered by inhalation and by ingestion. Med. Lav. 69(6):401-411.

Maltoni, C., A. Cilberti, G. Cotti, and G. Perino. 1988. Long-term carcinogenicity bioassay on acrylonitrile administered by inhalation and by ingestion to Sprague-Dawley rats. Ann. NY Acad. Sci. 534:179-202.

Martin, C.N., and J. Campbell. 1985. Tests for the induction of unscheduled DNA repair synthesis in HeLa cells. Pp. 375-379 in Evaluation of Short-Term Tests for Carcinogens, J. Ashby, F.J. de Serres, M. Draper, M. Ishidate, Jr., B.H. Margolin, B.E. Matter, and M.D. Shelby, eds. Progress in Mutation Research Vol. 5. New York: Elsevier.

Milvy, P., and M. Wolff. 1977. Mutagenic studies with acrylonitrile. Mutat. Res. 48(3-4):271-278.

Müller, G., C. Verkoyen, N. Soton, and K. Norpoth. 1987. Urinary excretion of acrylonitrile and its metabolites in rats. Arch. Toxicol. 60(6):464-466.

Murray, F.J., K.D. Nitschke, J.A. John, F.A. Smith, J.F. Quast, C.D. Blogg, and B.A. Schwetz. 1976. Teratologic Evaluation of Acrylonitrile Monomer given to Rats by Gavage. Toxicological Research Laboratory, Health and Environmental Research, Dow Chemical, USA, Midland, MI. October 22, 1976. Submitted to EPA by DuPont, Wilmington, DE with cover letter dated August 10, 1992. EPA Document No. 88920010410. Microfiche No. OTS0555785.

Murray, F.J., B.A. Schwetz, K.D. Nitsche, J.A. John, J.M. Norris, and P.J. Gehring. 1978. Teratogenicity of acrylonitrile given to rats by gavage or by inhalation. Food Cosmet. Toxicol. 16(6):547-551.

Muto, T., H. Sakurai, K. Omae, H. Minaguchi, and M. Tachi. 1992. Health profiles of workers exposed to acrylonitrile. Keio J. Med. 41(3):154-160.

Nagata, Y. 2003. Measurement of odor threshold by triangle odor bag method. Pp. 118-127 in Odor Measurement Review. Japan Ministry of the Environment, Tokyo [online]. Available: https://www.env.go.jp/en/air/odor/measure/02_3_2.pdf [accessed March 20, 2014].

Nemec, M.D., D.T. Kirkpatrick, J. Sherman, J.P. Van Miller, M.L. Pershing, and D.E. Strother. 2008. Two-generation reproductive toxicity study of inhaled acrylonitrile vapors in Crl:CD(SD) rats. Int. J. Toxicol. 27(1):11-29.

Nerland, E.E., F.W. Benz, and C. Babiuk. 1989. Effects of cysteine isomers and derivatives on acute acrylonitrile toxicity. Drug Metab. Rev. 20(2-4):233-246.

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs): Acrylonitrile. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/107131.html [accessed Mar. 24, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Acrylonitrile. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0014.html [accessed Mar. 24, 2014].

NPI (National Pollution Inventory). 2006. Acrylonitrile (2-Propenenitrile) Fact Sheet. Australian Government, Department of the Environment, Canberra [online]. Available: http://www.npi.gov.au/resource/acrylonitrile-2-propenenitrile [accessed Mar. 20, 2014].

NRC (National Research Council). 1985. Hydrazine. Pp. 5-21 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NTP (National Toxicology Program). 2011. Acrylonitrile. Pp. 28- 20 in Report on Carcinogens, 11th Ed. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program [online]. Available: http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Acrylonitrile.pdf [accessed March 24, 2014].

Obe, G., A. Hille, R. Jonas, S. Schmidt, and U. Thenhaus. 1985. Tests for the induction of sister-chromatid exchanges in human peripheral lymphocytes in culture. Pp. 439-442 in Evaluation of Short-Term Tests for Carcinogens, J. Ashby, F.J. de Serres, M. Draper, M. Ishidate, Jr., B.H. Margolin, B.E. Matter, and M.D. Shelby, eds. Progress in Mutation Research Vol. 5. New York: Elsevier.

O'Berg, M.T. 1980. Epidemiologic study of workers exposed to acrylonitrile. J. Occup. Med. 22(4):245-252.

O'Berg, M.T., J.L. Chen, C.A. Burke, J. Walrath, and S. Pell. 1985. Epidemiologic study of workers exposed to acrylonitrile: An update. J. Occup. Med. 27(11):835-840.

Perbellini, L., A. Ganzi, G. Venturi, M. Cerpelloni, and F. Brugnone. 1998. Biological monitoring of acrylonitrile exposure. G. Ital. Med. Lav. Ergon. 20(1):10-14.

Perocco, P., G. Pane, S. Bolognesi, and M. Zannotti. 1982. Increase in sister chromatid exchange and unscheduled synthesis of deoxyribonucleic acid by acrylonitrile in human lymphocytes in vitro. Scand. J. Work Environ. Health 8(4):290-293.

Peter, H., and H.M. Bolt. 1984. Experimental pharmacokinetics and toxicology of acrylonitrile. G. Ital. Med. Lav. 6(3-4):77-81.

Pilon, D., A.E. Roberts, and D.E. Rickert. 1988. Effect of glutathione depletion on the uptake of acrylonitrile vapors and on its irreversible association with tissue macromolecules. Toxicol. Appl. Pharmacol. 95(2):265-278.

Quast, J.F., D.J. Schuetz, M.F. Balmer, T.S. Gushow, C.N. Park, and M.J. McKenna. 1980. A Two-year Toxicity and Oncogenicity Study with Acrylonitrile Following Inhalation Exposure of Rats. Dow Chemical Co., Toxicology Research Laboratory, Midland, MI. EPA Document No. 88920002471. Microfiche No. OTS0537281.

Recio, L., D. Simpson, J. Cocharane, H. Liber, and T.R. Skopek. 1989. Mutational specifity of 2-cyanoethylene oxide in human lymphoblastoid cells. Environ. Mol. Mutagen. 14(suppl. 15):162.

Recio, L., D. Simpson, J. Cochrane, H. Liber, and T.R. Skopek. 1990. Molecular analysis of hprt mutants induced by 2-cyanoethylene oxide in human lymphoblastoid cells. Mutat. Res. 242(3):195-208.

Rinehart, W.E., and T. Hatch. 1964. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. Am. Ind. Hyg. Assoc. J. 25(6):545-553.

Rizzi, R., E. Chiesara, D. Cova, M. Mattioli, and R. Di Lernia. 1984. Acrylonitrile: Mutagenicity in yeasts and genotoxicity in HeLa cells. Mutat. Res. 130:223.

Roberts, A.E., G.L. Kedderis, M.J. Turner, D.E. Rickert, and J.A. Swenberg. 1991. Species comparison of acrylonitrile expoxidation by microsomes from mice, rats and humans: Relationship to epoxide concentrations in mouse and rat blood. Carcinogenesis 12(3):401-404.

Rongzhu, L., C. Ziqiang, J. Fusheng, and J.J. Collins. 2005. Neurobehavioral effects of occupational exposure to acrylonitrile in Chinese workers. Environ. Toxicol. Pharmacol. 19(3):695-700.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Saillenfait, A.M., and J.P. Sabate. 2000. Comparative developmental toxicities of aliphatic nitriles: In vivo and in vitro observations. Toxicol. Appl. Pharmacol. 163(2):149-163.

Saillenfait, A.M., P. Bonnet, J.P. Guenier, and J. De Ceaurriz. 1993a. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Saillenfait, A.M., J.P. Payan, I. Langonne, D. Beydon, M.C. Grandclaude, J.P. Sabate, and J. de Ceaurriz. 1993b. Modulation of acrylonitrile-induced embryotoxicity in vitro by glutathion depletion. Arch. Toxicol. 67(3):164-172.

Sakurai, H., and M. Kusumoto. 1972. Epidemiological study of health impairment among acrylonitrile workers [in Japanese]. J. Sci. Labour. 48(5):273-282.

Sakurai, H., M. Onodera, T. Utsunomiya, H. Minakuchi, H. Iwai, and H. Mutsumura. 1978. Health effects of acrylonitrile in acrylic fibre factories. Br. J. Ind. Med. 35(3):219-225.

Sekihashi, K., A. Yamamoto, Y. Matsumura, S. Ueno, M. Watanabe-Akanuma, F. Kassie, S. Knasmüller, S. Tsuda, and Y.F. Sasaki. 2002. Comparative investigation of multiple organs of mice and rats in the comet assay. Mutat. Res. 517(1-2):53-75.

Solomon, J.J., I.L. Cote, M. Wortman, K. Decker, and A. Segal. 1984. In vitro alkylation of calf thymus DNA by acrylonitrile. Isolation of cyanoethyl-adducts of guanine and thymine and carboxyethyl-adducts of adenine and cytosine. Chem. Biol. Interact. 51(2):167-190.

Sweeney, L.M., M.L. Gargas, D.E. Strother, and G.L. Kedderis. 2003. Physiologically based pharmacokinetic model parameter estimation and sensitivity and variability analyses for acrylonitrile disposition in humans. Toxicol. Sci. 71(1):27-40.

Sumner, S.C., T.R. Fennell, T.A. Moore, B. Chanas, F. Gonzalez, and B.I. Ghanayem. 1999. Role of cytochrome P450 2E1 in the metabolism of acrylamide and acrylonitrile in mice. Chem. Res. Toxicol. 12(11):1110-1116.

Takano, R., N. Murayama, K. Horiguchi, M. Kitajima, M. Kumamoto, F. Shono, and H. Yamazaki. 2010. Blood concentrations of acrylonitrile in humans after oral administration extrapolated from in vivo rat pharmacokinetics, in vitro human metabo-

lism, and physiologically based pharmacokinetic modeling. Regul. Toxicol. Pharmacol. 58(2):252-258.

Tardif, R., D. Talbot, M. Gerin, and J. Brodeur. 1987. Urinary excretion of mercapturic acids and thiocyanate in rats exposed to acrylonitrile: Influence of dose and route of administration. Toxicol. Lett. 39(2-3):255-261.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Thiess, A.M., and I. Fleig. 1978. Analysis of chromosomes of workers exposed to acrylonitrile. Arch. Toxicol. 41(2):149-152.

Van Doorn, R., M. Ruijten, and T. van Harreveld. 2002. Guidance for the Application of Odor in Chemical Emergency Response. Presented at the NAC/AEGL-Meeting September 2002.

Vernon, P.A., L.H. Dulak, and R. Deskin. 1990. Acute toxicologic evaluation of acrylonitrile. J. Am. Coll. Toxicol. 1:114-115.

Vodiĉka, P., I. Gut, and E. Frantík. 1990. Effects of inhaled acrylic acid derivatives in rats. Toxicology 65(1-2):209-221.

Vogel, R.A., and W.M. Kirkendall. 1984. Acrylonitrile (vinyl cyanide) poisoning: A case report. Tex. Med. 80(5):48-51.

Wakata, A., Y. Miyamae, S. Sato, T. Suzuki, T. Morita, N. Asano, T. Awogi, K. Kondo, and M. Hayashi. 1998. Evaluation of the rat micronucleus test with bone marrow and peripheral blood: Summary of the 9th collaborative study by CSGMT/JEMS.MMS. Environ. Mol. Mutagen. 32(1):84-100.

WHO (World Health Organization). 1983. Acrylonitrile. Environonmental Health Criteria. 28. Geneva: World Health Organization [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc28.htm [accessed March 20, 2014].

WIL Research Laboratories. 2005. Acute Inhalation Toxicity Study of Acrylonitrile in Albino Rats. WIL-542001. WIL Research Laboratories, Ashland, OH.

Willhite, C.C., and R.P. Smith. 1981. The role of cyanide liberation in the acute toxicity of aliphatic nitriles. Toxicol. Appl. Pharmacol. 59(3):589-602.

Willhite, C.C., V.H. Ferm, and R.P. Smith. 1981a. Teratogenic effects of aliphatic nitriles. Teratology 23(3):317-323.

Willhite, C.C., M. Marin-Padilla, V.H. Ferm, and R.P. Smith. 1981b. Morphogenesis of axial skeletal (dysraphic) disorders induced by aliphatic nitriles. Teratology 23(3): 325-333.

Wilson, R.H., and W.E. McCormick. 1949. Acrylonitrile: Its physiology and toxicology. Ind. Med. Surg. 18(6):243-245.

Wilson, R.H., G.V. Hough, and W.E. McCormick. 1948. Medical problems encountered in the manufacture of American-made rubber. Ind. Med. Surg. 17(6):199-207.

Xu, D.X., Q.X. Zhu, L.K. Zheng, Q.N. Wang, H.M. Shen, L.X. Deng, and C.N. Ong. 2003. Exposure to acrylonitrile induced DNA strand breakage and sex chromosome aneuploidy in human spermatozoa. Mutat. Res. 537(1):93-100.

Yates, J.M., S.C. Sumner, M.J. Turner, L. Recio, and T.R. Fennell. 1993. Characterization of an addict and its degradation product produced by the reaction of cyanoethylene oxide with deoxythymidine and DNA. Carcinogenesis 14(7):1363-1369.

Zotova, L.A. 1975. Working conditions in the production of acrylonitrile and their effect on workers. Gig. Tr. Prof. Zabol. (8):8-11.

APPENDIX A

DERIVATION OF LEVEL OF DISTINCT ODOR AWARENESS FOR ACRYLONITRILE

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance of van Doorn et al. (2002). The odor detection threshold (OT_{50}) for acrylonitrile was reported to be 8.8 ppm (Nagata 2003). Nagata (2003) also determined the odor threshold for the reference chemical *n*-butanol (OT_{50} = 0.038 ppm) for derivation of the corrected OT_{50}, as shown below:

OT_{50} for acrylonitrile: 8.8 ppm
OT_{50} for *n*-butanol: 0.038 ppm

Corrected OT_{50} for acrylonitrile = 8.8 ppm × 0.04 ppm ÷ 0.038 ppm = 9.3 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = kw \times \log (C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default of kw = 2.33 will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C \div 9.3) + 0.5$, which can be rearranged to
$\text{Log} (C \div 9.3) = (3 - 0.5) \div 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 9.3 = 109.3$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life factors such as sex, age, sleep, smoking, upper airway infections, and allergies, as well as distraction, may increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 ÷ 3 = 1.33.

$$LOA = C \times 1.33 = 110 \text{ ppm} \times 1.33 = 145.4 \text{ ppm}$$

Therefore, the LOA for acrylonitrile is 145 ppm.

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR ACRYLONITRILE

Carcinogenicity assessments for lifetime exposure to inhaled acrylonitrile have been conducted by EPA (1991) and Felter and Dollarhide (1997). On the basis of these assessments, two calculations for cancer risk are presented below.

Calculation A:

The EPA (1991) Integrated Risk Information System (IRIS) program derived an inhalation unit risk for acrylonitrile of 6.8×10^{-5} $(\mu g/m^3)^{-1}$ based on a statistically significant excess incidence of respiratory cancer from an occupational study (O'Berg 1980). In a cohort of 1,345 male textile workers exposed to acrylonitrile at 5-20 ppm (estimated) for at least 10 years, 25 cases of cancer, including eight cases of respiratory cancer, were reported. A positive trend was observed for increased cancer incidence with increased exposure duration and increased duration of follow-up time. However, a follow-up study of this cohort (O'Berg et al. 1985) did not find an increased incidence of respiratory cancer. The IRIS Program is currently reassessing this chemical.

To transform the unit risk for continuous lifetime exposure derived by EPA (1984) to a single 24-h exposure estimate, default procedures (linear transformation and correction by a factor of 6 to account for the relevance of sensitive stages in development) were applied, as recommended in the standing operating procedures for AEGL development (NRC 2001, see Appendix A).

On the basis of the inhalation unit risk of 6.8×10^{-5} $(\mu g/m^3)^{-1}$ derived by EPA (1991), an acrylonitrile concentration of 1.47 $\mu g/m^3$ (equivalent to 1.47×10^{-3} mg/m^3 or 6.78×10^{-4} ppm) is associated with a risk level of 1 in 10,000 for lifetime exposure.

To convert the 70-year exposure to a 24-h exposure, the concentration associated with a 1 in 10,000 risk level is multiplied by 25,600 (the number of days in 70 years):

$$\text{24-h exposure} = d \times 25{,}600; \text{ where } d = 6.78\times10^{-4} \text{ ppm}$$
$$= 6.78\times10^{-4} \text{ ppm} \times 25{,}600 \text{ days}$$
$$= 17.4 \text{ ppm}$$

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

$$= 17.4 \text{ ppm} \div 6$$
$$= 2.9 \text{ ppm}$$

Therefore, on the basis of the potential carcinogenicity of acrylonitrile, an acceptable 24-h exposure would be 2.9 ppm for a 10^{-4} risk.

If the exposure is limited to a fraction (*f*) of a 24-h period, the fractional exposure is 1/f × 24 h (NRC 1985). Extrapolation to 10 min was not calculated due to unacceptably large inherent uncertainty. For a 10^{-4} risk:

24-h exposure =2.9 ppm (5.6 mg/m^3)
8-h exposure = 8.7 ppm (20 mg/m^3)
4-h exposure = 17 ppm (38 mg/m^3)
1-h exposure = 70 ppm (150 mg/m^3)
30-min exposure = 140 ppm (300 mg/m^3)

Exposures relating to 10^{-4}, 10^{-5}, and 10^{-6} risk levels are shown below in Table B-1.

TABLE B-1 Potential Cancer Risk[a] Associated with Acute Inhalation to Acrylonitrile

	Exposure Duration				
Risk Level	0.5 h	1 h	4 h	8 h	24 h
1 in 10,000 (10^{-4})	140 ppm (300 mg/m^3)	69 ppm (150 mg/m^3)	17 ppm (38 mg/m^3)	8.7 ppm (20 mg/m^3)	2.9 ppm (6.3 mg/m^3)
1 in 100,000 (10^{-5})	14 ppm (30 mg/m^3)	6.9 ppm (15 mg/m^3)	1.7 ppm (3.8 mg/m^3)	0.87 ppm (2.0 mg/m^3)	0.29 ppm (0.56 mg/m^3)
1 in 1,000,000 (10^{-6})	1.4 ppm (3.0 mg/m^3)	0.69 ppm (1.5 mg/m^3)	0.17 ppm (0.38 mg/m^3)	0.087 ppm (0.20 mg/m^3)	0.029 ppm (0.056 mg/m^3)

[a]Based on the EPA (1984) carcinogenicity assessment.

A comparison of the AEGL-2 and AEGL-3 values with the estimated acrylonitrile concentration associated with a 10^{-4} cancer risk is shown in Table B-2. Estimated cancer risks for the AEGL-2 and AEGL-3 values are also provided, obtained by assuming a linear relationship between exposure concentration and cancer risk.

TABLE B-2 Comparison of AEGL Values and Potential Cancer Risk[a] Associated with Acute Inhalation Exposure to Acrylonitrile

	Exposure Duration					
Value	10 min	30 min	1 h	4 h	8 h	24 h
Cancer Risk (10^{-4})	–	140 ppm	70 ppm	17 ppm	8.7 ppm	2.9 ppm
AEGL-1 value:	1.5 ppm	1.5 ppm	NR[b]	NR[b]	NR[b]	–
Estimated cancer risk:	–	1.1×10^{-6}	–	–	–	–
AEGL-2 value:	8.6 ppm	3.2 ppm	1.7 ppm	0.48 ppm	0.26 ppm	–
Estimated cancer risk:	–	2.3×10^{-6}	2.4×10^{-6}	2.8×10^{-6}	3.0×10^{-6}	–
AEGL-3 value:	130 ppm	50 ppm	28 ppm	9.7 ppm	5.2 ppm	–
Estimated cancer risk:	–	3.6×10^{-5}	4.0×0^{-5}	5.6×10^{-5}	6.0×0^{-5}	–

[a]Based on the EPA (1984) carcinogenicity assessment.
[b]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effect.

Calculation B:

Felter and Dollarhide (1997) conducted a carcinogenicity assessment for acrylonitrile on the basis of rat tumor data from a 2-year inhalation study conducted by Quast et al. (1980). Briefly, Sprague-Dawley rats (100/sex/concentration) were exposed to acrylonitrile at 0 (control), 20, and 80 ppm for 6 h/day, 5 days/week for 2 years. The incidence of brain tumors, identified histopathologically as focal or multifocal glial cell tumors (astrocytomas), was significantly increased ($p < 0.05$) for both male and females at 80 ppm compared with the controls. Felter and Dollarhide (1997) developed a dose-response analysis of the astrocytoma incidence data reported by Quast et al. (1980). A polynomial dose-response model was applied to the data to estimate the EC_{10} and lower confidence limit on the EC_{10} (LEC_{10}). The calculated unit risks for lifetime continuous exposure ranged from 8.2×10^{-6} per 1 $\mu g/m^3$ (on the basis of the EC_{10}) to 1.1×10^{-5} per 1 $\mu g/m^3$ (on the basis of the LEC_{10}). The unit risk based on the LEC_{10} corresponds to a lifetime 1×10^{-4} risk specific exposure concentration of 9 $\mu g/m^3$ (4.1×10^3 ppm).

To transform the unit risk for continuous lifetime exposure derived by Felter and Dollarhide (1997) to a single 24-h exposure estimate, default procedures (linear transformation and correction by a factor of 6 to account for the relevance of sensitive stages in development) were applied, as recommended in the standing operating procedures on AEGL development (NRC 2001, see Appendix A).

To convert the 70-year exposure to a 24-h exposure, the concentration associated with a 1 in 10,000 risk level is multiplied by 25,600 (the number of days in 70 years):

$$\text{24-h exposure} = d \times 25{,}600; \text{ where } d = 4.1 \times 10^{-3} \text{ ppm}$$
$$= 4.1 \times 10^{-3} \text{ ppm} \times 25{,}600 \text{ days}$$
$$= 106 \text{ ppm}$$

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

$$= 106 \text{ ppm} \div 6$$
$$= 18 \text{ ppm}$$

Therefore, on the basis of the potential carcinogenicity of acrylonitrile, an acceptable 24-h exposure would be 18 ppm for a 10^{-4} risk.

If the exposure is limited to a fraction (*f*) of a 24-h period, the fractional exposure is 1/f × 24 h (NRC 1985). Extrapolation to 10 min was not calculated due to unacceptably large inherent uncertainty. For a 10^{-4} risk:

24-h exposure = 18 ppm (39 mg/m^3)
8-h exposure = 54 ppm (120 mg/m^3)
4-h exposure = 110 ppm (240 mg/m^3)
1-h exposure = 430 ppm (940 mg/m^3)
30-min exposure = 860 ppm (1,800 mg/m^3)

Exposures relating to 10^{-4}, 10^{-5}, and 10^{-6} risk levels are shown in Table B-3.

TABLE B-3 Potential Cancer Risk Associated with Acute Inhalation to Acrylonitrile, Based on the Felter and Dollarhide (1997) Carcinogenicity Assessment

	Exposure Duration				
Risk Level	0.5 h	1 h	4 h	8 h	24 h
1 in 10,000 (10^{-4})	860 ppm (1900 mg/m^3)	430 ppm (940 mg/m^3)	110 ppm (240 mg/m^3)	54 ppm (120 mg/m^3)	18 ppm (39 mg/m^3)
1 in 100,000 (10^{-5})	86 ppm (190 mg/m^3)	43 ppm (94 mg/m^3)	11 ppm (24 mg/m^3)	5.4 ppm (12 mg/m^3)	1.8 ppm (3.9 mg/m^3)
1 in 1,000,000 (10^{-6})	8.6 ppm (19 mg/m^3)	4.3 ppm (9.4 mg/m^3)	1.1 ppm (2.4 mg/m^3)	0.54 ppm (1.2 mg/m^3)	0.018 ppm (0.39 mg/m^3)

A comparison of the AEGL-2 and AEGL-3 values with the estimated acrylonitrile concentration associated with a 10^{-4} cancer risk is shown in Table B-4. Estimated cancer risks for the AEGL-2 and AEGL-3 values are also provided, obtained by assuming a linear relationship between exposure concentration and cancer risk.

TABLE B-4 Comparison of AEGL-values and Potential Cancer Risk Associated[a] with Acute Inhalation Exposure to Acrylonitrile

	Exposure Duration					
Value	10-min	30-min	1-h	4-h	8-h	24-h
Cancer Risk (10^{-4})	–	860 ppm	430 ppm	110 ppm	54 ppm	18 ppm
AEGL-1 value:	1.5 ppm	1.5 ppm	NR[b]	NR[b]	NR[b]	–
Estimated cancer risk:	–	1.7×10^{-7}	–	–	–	–
AEGL-2 value:	8.6 ppm	3.2 ppm	1.7 ppm	0.48 ppm	0.26 ppm	–
Estimated cancer risk:	–	3.7×10^{-7}	4.0×10^{-7}	4.5×10^{-7}	4.8×10^{-7}	–
AEGL-3 value:	130 ppm	50 ppm	28 ppm	9.7 ppm	5.2 ppm	–
Estimated cancer risk:	–	5.8×10^{-6}	6.5×10^{-6}	9.0×10^{-6}	9.7×10^{-6}	–

[a]Based on the Felter and Dollarhide (1997) carcinogenicity assessment.
[b]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effect.

APPENDIX C

DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values

Key study:	Jakubowski, M., I. Linhart, G. Pielas, and J. Kopecky. 1987. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br. J. Ind. Med. 44(12):834-840. Sakurai, H., M. Onodera, T. Utsunomiya, H. Minakuchi, H. Iwai, and H. Mutsumura. 1978. Health effects of acrylonitrile in acrylic fibre factories. Br. J. Ind. Med. 35(3):219-225.
Critical effect:	Absence of effects in volunteer subjects exposed for 8 h to acrylonitrile at 4.6 ppm (Jakubowski et al. 1987), supported by observations of mild effects (initial conjunctival irritation, for which there was some accommodation) in workers routinely exposed to acrylonitrile at approximately 5 ppm (Sakurai et al. 1978). That concentration is approximately 3-fold lower than concentrations reported by Wilson et al. (1948) to be associated with more severe effects in occupational settings (16-100 ppm for 20-45 min: headache, nasal and ocular irritation, discomfort of the chest, nervousness, and irritability).
Time scaling:	None applied. No data are available on the relationship between exposure duration and severity of responses to acrylonitrile. Typically, in the absence of this information, AEGL-1 values based on an 8-h point-of-departure would be time scaled. However, in this case, the effect is ocular irritation, which would not be expected to have a response threshold that varies with exposure duration. Therefore, it is prudent to not time scale and the AEGL-1 values were held constant at 1.5 ppm for the 10-min and 30-min values. That concentration exceeds AEGL-2 values for longer exposure durations; therefore, AEGL-1 values for the 1-h, 4-h, and 8-h durations are not recommended.
Uncertainty factors:	Total uncertainty factor: 3 Interspecies: 1, human subjects. Intraspecies: 3, pharmacokinetic variability is not likely to be significant for mild effects (ocular irritation) of low-level exposure. However, the point-of-departure is

based on studies of healthy adults and, in the occupational studies, subjects who experienced repeated exposures to acrylonitrile, which may have resulted in some accommodation to the ocular irritation.

Modifying factor: None

Calculations:

10-min AEGL-1: 6 ppm ÷ 3 = 4. 1.5 ppm

30-min AEGL-1: 6 ppm ÷ 3 = 4. 1.5 ppm

1-, 4-, and 8-h AEGL-1: Not recommended

Derivation of AEGL-2 Values

Key study: Saillenfait, A.M., P. Bonnet, J.P. Guenier, and J. De Ceaurriz. 1993a. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Critical effect: No-effect level for fetal toxicity (no decrease fetal body weight and no effects on development or reproduction end points) in pregnant rats exposed to acrylonitrile at 12 ppm for 6 h/day on gestation days 6-20.

Support: Sakurai et al. (1978) and Sakurai and Kusumoto (1972) noted that many of the symptoms (headache, fatigue, nausea, and insomnia) reported after initial occupational exposure were associated with exposures in excess of 5 ppm, and that the findings were not contradictory to those of Wilson et al. (1948), who reported that occupational exposure at 16-100 ppm for 20-45 min produced transient dull headaches, nasal and ocular irritation, discomfort in the chest, nervousness, and irritability. In monkeys, slight or modest reversible effects (transient skin flushing and elevation of respiration rats) were observed with 4-h exposures at 65 or 90 ppm (Dudley and Neal 1942). Slight transient effects (ocular and nasal irritation, redness of skin) were observed following a 2-h exposure at 305 ppm (Dudley and Neal 1942).

Time scaling: $C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986)
$(12 \text{ ppm})^{1.1} \times 360 \text{ min} = 5{,}539 \text{ ppm-min}$

Uncertainty factors:	Total uncertainty factor: 36 Interspecies: 6, a factor of 3 was applied to account for possible species differences in toxicodynamics of acrylonitrile and a factor of 2 to account for interspecies differences in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted a 2-fold difference the concentrations of acrylonitrile and its metabolite, cyanoethylene oxide (the metabolic precursor to cyanide), in blood and brain during exposures to acrylonitrile at 2 ppm. Higher cyanoethylene oxide concentrations were predicted in human blood and brain than in rats. A PBPK model developed by Takano et al. (2010) used data on in vitro metabolism of acrylonitrile in rat and human liver microsomes to estimate hepatic clearance of cyanoethylene oxide. The model predicted that repeated oral exposures at 30 mg/kg/day for 14 days would result in peak blood acrylonitrile concentrations that were approximately 2-fold higher in rats than in humans. Although the Takano et al. (2010) model was evaluated using oral exposure data, experimental data for metabolism were obtained from in vitro microsome studies. Taken together, the Sweeney et al. (2003) and Takano et al. (2010) PBPK models support application of a factor of 2 to account for differences in toxicokinetics.
Intraspecies:	6, a factor of 3 was applied to account for possible variation in toxicodynamics of acrylonitrile in the human population and a factor of 2 to account for variability in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted that human variability in toxicokinetics of acrylonitrile would result in the 95th percentile individual having acrylonitrile or cyanoethylene oxide concentrations in blood 1.8-fold higher than the average (mean) individual. This suggests that a factor of 2 would accommodate toxicokinetic variability in the human population.
Modifying factor:	None
Calculations:	
10-min AEGL-2	$C^{1.1} \times 10$ min = 5,538 ppm-min 312 ppm ÷ 36 = 8.6 ppm
30-min AEGL-2	$C^{1.1} \times 30$ min = 5,538 ppm-min 115 ppm ÷ 36 = 3.2 ppm

1-h AEGL-2	$C^{1.1} \times 60$ min = 5,538 ppm-min 61 ppm ÷ 36 = 1.7 ppm
4-h AEGL-2	$C^{1.1} \times 240$ min = 5,538 ppm-min 17.3 ppm ÷ 36 = 0.48 ppm
8-h AEGL-2	$C^{1.1} \times 480$ min = 5,538 ppm-min 9.2 ppm ÷ 36 = 0.26 ppm

Derivation of AEGL-3 Values

Key studies:	Dudley, H.C., and P.A. Neal. 1942. Toxicology of acrylonitrile (vinyl cyanide). I. Study of the acute toxicity. J. Ind. Hyg. Toxicol. 24(2):27-36. Appel, K.E., H. Peter, and H.M. Bolt. 1981a. Effect of potential antidotes on the acute toxicity of acrylonitrile. Int. Arch. Occup. Environ. Health 49(2):157-163.
Critical effect:	Estimated lethality threshold (30-min, 1-h, 2-h, 4-h, and 8-h $BMCL_{05}$ values are 1,784.0, 1,024.4, 491.3, 179.5, and 185.8 ppm, respectively) for rats exposed at various concentrations of acrylonitrile for 30 min, 1, 2, 4, or 8 h. With the exception of the 4-h value, the resulting $BMCL_{05}$ values show a consistent duration-dependent relationship; therefore, the 30-min, 1-h, and 8-h estimates were used to derive corresponding AEGL-3 values. Because the 4-h $BMCL_{05}$ was essentially equivalent to the 8-h $BMCL_{05}$, the 4-h AEGL-3 value was derived by time-scaling the 8-h $BMCL_{05}$ of 185.9 ppm.
Time scaling:	$C^n \times t = k$, where n = 1.1 (ten Berge et al. 1986); applied for derivation of 10-min and 4-h values only.
Uncertainty factors:	Total uncertainty factor: 36 Interspecies: 6, although the dog appears to be the most sensitive species, the overall database for rats is more robust thereby justifying use of the rat data. A factor of 3 was applied to account for possible species differences in toxicodynamics of acrylonitrile and a factor of 2 to account for interspecies differences in toxicokinetics. On the basis of PBPK modeling, Sweeney et al. (2003) predicted a 2-fold higher concentration of acrylonitrile and its metabolite, cyanoethylene oxide (the metabolic precursor to cyanide), in the blood and brain of humans than rats during exposures to acrylonitrile at 2 ppm. A

	PBPK model developed by Takano et al. (2010) used data on in vitro metabolism of acrylonitrile in rat and human liver microsomes to estimate hepatic clearance of cyanoethylene oxide in rats and humans. The model predicted that repeated oral exposures at 30 mg/kg/day for 14 days would result in peak blood acrylonitrile concentrations that were approximately 2-fold higher in rats than humans. Although the Takano et al. (2010) model was evaluated using oral exposure data, experimental data for metabolism were obtained from in vitro microsome studies. Taken together, the Sweeney et al. (2003) and Takano et al. (2010) PBPK models support application of a factor of 2 to account for differences in toxicokinetics.
Intraspecies:	6, a factor of 3 was applied to account for possible variation in toxicodynamics of acrylonitrile in the human population and a factor of 2 was applied to account for variability in toxicokinetics. On the basis of PBPK models, Sweeney et al. (2003) predicted that human variability in toxicokinetics of acrylonitrile would result in the 95th percentile individual having acrylonitrile or cyanoethylene oxide concentrations in blood 1.8-fold higher than the average (mean) individual. That suggests that a factor of 2 would accommodate expected toxicokinetics variability in the human population.
Calculation:	For the 30-min, 1-h, and 8-h AEGL-3 values the 1-h and 8-h rat $BMCL_{05}$ values were adjusted by the total uncertainty factor product of 36. The 10-min value was derived by time-scaling from the 30-min rat $BMCL_{05}$: $(1{,}784 \text{ ppm})^{1.1} \times 0.5 \text{ h} = 1{,}885.8 \text{ ppm-h}$ The 4-h value was derived by scaling from the 8-h rat $BMCL_{05}$ (the 8-h $BMCL_{05}$ was considered more appropriate that the 2-h value because it was derived from data for five dose groups rather than three): $(185.8 \text{ ppm})^{1.1} \times 8 \text{ h} = 2{,}506.3 \text{ ppm-h}$
10-min AEGL-3:	$C^{1.1} \times 0.1667 \text{ h} = 1{,}885.8 \text{ ppm-h}$ 4,842.4 ppm ÷ 36 = 134 ppm (rounded to 130 ppm)

30-min AEGL-3:	30-min $BMCL_{05}$ = 1,784 ppm 1,784 ppm ÷ 36 = 49.6 ppm (rounded to 50 ppm)
1-h AEGL-3:	1-h $BMCL_{05}$ = 1,024.42 ppm 1,024.42 ppm ÷ 36 = 28.46 ppm (rounded to 28 ppm)
4-h AEGL-3	$C^{1.1} \times 4$ h = 2,506.3 ppm-h 348.9 ppm ÷ 36 = 9.7 ppm
8-h AEGL-3:	8-h $BMCL_{05}$ = 185.8 ppm 185.8 ppm ÷ 36 = 5.2 ppm

APPENDIX D

TIME SCALING CALCULATIONS

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 toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule ($C \times t = k$, 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 on 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-end-point 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, 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 end point. 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.

For acrylonitrile, analysis of available data by ten Berge et al. (1986) showed that the relationship between exposure concentration and exposure duration was near linear, where n = 1.1 for the relationship $C^n \times t = k$.

APPENDIX E

ACUTE EXPOSURE GUIDELINE LEVELS FOR ACRYLONITRILE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR[a]	NR[a]	NR[a]

Reference: Jakubowski, M., I. Linhart, G. Pielas, and J. Kopecky. 1987. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br. J. Ind. Med. 44(12):834-840.
Sakurai, H., M. Onodera, T. Utsunomiya, H. Minakuchi, H. Iwai, and H. Mutsumura. 1978. Health effects of acrylonitrile in acrylic fibre factories. Br. J. Ind. Med. 35(3): 219-225.

Test species/Strain/Number: Six informed volunteer male human subjects (Jakubowski et al. 1987); occupational exposures (Sakurai et al. 1978).

Exposure route/Concentrations/Durations: Inhalation; 2.3 or 4.6 ppm for 8 h.

Effects: Absence of effects in volunteer subjects exposed for 8 h at 4.6 ppm (Jakubowski et al. 1987) supported by observations of mild effects (initial conjunctival irritation, for which there was some accommodation) in workers routinely exposed at approximately 5 ppm (Sakurai et al. 1978).

End point/Concentration/Rationale: Ocular irritation, 4.6 ppm for 8 h, is considered a level at which mild effects may occur in some healthy adults.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because study involved human subjects.
Intraspecies: 3, pharmacokinetic variability is not likely to be significant for mild effects (ocular irritation) of low-level exposure. However, the point-of-departure is based on studies of healthy adults and, in the occupational studies, subjects experienced repeated exposures to acrylonitrile, which may have resulted in some accommodation to the ocular irritation.

Modifying factor: None applied

Animal-to-human dosimetric adjustment: No adjustments

Time scaling: No data are available on the relationship between exposure duration and severity of responses to acrylonitrile. Typically, in the absence of this information, AEGL-1 values based on an 8-h point-of-departure would be scaled. However, in this case, the effect is ocular irritation, which would not be expected to have a response threshold that varies with exposure duration. Therefore, it is prudent to not time scale and the AEGL-1 values were held constant at 1.5 ppm for exposure durations of 10 and 30 min. However, 1.5 ppm exceeds the AEGL-2 values for longer exposure durations; therefore, AEGL-1 values for 1 h, 4 h and 8 h are not recommended.

Data adequacy: AEGL-1 values for acrylonitrile are developed based on results from a controlled experiment with human volunteers, and also on occupational exposure data. The data effectively define a concentration at which mild effects (ocular irritation) may occur in some healthy adults for an AEGL-specific exposure duration (8 h). Because the AEGL-1 value (1.5 ppm) exceeds AEGL-2 values for longer exposure durations, AEGL-1 values for 1 h, 4 h and 8 h are not recommended.

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
8.6 ppm (19 mg/m^3)	3.2 ppm (6.9 mg/m^3)	1.7 ppm (3.7 mg/m^3)	0.48 ppm (1.0 mg/m^3)	0.26 ppm (0.56 mg/m^3)

Reference: Saillenfait, A.M., P. Bonnet, J.P. Guenier, and J. De Ceaurriz. 1993a. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Test Species/Strain/Sex/Number: Rat; Sprague-Dawley; 20-23/group

Exposure route/Concentrations/Durations: Inhalation; 12, 25, 50, or 100 ppm for 6 h/day on gestation days 6-20.

Effects: Dose-related decrease in fetal body weight at 25-100 ppm.

End point/Concentration/Rationale: No decrease in fetal body weight or other developmental or reproductive effect in rats at 12 ppm, 6 h/day.

Uncertainty factors/Rationale:
Total uncertainty factor: 36
Interspecies: 6; 3 for toxicodynamics and 2 for toxicokinetics based on PBPK modeling (Sweeney et al. 2003; Takano et al. 2010).
Intraspecies: 6; 3 for toxicodynamics and 2 for toxicokinetics based on PBPK modeling (Sweeney et al. 2003).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 1.1 as reported by ten Berge et al. (1986)

Data adequacy: The AEGL-2 values are based on effects that are indicative of acrylonitrile exposure, but not yet demonstrating more severe toxicity (e.g., convulsions, extreme respiratory alterations) or irreversible effects.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 (11 mg/m^3)

Reference: Dudley, H.C., and P.A. Neal. 1942. Toxicology of acrylonitrile (vinyl cyanide). I. Study of the acute toxicity. J. Ind. Hyg. Toxicol. 24(2):27-36.
Appel, K.E., H. Peter, and H.M. Bolt. 1981a. Effect of potential antidotes on the acute toxicity of acrylonitrile. Int. Arch. Occup. Environ. Health 49(2):157-163.

(Continued)

AEGL-3 VALUES Continued

Test species/Strain/Sex/Number: Rats; Osborne-Mendel; sex not specified; 16/group (Dudley and Neal 1942). Rats; Wistar; male; 3-6/group (Appel et al. 1981a.)

Effects: Lethal response frequency (see Tables 1-3 and 1-5, Section 3.1.2 for details).

Exposure duration (h)	Concentration (ppm)	Mortality
0.5 (Appel et al. 1981a)	1,600	0/3
	2,600	1/3
	3,000	6/6
1 (Dudley and Neal 1942)	665	0/16
	1,270	0/16
	1,490	4/16
	2,445	13/16
2 (Dudley and Neal 1942)	305	0/16
	595	1/16
	1,260	16/16
4 (Dudley and Neal 1942)	130	0/16
	315	2/16
	635	16/16
8 (Dudley and Neal 1942)	90	0/16
	135	0/16
	210	1/16
	270	7/16
	320	15/16

End point/Concentration/Rationale: Estimated lethality threshold (30-min, 1-h, 2-h,4-h, and 8-h $BMCL_{05}$ values are 1,784.0, 1,024.4, 491.3, 179.5, and 185.8 ppm, respectively) for rats exposed at various concentrations of acrylonitrile for 30 min, 1, 2, 4, or 8 h. With the exception of the 4-h value, the resulting $BMCL_{05}$ values show a consistent duration-dependent relationship; therefore, the 30-min, 1-h, and 8-h estimates were used to derive corresponding AEGL-3 values. Because the 4-h $BMCL_{05}$ was essentially equivalent to the 8-h $BMCL_{05}$, the 4-h AEGL-3 value was derived by time-scaling the 8-h $BMCL_{05}$. The 10-min AEGL-3 value was also derived by time-scaling from the 30-min rat $BMCL_{05}$.

Uncertainty factors/Rationale:
Total uncertainty factor: 36
Interspecies: 6; 3 for toxicodynamics and 2 for toxicokinetics based on PBPK modeling (Sweeney et al. 2003; Takano et al. 2010).
Intraspecies: 6; 3 for toxicodynamics and 2 for toxicokinetics based on PBPK modeling (Sweeney et al. 2003).

Modifying factor: None applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Conducted for the 10-min and 4-h values using the equation $C^n \times t = k$, with n = 1.1.
The 4-h value was derived by scaling from the 8-h rat $BMCL_{05}$ rather than the 2-h value because it was derived from data from five dose groups rather than three.

Data adequacy: Although definitive exposure-response data for lethality in humans are not available, data are available from acute and subchronic bioassays in multiple species. The animal data are sufficient for development of scientifically justified AEGL values.

APPENDIX F

BENCHMARK-CONCENTRATION ANALYSIS FOR ACRYLONITRILE

$BMCL_{01}$ 30-minute Exposure of Rats (Appel et al. 1981a)

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\APPEL_30-MIN.(d)
Gnuplot Plotting File: C:\BMDS\APPEL_30-MIN.plt
Fri Jul 13 13:22:35 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) *
CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -30.2755
Slope = 3.91797

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background -slope have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Intercept
Intercept	1

Parameter Estimates (95.0% Wald Confidence Interval)

Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA	–	–
Intercept	-141.863	0.665192	-143.167	-140.559
Slope	18	NA	–	–

NA, indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance	Test d.f.	P-value
Full model	-1.90954	3			
Fitted model	-1.99323	1	0.167371	2	0.9197
Reduced mode	-8.15032	1	12.4816	2	0.001948

AIC: 5.98646

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
1,600.0000	0.0000	0.000	0	3	-0.000
2,600.0000	0.3729	1.119	1	3	-0.142
3,000.0000	0.9878	5.927	6	6	0.272

Chi-square = 0.09 d.f. = 2 P-value = 0.9541

Benchmark dose computation
Specified effect = 0.05
Risk type = Extra risk
Confidence level = 0.95
BMC = 2,416.07
BMCL = 1,784.1

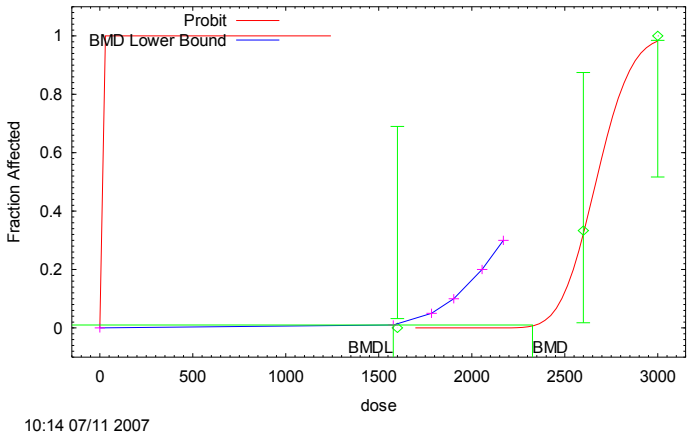


FIGURE F-1 Probit model with 0.95 confidence level.

$BMCL_{05}$ 1-h Exposure of Rats (Dudley and Neal 1942)

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Mar 01 08:34:09 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) *
CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -16.2084
Slope = 2.13067

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

Intercept	Slope	
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	-29.6647	6.43448
Slope	3.92636	0.860001

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test d.f.	P-value
Full model	-16.7186			
Fitted model	-18.0178	2.5984	2	0.2728
Reduced mode	-37.047	40.6567	3	<0.0001

AIC: 40.0356

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
665.0000	0.0000	0.000	0	16	-0.01652
1,270.0000	0.0544	0.870	0	16	-0.9591
1,490.0000	0.1644	2.630	4	16	0.9241
2,445.0000	0.8335	13.336	13	16	-0.2251

Chi-square = 1.82 d.f. = 2 P-value = 0.4015

Benchmark dose computation
Specified effect = 0.05
Risk type = extra risk
Confidence level = 0.95
BMC = 256.83
BMCL = 1,024.42

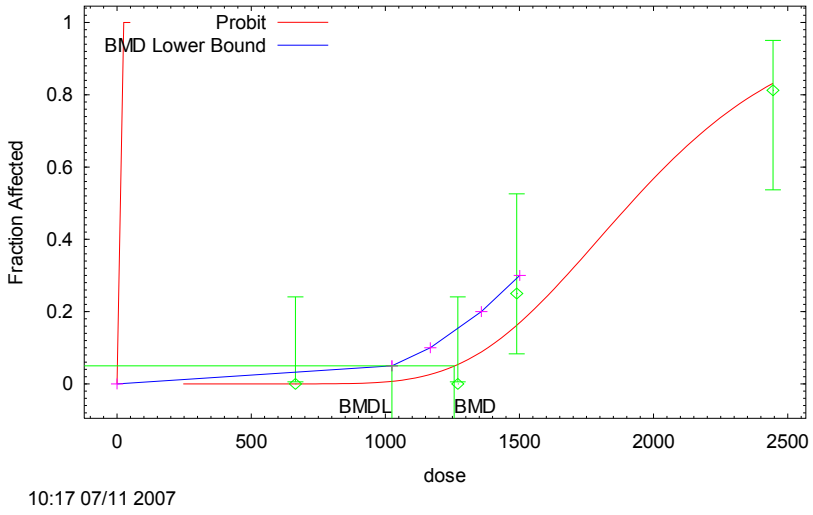


FIGURE F-2 Probit model with 0.95 confidence level.

$BMCL_{05}$ 2-h Exposure of Rats (Dudley and Neal 1942)

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Mar 01 08:39:20 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) *
CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -17.8516
Slope = 2.70268

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

Intercept	Slope	
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	64.9721	4558.92
Slope	9.92993	713.606

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test d.f.	P-value
Full model	-3.74067			
Fitted model	-3.74067	5.37593e-008	1	0.9998
Reduced mode	-31.199	54.9175	2	<.0001

AIC: 11.4813

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
305.0000	0.0000	0.000	0	16	-4.972e-008
595.0000	0.0625	1.000	1	16	-3.32e-005
1260.0000	1.0000	16.000	16	16	0.0001623

Chi-square = 0.00 d.f. = 1 P-value = 0.9999

Benchmark dose computation
Specified effect = 0.05
Risk type = extra risk
Confidence level = 0.95
BMC = 588.401
BMCL = 491.304

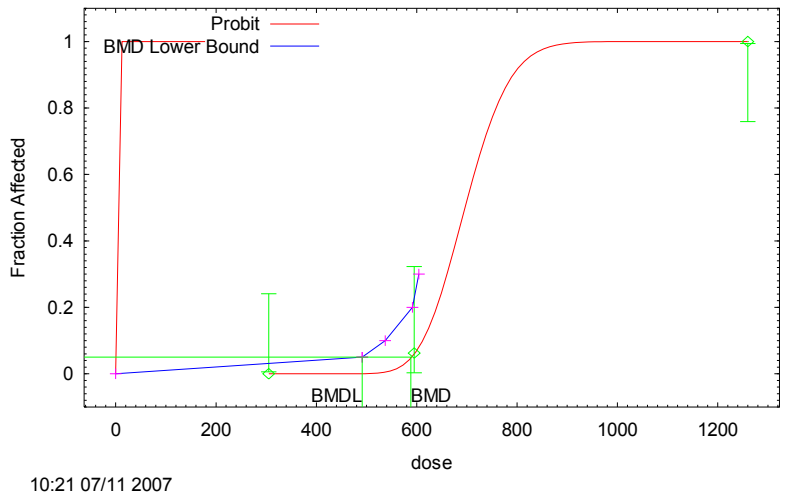


FIGURE F-3 Probit model with 0.95 confidence level.

$BMCL_{05}$ 4-h exposure of rats (Dudley and Neal 1942)

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Mar 01 08:43:13 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) *
CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -13.5273
Slope = 2.34824

Asymptotic Correlation Matrix of Parameter Estimates:
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	50.8405	3148.13
Slope	8.75291	547.256

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test d.f.	P-value
Full model	-9.93738			
Fitted model	-9.93738	2.60525e-007	1	0.9996
Reduced mode	-32.8951	45.9154	2	<0.0001

AIC: 23.8748

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
130.0000	0.0000	0.000	0	16	-3.783e-008
315.0000	0.3125	5.000	5	16	-3.304e-006
635.0000	1.0000	16.000	16	16	0.0003609

Chi-square =0.00 d.f. = 1 P-value = 0.9997

Benchmark dose computation
Specified effect = 0.05
Risk type = extra risk
Confidence level = 0.95
BMC = 276.026
BMCL = 179.532

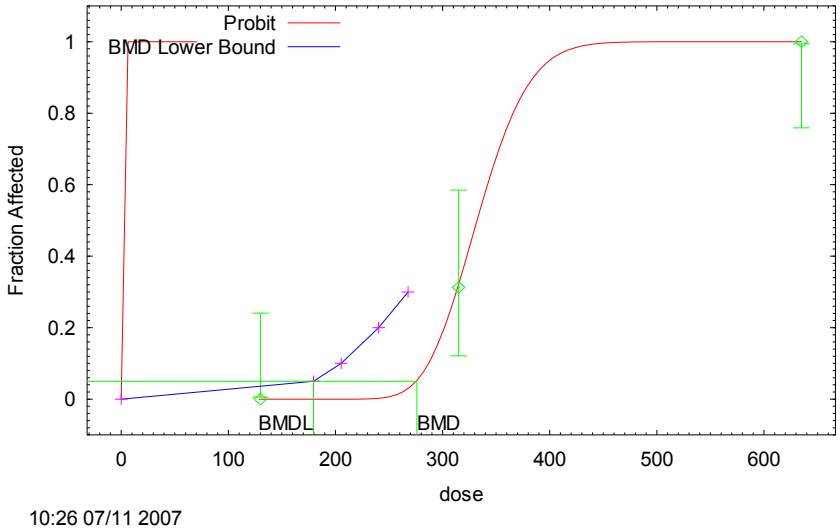


FIGURE F-4 Probit model with 0.95 confidence level.

$BMCL_{05}$ 8-h Exposure of Rats (Dudley and Neal 1942)

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Mar 01 08:46:12 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) *
CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -13
Slope = 2.37276

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	40.1969	9.34116
Slope	7.18845	1.66722

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test d.f.	P-value
Full model	-18.4464			
Fitted model	-18.9141	0.935409	3	0.8169
Reduced mode	-47.991	59.091	4	<0.0001

AIC: 41.8281

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
90.0000	0.0000	0.000	0	16	-1.822e-007
135.0000	0.0000	0.000	0	16	-0.002528
210.0000	0.0392	0.628	1	16	0.479
270.0000	0.5188	8.300	7	16	-0.6506
320.0000	0.8977	14.363	15	16	0.5257

Chi-square = 0.93 d.f. = 3 P-value = 0.8184

Benchmark dose computation
Specified effect = 0.05
Risk type = extra risk
Confidence level = 0.95
BMC = 213.376
BMCL = 185.797

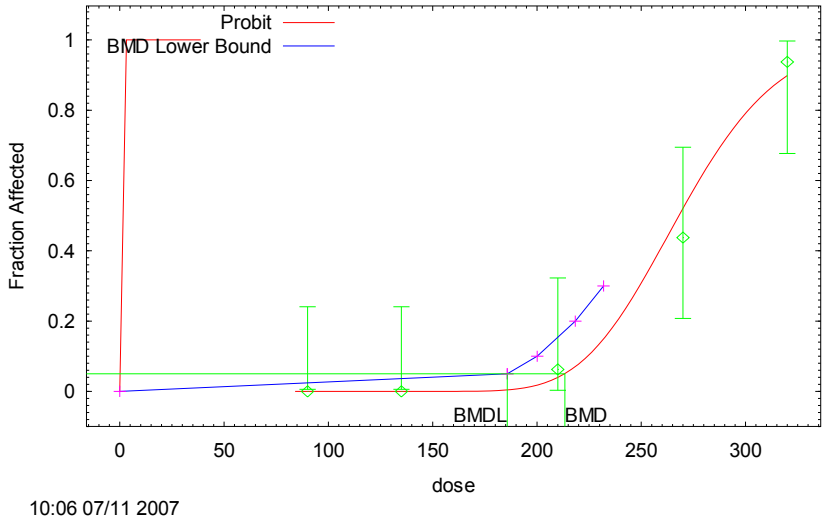


FIGURE F-5 Probit model with 0.95 confidence level.

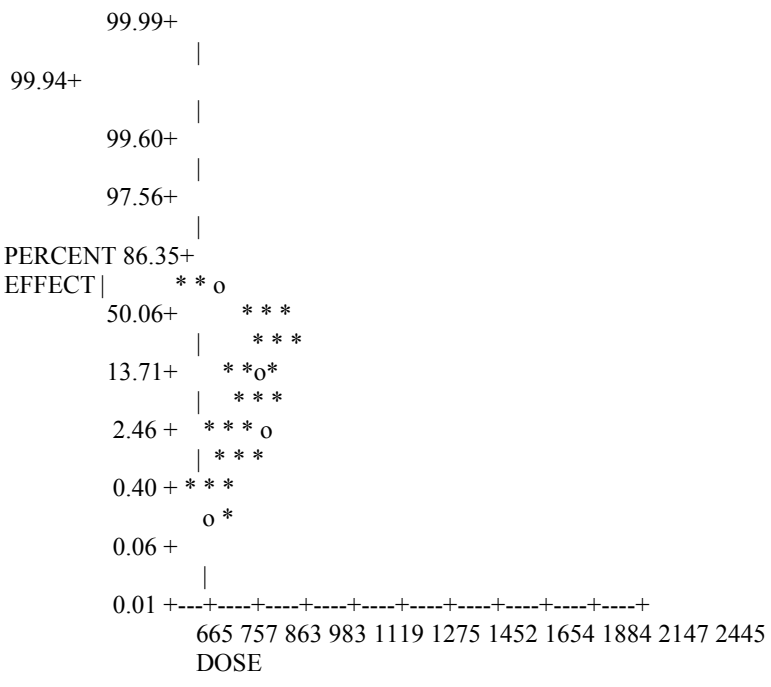
APPENDIX G

LITCHFIELD AND WILCOXON LC_{50} CALCULATION

Dudley and Neal (1942): Lethality in Rats Exposed for 1 Hour to Acrylonitrile

Dose	Mortality	Observed%	Expected%	Observed Expected	Chi-Square
665.000	0/16	0 (0.30)	0.28	0.02	0.0000
1,270.000	0/16	0 (3.80)	9.95	-6.15	0.0422
1,490.000	4/16	25.00	21.53	3.47	0.0071
2,445.000	13/16	81.25	82.13	-0.88	0.0005

Values in parentheses are corrected for 0 or 100 percent Total = 0.0499
LC_{50} = 1870.153(1621.558-2156.859)*
Slope = 1.34(1.22-1.47)*
*These values are 95% confidence limits
Total animals = 64 Total doses = 4 Animals/dose = 16.00
Chi-square = total chi-square × animals/dose = 0.7986
Table value for Chi-square with 2 Degrees of Freedom = 5.9900
LC_{84} = 2502.530 LC_{16} = 1397.574 FED = 1.15 FS = 1.10 A = 1.07



Expected Lethal Dose Values

$LC_{0.1}$ 555.726

$LC_{1.0}$ 834.159

$LC_{5.0}$ 1,114.816

LC_{10} 1,271.215

LC_{25} 1,541.871

LC_{50} 1,870.153

LC_{75} 2,268.330

LC_{90} 2,751.283

LC_{99} 4,192.812

APPENDIX H

CATEGORY PLOT FOR ACRYLONITRILE

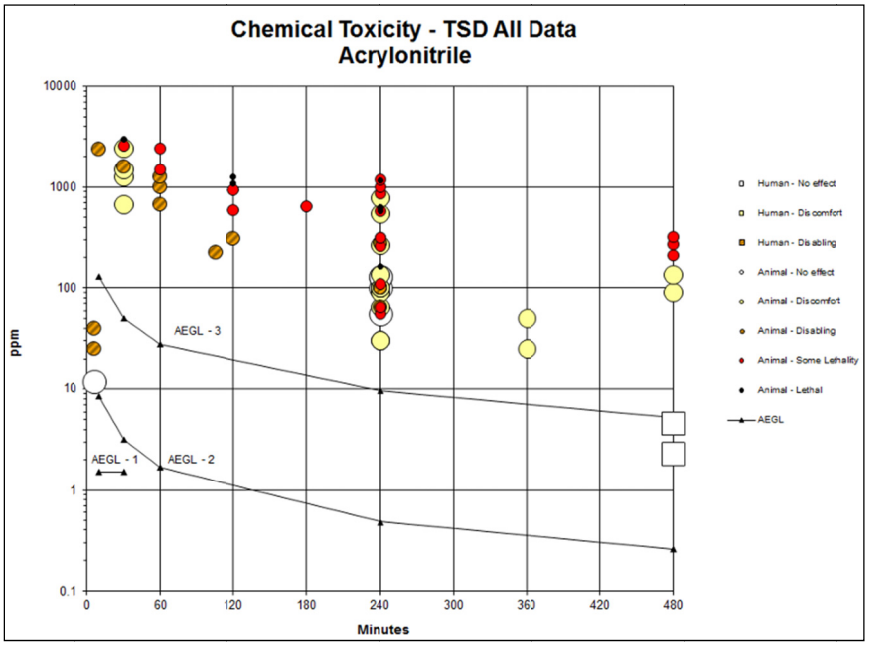


FIGURE H-1 Category plot of toxicity data and AEGL values for acrylonitrile.

TABLE H-1 Data Used in Category Plot for Acrylonitrile

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				1.5	10	AEGL	
AEGL-1				1.5	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				8.6	10	AEGL	
AEGL-2				3.2	30	AEGL	
AEGL-2				1.7	60	AEGL	
AEGL-2				0.48	240	AEGL	
AEGL-2				0.26	480	AEGL	
AEGL-3				130	10	AEGL	
AEGL-3				50	30	AEGL	
AEGL-3				28	60	AEGL	
AEGL-3				9.7	240	AEGL	
AEGL-3				5.2	480	AEGL	
Appel et al. 1981a	Rat	m	1	2400	10	2	No mortality.
Dudley and Neal 1942	Rat		1	665	30	1	Moderate transitory effects.
Dudley and Neal 1942	Rat		1	1270	30	1	Marked; no residual effects in 24 h.
Dudley and Neal 1942	Rat		1	1490	30	1	Marked; no residual effects in 24 h.
Appel et al. 1981a	Rat	m	1	1600	30	2	No mortality.
Dudley and Neal 1942	Rat		1	2445	30	1	Marked; slight residual effects to 24 h.
Appel et al. 1981a	Rat	m	1	2600	30	SL	33% mortality.

(Continued)

TABLE H-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Appel et al. 1981a	Rat	m	1	3000	30	3	100% mortality.
Dudley and Neal 1942	Rat		1	665	60	2	Marked transitory effects.
Vernon et al. 1990	Rat	b	1	1008	60	2	Rapid shallow breathing, decreased activity, nasal discharge, salivation, lacrimation, and coma (in 3 of 10 animals).
Dudley and Neal 1942	Rat		1	1270	60	2	Marked effects; slight effects at 24 h; normal at 48 h.
Dudley and Neal 1942	Rat		1	1490	60	SL	25% mortality; deaths in 4 h; slight effects at 24 h in survivors.
Dudley and Neal 1942	Rat		1	2445	60	SL	81% mortality; deaths in 4 h; slight effects at 24 h in survivors.
Dudley and Neal 1942	Rat		1	305	120	2	Slight transitory effects.
Dudley and Neal 1942	Rat		1	595	120	SL	6% mortality; marked transitory effects.
Appel et al. 1981a	Rat	m	1	950	120	SL	33% mortality.
Appel et al. 1981a	Rat	m	1	1100	120	3	100% mortality.
Dudley and Neal 1942	Rat		1	1260	120	3	100% mortality; deaths within 4 h.
Appel et al. 1981a	Rat	m	1	650	180	SL	33% mortality.
Dudley and Neal 1942	Dog	b	1	30	240	1	Slight salivation by end of exposure period; no other effects.
Dudley and Neal 1942	Dog		1	30	240	1	
Dudley and Neal 1942	Monkey		1	56	240	0	
Dudley and Neal 1942	Cat		1	56	240	SL	
Dudley and Neal 1942	Monkey		1	65	240	1	
Dudley and Neal 1942	Dog		1	65	240	2	

Dudley and Neal 1942	Dog	b	1	65	240	SL	Mortality (1/2).
Dudley and Neal 1942	Monkey		1	90	240	1	
Dudley and Neal 1942	Guinea Pig		1	100	240	0	Slight to no effect.
Dudley and Neal 1942	Cat		1	100	240	1	
Dudley and Neal 1942	Rabbit		1	100	240	1	
Dudley and Neal 1942	Rabbit		1	100	240	1	
Dudley and Neal 1942	Rat	m	1	100	240	2	Slight transitory effects.
Dudley and Neal 1942	Dog	b	1	100	240	2	
Dudley and Neal 1942	Dog		1	100	240	2	
Dudley and Neal 1942	Dog	b	1	110	240	SL	Mortality (2/3).
Dudley and Neal 1942	Rat		1	130	240	0	Slight transitory effects.
Dudley and Neal 1942	Rat		1	130	240	0	Slight transitory effects.
Dudley and Neal 1942	Rabbit		1	135	240	1	
Dudley and Neal 1942	Dog	b	1	165	240	3	Mortality (2/2).
Dudley and Neal 1942	Rabbit		1	260	240	SL	Mortality (1/2).
Dudley and Neal 1942	Guinea Pig		1	265	240	1	Slight transitory effect; reduced feed consumption for 4 d.
Dudley and Neal 1942	Cat		1	275	240	2	
Dudley and Neal 1942	Rat		1	315	240	SL	31% mortality; marked; no effects in survivors at 24 h.
Dudley and Neal 1942	Rat		1	315	240	SL	31% mortality; marked; no residual effects in survivors.
Wil Research Laboratories, 2005	Rat	b	1	539	240	1	No mortality.

(Continued)

TABLE H-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Dudley and Neal 1942	Guinea Pig		1	575	240	SL	63% mortality.
Dudley and Neal 1942	Rabbit		1	580	240	3	100% mortality.
Dudley and Neal 1942	Cat		1	600	240	3	100% mortality.
Dudley and Neal 1942	Rat		1	635	240	3	100% mortality.
Dudley and Neal 1942	Rat		1	635	240	3	100% mortality.
Wil Research Laboratories 2005	Rat	b	1	775	240	1	No mortality.
Wil Research Laboratories 2005	Rat	b	1	871	240	SL	Mortality (4/10).
Wil Research Laboratories 2005	Rat	b	1	1006	240	SL	Mortality (7/10).
Dudley and Neal 1942	Guinea Pig		1	1160	240	3	100% mortality.
Wil Research Laboratories 2005	Rat	b	1	1181	240	SL	Mortality (9/10).
Haskell Laboratory 1942	Dog		1	25	360	1	
Haskell Laboratory 1942	Dog		1	50	360	1	
Jakubowski et al. 1987	Human	m	1	2.3	480	0	
Jakubowski et al. 1987	Human			4.6	480	0	
Dudley and Neal 1942	Rat		1	90	480	1	Slight discomfort.
Dudley and Neal 1942	Rat		1	135	480	1	Moderate transitory effects.
Dudley and Neal 1942	Rat		1	210	480	SL	6% mortality; marked transitory effects.
Dudley and Neal 1942	Rat		1	270	480	SL	44% mortality; marked; no effects in survivors at 24 h.
Dudley and Neal 1942	Rat		1	320	480	SL	94% mortality.
Haskell Laboratory 1942	Dog		1	225	105	2	Ocular and nasal irritation, vomiting, incoordination, and “noisy” respiration.

Saillenfait et al. 1993a	Rat	f	15	12	6	0	Fetal toxicity (fetal body weight).
Saillenfait et al. 1993a	Rat	f	15	25	6	2	Fetal toxicity (fetal body weight).
Murray et al. 1978	Rat	f	10	40	6	2	Fetal malformations.

For Category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

2

Carbon Tetrachloride[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could

[1]This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager William Bress (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory 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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Carbon tetrachloride is a colorless, nonflammable, heavy liquid that is only slightly soluble in water. It is used as a laboratory and industrial solvent, an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and fire suppressant.

Numerous case reports were available on acute inhalation exposure of humans to carbon tetrachloride, but most lacked adequate exposure characterization. These reports, however, affirmed the hepatotoxic and renal toxicity of carbon tetrachloride, as well as a delayed response for serious and fatal effects. Additionally, data from controlled exposures of humans to carbon tetrachloride were also available.

Animal toxicity data on carbon tetrachloride indicate hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points. The most sensitive end point for evaluating the toxicity of carbon tetrachloride in animals appears to be measurement of serum-enzyme activities that reflect hepatic damage. Several studies provided lethality data for various concentrations and exposure durations, but data on nonlethal effects were few or available only from long-term exposure studies.

Studies in animals have shown the metabolism and disposition of carbon tetrachloride to be complex and varied between species. Although the precise mechanism of toxicity is equivocal, the biotransformation of carbon tetrachloride by the monooxygenase enzymes (specifically CYP2E1) to reactive intermediates is critical for expression of toxicity. That activation process is critical in modifying the toxic response to carbon tetrachloride.

Data on carbon tetrachloride were inadequate to derive AEGL-1 values, so no values are recommended.

AEGL-2 values for carbon tetrachloride were derived on the basis of the highest no-effect level of 76 ppm for central nervous system (CNS) effects in humans exposed for 4 h (Davis 1934). An interspecies uncertainty factor of 1 was used because the study was conducted in humans. An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Temporal scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where an empirical value of n was determined to be 2.5 on the basis of rat lethality data.

AEGL-3 values for carbon tetrachloride were based on a 1-h LC_{01} (lethal concentration, 1% lethality) of 5,135.5 ppm on the basis of data from multiple studies in laboratory rats (Adams et al. 1952; Dow Chemical 1960). Results of a physiologically-based pharmacokinetic (PBPK) model predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans, with greater metabolism of carbon tetrachloride by rats relative to humans (Paustenbach et al. 1988; Delic et al. 2000). PBPK models predict that at equal exposure concentrations, humans will have lower rates of production of reactive metabolites of carbon tetrachloride (human ÷ rat = 0.5). On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total interspecies uncertainty factor is 1.5 ($3 \times 0.5 = 1.5$). An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition of carbon tetrachloride). Thus, the total uncertainty factor is 15. Temporal scaling was performed in the same manner as that for the AEGL-2 values.

The US Environmental Protection Agency (EPA 2010a, b) derived an inhalation unit risk for carbon tetrachloride of 6×10^{-6} per $\mu g/m^3$, and judged that the chemical is "likely to be carcinogenic to humans" on the basis of inadequate evidence of carcinogenicity in humans and sufficient evidence in animals by oral and inhalation exposure. Hepatic tumors were found in several species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) were found in mice. Carbon tetrachloride is classified as a Group 2B carcinogen (possibly carcinogenic to humans) by the International Agency for Research on Cancer. The National Toxicology Program has classified carbon tetrachloride as

reasonably anticipated to be a human carcinogen. Extrapolation of EPA's inhalation unit risk to AEGL-specific exposure durations results in 10^{-4} cancer risk estimates at exposure concentrations that are higher than AEGL-2 values.

AEGL values for carbon tetrachloride are presented in Table 2-1.

1. INTRODUCTION

Carbon tetrachloride is a colorless, nonflammable, and heavy liquid (O'Neil et al. 2006). It has been used as a laboratory and industrial solvent, as an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and as a fire suppressant (Walsh 1989). Carbon tetrachloride has a sweet, pungent odor that is not unpleasant. An odor threshold of 21.4-238.5 ppm has been reported (Billings and Jones 1981; Ruth 1989).

The hepatotoxicity of carbon tetrachloride is well documented and has been reviewed by Rechnagel and Glende (1973). Carbon tetrachloride is also known to affect the CNS and to induce renal toxicity. The toxicity of carbon tetrachloride has been summarized by ATSDR (2005). For derivation of AEGL values, acute exposure studies are preferentially examined in this chapter. Subchronic and chronic studies generally have not been included because of the uncertainty associated with extrapolating such data to acute exposure scenarios. Studies of subchronic or chronic exposure may be addressed when the data provided relate to effects following acute exposures, meaningful insight into understanding toxicity mechanisms, or for other special considerations. The primary physical and chemical data on carbon tetrachloride are presented in Table 2-2.

TABLE 2-1 AEGL Values for Carbon Tetrachloride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (non-disabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Inadequate data.
AEGL-2 (disabling)	27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)	No-effect level for CNS effects in humans (Davi 1934).
AEGL-3 (lethal)	700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)	Estimated LC_{01} in rats (Adams et al. 1952; Dow chemical 1960).

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.
Abbreviations: CNS, central nervous system; LC_{01}, lethal concentration, 1% lethality.

TABLE 2-2 Physical and Chemical Data on Carbon Tetrachloride

Parameter	Value	Reference
Synonyms	Carbon chloride; carbona; carbon tet; freon 10; methane tetrachloride; perchloromethane; tetrachloromethane; tetrachlorocarbon; tetrafinol.	Walsh 1989; HSDB 2005
CAS registry no.	56-23-5	HSDB 2005
Chemical formula	CCl_4	HSDB 2005
Molecular weight	153.82	HSDB 2005
Physical state	Liquid	HSDB 2005
Boiling point	77°C	HSDB 2005
Melting point	-23°C	HSDB 2005
Density	1.5940 at 20°C	HSDB 2005
Solubility	1,160 mg/L at 25°C in water; miscible with alcohol, benzene, chloroform, ether, petroleum ether, oils, carbon disulfide.	HSDB 2005
Vapor pressure	115 mmHg at 25°C	HSDB 2005
Conversion factors in air	1 mg/m^3 = 0.159 ppm 1 ppm = 6.29 mg/m^3	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1 Acute Lethality

The acute toxicity and lethality of carbon tetrachloride in humans following inhalation exposure has been reviewed by Norwood et al. (1950), Umiker and Pearce (1953), and ATSDR (2005). Most human case reports lack reliable quantitative exposure data. The more relevant reports are summarized in the following sections. Most lethal cases involve renal failure and are characterized by oliguria or anuria prior to death.

Norwood et al (1950) reported on two fatalities involving exposure to carbon tetrachloride vapors. In one of the fatalities, a exposure concentration was estimated on the basis of reconstruction of the incident. The case involved a 22-year old male who was mopping a floor with carbon tetrachloride that was placed in an open bucket (approximately 1 gallon). The subject reported experiencing headache and dizziness after mopping for approximately 15 min. The investigators reported that "exposure conditions were duplicated to the best of our ability, and the measured concentration was 250 part carbon tetrachloride per million parts of air." The possibility of dermal contact with carbon tetrachloride was not discussed in the case report. The patient was admitted to a hospital with complaints of "generalized aches and pains, nausea and vomiting" and subsequently experienced renal failure and died 6 days after the reported exposure. Histopathologic examination conducted at autopsy confirmed centrilobular ne-

crosis of the liver and interstitial edema and tubular (loop of Henle and distal convoluted tubule) degeneration in the kidney. The findings in the liver were consistent with, but not diagnostic of, carbon tetrachloride toxicity. The case history indicated that the patient had a history of heavy alcohol consumption. His coworkers reported that he did not work on the day previous to the exposure and did not "feel well" when he reported to work. Prior history of similar exposures to carbon tetrachloride was not reported (in this case, carbon tetrachloride was used during a night shift without the knowledge or sanction from the supervisor). Two coworkers who continued cleaning the floor for 4 h reported only mild headaches and dizziness, which subsided after the work was completed. Those symptoms are consistent with clinical studies in which exposures to carbon tetrachloride at approximately 300-2,400 ppm for periods of 3-30 min resulted in headache, nausea and dizziness, but no deaths (Davis 1934). Collectively, these observations suggest that the case may represent an example of ethanol potentiation of carbon tetrachloride toxicity; although other factors noted above may also have contributed to the severe effects observed in this case (see Section 4 for further discussion of mechanism of toxicity and interactions with ethanol).

Another fatality also reported by Norwood et al. (1950) involved an ethanol intoxicated woman with a respiratory infection who used carbon tetrachloride to clean her trailer. The patient experienced nausea and vomiting, abdominal tenderness, and anuria, and died 12 h after admission to the hospital. Histopathologic examinations revealed fatty degeneration and centrilobular necrosis of the liver and tubular degeneration of the kidneys. Exposure concentrations and duration were not reported.

2.2 Nonlethal Toxicity

2.2.1 Acute Exposure Case Reports

Although many case reports are available regarding acute exposures to carbon tetrachloride, most are deficient in exposure details. Most of the reports do, however, describe a similar clinical picture of carbon tetrachloride poisoning that includes initial dizziness and nausea, abdominal discomfort, oliguria, anuria, and subsequent renal failure and death (Ashe and Sailer 1942; Gray 1947; Jennings 1955; Guild et al. 1958; New et al. 1962; Ruprah et al. 1985; Manno et al. 1996). The increased potential for carbon tetrachloride-induced toxicity (both renal and hepatic) associated with alcohol consumption or abuse has been documented in several of the case reports.

Davis (1934) reported the results of several experiments in which human subjects were exposed to carbon tetrachloride. The carbon tetrachloride concentrations were determined on the basis of the room volume and the amount of carbon tetrachloride necessary to achieve the desired concentration; there was no mention of air-flow rate or ventilation in the test room. In one experiment four individuals (ages 20, 28, 28, and 30 years; gender not specified) were exposed to

carbon tetrachloride at158 ppm for 30 min. One subject experienced nervousness and slight nausea but the remaining three were asymptomatic. There were no physiologically significant alterations in blood pressure, heart rate, respiratory rate, blood counts, or hemoglobin content. Urinalyses at 24 h postexposure revealed no signs of toxicity.

In the second experiment, four subjects (ages 35, 48, 22, and 30; gender not specified) were exposed to a carbon tetrachloride at 76 ppm for 2.5 h. There were no symptoms or signs of toxicity in any of the subjects. In the third experiment, the same subjects used in the previous experiment were exposed 24 h later to carbon tetrachloride at 76 ppm for 4 h and did not have signs or symptoms. Urinalyses at 72 h postexposure were normal. In the fourth experiment, three additional subjects (ages 20, 45, and 36; gender not specified) were exposed at 317 ppm for 30 min. Although clinical tests (blood pressure, hemoglobin, blood count, pulse, and urinalysis) were normal, one subject experienced nausea, another nausea and vomiting, and the third complained of headache. In fifth experiment, four subjects (ages 19, 21, 28, and 40; gender not specified) were exposed for 15 min to carbon tetrachloride at 1,191 ppm. Two of the subjects (one of which could only tolerate a 9-min exposure) experienced headache, nausea, and vomiting, another experienced nausea and vomiting, and another reported nausea and headache. Pulse rate and blood pressure appeared somewhat elevated, but no baseline data were provided for comparison. Urinalyses at 48-h postexposure were negative except for slightly increased acidity and phosphates. In the six experiment, three subjects (ages 40, 26, and 19; gender not specified) were exposed to carbon tetrachloride at 2,382 ppm for 5, 3, and 7 min, respectively. The first subject became dizzy, nauseated, sleepy, and experienced a throbbing headache. The second subject became nervous, nauseated, and listless, and the third subject experienced nausea, vomiting, dizziness, and became sleepy. Clinical examination 2 weeks after exposure revealed no adverse effects.

In a less controlled experiment, Davis (1934) measured the carbon tetrachloride concentration near the faces of men asked to use the solvent in an enclosed room. Using an alcohol potassium hydroxide and combustion method, the carbon tetrachloride concentration was found to be 0.23 % (≈2,300 ppm). None of the three subjects could work for more than 10 min without becoming nauseated and sleepy. One of the three experienced vomiting, dizziness, and a throbbing headache.

Davis (1934) also provided anecdotal data regarding compromised renal function in a worker experimentally exposed to carbon tetrachloride during an 8-h work day. The concentration was estimated at 0.02% (200 ppm). Renal function was recovered 2 months after the exposure.

Smyth et al. (1936) conducted surveys in various occupational settings (e.g., dry cleaning, distillation processes) and found average concentrations of carbon tetrachloride ranging from 10-650 ppm, with peak concentrations of up to 7,860 ppm. On the basis of average working time, 8-h TWA values of 5-117 ppm were calculated for these subchronic exposure settings. The effects associated with these exposures were minimal (evidence of restricted visual field and

elevated bilirubin) but indicative of carbon tetrachloride exposure. Actual daily exposures concentrations were unknown.

Elkins (1942) summarized the findings of case reports of workers in various facilities and tasks, including dry cleaning, spot cleaning, multigraphing, and coating. Reports of nausea, vomiting, and weight loss were associated with acute, albeit probably repeated, exposures to carbon tetrachloride at concentrations of 20-85 ppm. Elkins proposed that the maximum allowable concentration for carbon tetrachloride should be 25-50 ppm.

Norwood et al (1950) reported on 56 nonlethal cases of carbon tetrachloride poisoning resulting from various activities (e.g., use of a carbon tetrachloride fire extinguisher, degreasing operations). Exposures were to carbon tetrachloride vapors and possibly dermal contact with liquid carbon tetrachloride. Exposure concentrations were not reported for any of these cases. During an industrial degreasing operation in which carbon tetrachloride was used as the degreasing agent, 51 workers reported for first aid with complaints that included: nausea (21), headache (22), vomiting (15), vertigo and dizziness (12), malaise (7), gastric upset (5), rawness of throat or nasal passages (4), abdominal cramps (4), anorexia (3), nervousness (3), insomnia (2), nocturia (1), and cough (1).

Although lacking in exposure details, Stevens and Forster (1953) provided case reports with an emphasis on the neurologic signs and symptoms of carbon tetrachloride poisoning following inhalation and oral exposures. These included CNS effects (cerebellar degeneration, encephalomyelitis, cerebral hemorrhage) and peripheral neuritis.

Kazantzis and Bomford (1960) reported on the response of workers exposed to carbon tetrachloride vapors while cleaning quartz crystals used in electronic components. Although precise exposure data were not presented, the workers (14 men and four women, 16-54 years of age) were apparently exposed for about 8 h/day at concentrations of approximately 67-97 ppm. Fifteen workers complained of gastrointestinal disturbances (nausea, anorexia, vomiting, flatulence, epigastric distention, and discomfort), headaches, and depression. The effects were first noticed on Tuesday or Wednesday afternoons and increased in severity as the week progressed. The effects were first manifested during the preceding 4 months and increased in severity a few weeks before the investigation up to the point described. The cumulative exposures were apparently aggravated by closed windows during the winter months. The effects described could not necessarily be attributed to acute exposure (a single 8-h exposure) and two subjects with prior exposures presented with no signs or symptoms. The findings, however, suggest that intermittent exposures to carbon tetrachloride at less than 100 ppm over typical occupational exposure scenarios may result in notable signs of toxicity.

Groups of six male human volunteers (30-59 years of age) were subjected to carbon tetrachloride using several different exposure protocols (Stewart et al. 1961). In the first experiment, six individuals were exposed to a time-weighted-average (TWA) concentration of 49 ppm (31-87 ppm) for 70 min. During the exposure, all subjects noted a sweetish odor. There were no instances of ocular

or soft palate irritation, no nausea, and Romberg test and heel-to-toe testing remained normal. The only changes observed in clinical chemistry parameters (serum iron, serum transaminases, urinary urobilinogen, and urinalysis) were a transient reduction in serum iron in two subjects during the first 48 h after exposure, and an elevated urinary urobilinogen in one subject 7 days postexposure. The authors suggested that the depression of serum iron and elevated urine urobilinogen might have been the result of minor changes in metabolism and could be indicative of minimal liver insult. Serum enzyme activities were monitored up to 7 days postexposure and remained within normal ranges. In experiment 2, six subjects were exposed at 10.9 ppm (TWA) for 180 min. That was followed 4 weeks later by a repeat 180-min exposure (experiment 3) to carbon tetrachloride at 10 ppm. No adverse effects were reported by any of the subjects and no changes in blood pressure or timed vital capacities were detected.

Barnes and Jones (1967) reported on three cases of carbon tetrachloride poisoning; two in an industrial setting and one involving a tank truck driver delivering carbon tetrachloride. Exposure durations ranged from several minutes to approximately 3 h. Signs and symptoms were typical of carbon tetrachloride poisoning and included dizziness, nausea, delirium, abdominal discomfort, and oliguria. In the first case, a worker was cleaning sludge from a carbon tetrachloride tank without a respirator or other protective device during the 3-h duration of the work. Soon afterward, he experienced nausea, vomiting, drowsiness, and anuria. Following medical intervention, his condition improved over several weeks. Liver biopsy revealed indications consistent with carbon tetrachloride poisoning. No exposure concentration was provided. The second case involved a worker draining a carbon tetrachloride storage tank. The incident involved an exposure of only several minutes and produced a strong odor. By evening the worker experienced dizziness, nausea, and delirium, and medical intervention was required. Simulation of the procedure resulted in carbon tetrachloride concentrations of in excess of 600 ppm. The third case involved a truck driver exposed to carbon tetrachloride during loading of the tanker. Measurement of the carbon tetrachloride concentrations up to 30 ppm were made at various breathing zone vicinities around the truck at the discharge end of the trip but these were made during periods of high wind and unlikely to be representative of the actual accident. Concentrations of carbon tetrachloride detected during a 20-min period in the breathing zones of pipe fitters at the plan where the cases occurred ranged from 30 ppm to over 600 ppm. For one case, the "main exposure level" was estimated at 210 ppm. Although all three subjects recovered, the exposures resulted in notable toxicity.

2.2.2 Epidemiologic Studies

A cross-sectional study of hepatic function in workers occupationally exposed to carbon tetrachloride was conducted by Tomenson et al. (1995). Multivariate analysis of liver function variables and various other hematologic and biochemical parameters were compared in 135 exposed workers and 276 nonex-

posed controls. Exposures were categorized on the basis of mean exposures; low (≤1 ppm), medium (>1-3 ppm), and high (≥4 ppm). Four liver function variables (alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma glutamyl transferase) exhibited statistically significant differences from nonexposed controls, but no exposure-response relationship was demonstrated. The absence of an exposure-response may have been the result of imprecision in ranking worker exposures. The biologic relevance of the observed changes in serum enzyme activities was marginal and possibly of questionable clinical significance. The authors reported that there were no clinical signs concurrent with the aforementioned changes and that a 3-year follow-up study at the site with the highest exposures showed no evidence of further changes in liver function variables.

2.3 Reproductive and Developmental Toxicity

Human data on the reproductive and developmental toxicity after acute exposure to carbon tetrachloride were not available.

2.4 Genotoxicity

No information was available regarding the genotoxicity of carbon tetrachloride in humans following inhalation exposure.

2.5 Carcinogenicity

Information regarding the potential carcinogenicity of carbon tetrachloride in humans following acute inhalation exposure include two anecdotal case reports (Tracey and Sherlock 1968). In one case, a 59-year-old man (with a history of moderate alcohol usage but not to the extent of inducing cirrhosis) died of hepatocellular carcinoma 7 years after an acute exposure to carbon tetrachloride (exposure details not provided). In a second case, a 30-year-old woman died of liver cancer after 2-3 years of occupational exposure to carbon tetrachloride at concentrations sufficient to produce signs of toxicity.

EPA (2010b) states that carbon tetrachloride is "likely to be carcinogenic to humans" on the basis of inadequate evidence of carcinogenicity in humans but sufficient evidence in animals by oral and inhalation exposure. The animal evidence included hepatic tumors in three species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in mice. On the basis of the increased incidence of pheochromocytomas in male BDF1 mice (Nagano et al. 2007), EPA (2010b) derived an inhalation unit risk of 6×10^{-6} per $\mu g/m^3$. Carbon tetrachloride is classified as a Group 2B (possibly carcinogenic to humans) carcinogen by the International Agency for Research on Cancer. NTP has classified carbon tetrachloride as reasonably anticipated to be a human carcinogen.

2.6 Summary

Case reports of human fatalities resulting from acute exposure to carbon tetrachloride provide a clinical picture of dizziness, nausea, abdominal pain, oliguria, anuria, and death being attributed to renal failure and hepatotoxicity. Also well documented is the potential for greater carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage, a phenomenon that is consistent with the known dispositional potentiation of carbon tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes (Plaa 2000; ATSDR 2005; EPA 2010a). Most human case reports were lack information on exposure concentrations and durations. Controlled exposure studies by Davis (1934) and Stewart et al. (1961) showed a varied response to inhaled carbon tetrachloride among the tested subjects. Cumulative exposures to carbon tetrachloride at 30-57 ppm-h resulted in odor detection but no irritation or clinical effects in most subjects, whereas cumulative exposures at 79-2,133 ppm-h produced effects ranging from nervousness and headaches to nausea and vomiting. The variability in response to carbon tetrachloride is emphasized by the fact that an estimated exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppm-h were without effect.

Quantitative data pertaining to inhalation exposures of humans to carbon tetrachloride are presented in Table 2-3.

3. ANIMAL TOXICITY DATA

The discussion of animal toxicity studies on carbon tetrachloride focuses on acute exposure studies (durations of less than 24 h) or longer-term studies that provided response data for exposure periods that were of possible use in the derivation of AEGL values or as a basis for comparison with AEGL values.

3.1 Acute Lethality

Lethality following acute exposures to carbon tetrachloride has been documented in various laboratory species. Where available, histopathologic findings revealed hepatic injury. For some studies, data are presented that are not strictly from acute exposures, as some of the data may provide reference points with which to evaluate AEGL values.

3.1.1 Nonhuman Primates

In a repeated exposure study (8 h/day, 5 days/week for 6 weeks), one of three squirrel monkeys died after the seventh exposure to carbon tetrachloride at 82 ppm (Prendergast et al. 1967).

TABLE 2-3 Exposure-Response Data from Studies of Human Subjects Exposed to Carbon Tetrachloride

No. of Subjects	Exposure Concentration and Duration	Response	Reference
6	TWA of 49 ppm (31-87 ppm) for 70 min Ct = 57 ppm-h	Odor detection; transient decline in serum iron 20-68 h postexposure; elevated urinary urobilinogen in one subject; no clinically significant effects and no irritation.	Stewart et al. (1961)
6	TWA of 10.9 ppm (10-14.2 ppm) for 180 min; Ct = 33 ppm-h	Odor detection; no clinically significant effects; no irritation.	Stewart et al. (1961)
6	TWA of 10.1 (9-14 ppm) for 180 min; Ct = 30 ppm-h	Odor detection; no clinically significant effects; no irritation.	Stewart et al. (1961)
1	250 ppm (estimated) for 15 min; Ct = 63 ppm-h	Dizziness and nausea followed by renal failure and death 6 d postexposure (subject was heavy drinker).	Norwood et al. (1950)
2	250 ppm (estimated) for 4 h; Ct = 1,000 ppm-h	Mild headache and dizziness during exposure (nondrinkers).	Norwood et al. (1950)
4	158 ppm for 30 min; Ct = 79 ppm-h	Nervousness in one subject, no effect in three subjects.	Davis (1934)
4	76 ppm for 2.5 h; Ct = 190 ppm-h	No effects.	Davis (1934)
4	76 ppm for 4 h (same subjects as above, 24 h later); Ct = 304 ppm-h	No effects.	Davis (1934)
3	317 ppm for 30 min; Ct = 159 ppm-h	Slight nausea and vomiting, headache.	Davis (1934)
4	1,191 ppm for 15 min; Ct = 298 ppm-h	Nausea, vomiting, headache; intolerable for one subject (9-min exposure only).	Davis (1934)
3	2,382 ppm for 3-7 min; Ct = 640 ppm-h	Nausea, vomiting, dizziness, listlessness, headache, sleepiness.	Davis (1934)
3	2,382 ppm for ≤10 min; Ct ≤ 2,133 ppm-h	Nausea, vomiting, sleepiness, headache.	Davis (1934)
NS	5-117 ppm, 8-h TWA; Ct = 40-936 ppm-h	Elevated bilirubin, restricted visual field (imprecise assessments for both).	Smyth et al. (1936)

Abbreviation: NS, not specified; TWA, time-weighted average.

3.1.2 Rats

Rhe Mellon Institute (1947) conducted range-finding studies of chlorinated hydrocarbons in which groups of 12 albino rats (sex not specified) were exposed to carbon tetrachloride at 8,000 ppm for 6.5 h, 4,000 ppm for 8 h, 3,000 ppm for 8 h, or 1,000 ppm for five 8-h exposures. Mortality incidence after 14 days were 12/12, 2/12, 0/12, and 0/12, respectively.

In studies reported by Adams et al. (1952), albino rats (5-30 animals per group) were exposed to carbon tetrachloride at 3,000-19,000 ppm for various time periods (Table 2-4). Surviving animals "were observed for two to three weeks, or until it was certain that they had fully recovered from the effects of exposure as judged by appearance, behavior and recovery weight." Carbon tetrachloride produced drowsiness and stupor at concentrations of 4,600 ppm and lower, loss of equilibrium and coordination at 7,300 ppm, and loss of consciousness at 12,000 and 19,000 ppm. Animals surviving 16-24 h after exposure to potentially lethal or near-lethal concentrations exhibited marked hepatic injury (increased serum enzyme activity, increased liver weight, lipidosis, and fatty degeneration). The investigators estimated that exposures of 3,000 ppm for 6 min, 800 ppm for 30 min, and 50 ppm for 7 h would likely be without adverse effects in rats.

Dow Chemical (1960) reported the results of acute inhalation studies in rats (age, weight, and strain not specified) exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 2-5). Lethality in rats exposed at 10,000 ppm for 1, 1.5, 2.0, or 2.5 h was 0/5, 0/5, 5/10, and 5/5, respectively. In rats exposed to carbon tetrachloride at 20,000 ppm for 0.1, 0.25, or 0.5 h, lethality was 0/10, 5/10 and 8/10, respectively.

3.1.3 Mice

Svirbaly et al. (1947) exposed groups of 20 Swiss mice (20 g; gender not specified) to carbon tetrachloride vapors for 8 h. The concentrations were calculated by dividing the amount of carbon tetrachloride volatilized during the 8-h exposure by the volume of air that flowed through the chamber. The concentrations were confirmed by chemical analysis. The results are shown in Table 2-6.

Gehring (1968) reported an 11.5-h LC_{50} of 8,500 ppm for female Swiss-Webster mice. The lethality response appeared to be biphasic. The study also reported two LCt_{50} values (680 and 850 min) for the steep exposure-response curve.

The lethal response of mice (strain and gender not specified) to a 3.5 min exposure to carbon tetrachloride was provided by Merck and Co. in a report to the EPA Office of Toxic Substances (Merck 1983). Lethality incidence in groups of mice exposed at 150,000, 75,000, 37,500, 18,800, or 9,400 ppm were 6/6, 2/6, 0/5, 0/5, and 0/5, respectively. No additional details were provided.

TABLE 2-4 Lethality in Rats Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
19,000	0.1	1/10
	0.2	1/5
	0.3	3/5
	0.5	2/5
	0.6	14/15
	0.7	5/5
	0.8	4/5
	1.0	9/19
	2.2	20/20
12,000	0.25	0/20
	0.5	1/10
	1.0	3/10
	2.0	7/10
	3.0	8/10
	4.0	20/20
7,300	1.0	0/20
	1.5	0/20
	2.0	1/10
	3.0	1/10
	4.0	4/10
	6.0	6/10
	7.0	4/10
	8.0	20/20
4,600	5.0	0/20
	6.0	1/11
	8.0	2/10
3,600	8.0	4/20
	12.0	1/10
3,000	8.0	0/20
	10.0	1/30

Source: Adapted from Adams et al. 1952.

3.1.4 Guinea Pigs

In a repeated exposure study (8 h/day, 5 days/week for 6 weeks), three of 15 guinea pigs died on the after 20, 22, and 30 days of exposure to carbon tetrachloride at 82 ppm (Prendergast et al. 1967). Histopathologic findings in the

liver were consistent with carbon tetrachloride-induced hepatotoxicity. Data for time frames that would be appropriate for AEGL derivations were not provided.

3.1.5 Rabbits

A single rabbit was exposed to carbon tetrachloride at 20 mg/L (3,178.6 ppm) for 3 h/day for 3 days. The rabbit died on the fifth day; necropsy revealed pulmonary, renal, and hepatic involvement (Davis 1934).

3.1.6 Summary of Lethal Toxicity in Animals

Quantitative data regarding the lethality of carbon tetrachloride following acute inhalation exposure are available for several laboratory species (rats, mice, and guinea pigs). A smaller set of data are available on nonhuman primates and dogs.

Dow Chemical (1960) reported the results of acute inhalation studies in guinea pigs (age, weight, and strain not specified) exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 2-7). Lethality in guinea pigs exposed at 10,000 ppm for 1, 1.5, 2.0, 2.5, or 3.0 h was 0/5, 1/10, 4/5, 1/5, and 1/5, respectively. For exposure at 20,000 ppm for 0.25, 0.5, or 1.0 h, lethality was 0/5, 2/5 and 4/5, respectively.

TABLE 2-5 Lethality in Rats Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
10,000	1.0	0/5
	1.5	0/5
	2.0	5/10
	2.5	5/5
20,000	0.1	0/10
	0.25	5/10
	0.5	8/10

Source: Adapted from Dow Chemical 1960.

TABLE 2-6 Lethality in Mice Exposed to Carbon Tetrachloride for Eight Hours

Concentration (ppm)	Mortality
6,340	0/20
7,628	2/20
8,088	19/20
8,787	10/20
9,327	20/20

Source: Adapted from Svirbaly et al. 1947.

TABLE 2-7 Lethality in Guinea Pigs Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
10,000	1.0	0/5
	1.5	1/10
	2.0	4/5
	2.5	1/5
	3.0	1/5
	0.25	0/5
20,000	0.5	2/5
	1.0	4/5

Source: Adapted from Dow Chemical 1960.

3.2 Nonlethal Toxicity

3.2.1 Nonhuman Primates

A subchronic exposure study by Smyth et al. (1936) reported little harm to groups of four rhesus monkeys exposed to carbon tetrachloride at 50 or 200 ppm for 8 h/day, 5 days/week for 10.5 months. Liver damage (slight fatty degeneration) was detected but resolved 28 days following cessation of exposure. No data were provided that were specific to acute exposure times frames.

3.2.2 Dogs

In a study submitted to the EPA Office of Toxic Substances by Union Carbide (Mellon Institute 1947), a mongrel dog was exposed to carbon tetrachloride at 400 ppm for 7 h/day for 6months. The dog did not die but exhibited a significant decrease in body weight relative to unexposed controls.

3.2.3 Rats

In a subchronic inhalation exposure study, groups 21-25 albino rats were exposed to carbon tetrachloride at 50, 100, 200, or 400 ppm for 8 h/day, 5 days/week for 10.5 months. Hepatic and renal damage was observed; however, with the exception of two rats in the 400-ppm group, was not severe enough to compromise what the investigators termed as adequate function (Smyth et al. 1936). Data specific to acute exposure periods were not provided.

Adams et al. (1952) exposed groups of three or four male albino rats to carbon tetrachloride using various protocols (3-420 min) to determine the maximum exposure without overt signs of toxicity. Toxicity end points evaluated included changes in hepatic weight, alterations in total lipid content of the liver, and gross and microscopic evidence of fatty degeneration. The results are sum-

marized in Table 2-8. The no-effect responses identified in this study are based on end points characteristic of notable hepatic damage; an evaluation of more sensitive end points (e.g., serum enzyme activities) probably would have detected a toxic response at lower concentrations or shorter exposure durations.

Cornish and Block (1960) exposed male and female Sprague-Dawley rats to carbon tetrachloride at 50, 100, 250, 1,000, or 1,500 ppm for 4 h. Exposure concentrations were found to be within 10% of the calculated target concentrations. Twenty-four hours after a single 4-h exposure at 1,500 ppm, activities of serum glutamatic-oxaloacetic transaminase (SGOT) and xanthine oxidase were increased by 750% and 250%, respectively, relative to controls (Table 2-9). Males and females responded similarly at 1,500 ppm. Serum enzyme activities returned to normal 5 days after the exposure. SGOT and xanthine oxidase activities increased in males exposed at 1,000 ppm; increases 24 and 48 h after exposure were by 275% and 180% respectively. Respective increases in females were by 800% and 285%. Twenty-four hours after exposure at 250 ppm, SGOT activity in males was increased 160%; xanthine oxidase was unaffected. For females, SGOT activity was increased by 250% and xanthine oxidase by 135% compared with unexposed controls. At 50 and 100 ppm, no significant changes in enzyme activities were found.

The relationship between exposure time and exposure concentration was examined by David et al. (1981) (Table 2-9). Serum glutamic-pyruvate transaminase (SGPT) activity was used to assess the toxic response of male Wistar rats (12 per group) subjected to various exposure protocols that provided identical cumulative exposures (Ct = 300 ppm-h). The protocols included a 72-min exposure at 250 ppm, a 6-h exposure at 50 ppm, six 3-min exposures at 1,000 ppm at 1-hr intervals, and an 18-min exposure at 1,000 ppm. A control group of 12 rats were exposed to clean air. Even though the cumulative exposure was the same for all protocols, exposures at greater concentrations of short duration resulted in a greater increase in serum SGPT activity than did exposures at lower concentrations for longer durations (Table 2-8). Histologic examination of the exposed

TABLE 2-8 Nonlethal Responses of Rats Exposed to Carbon Tetrachloride

Concentration (ppm)	Exposure Duration (min)	Exposure Duration (min)
	No adverse effect[a]	Adverse effect[a]
12,000	–	3
3,000	6	9
800	30	60
400	–	60
100	–	420
50	420	–

Source: Adapted from Adams et al. 1952.

[a]Adverse effects characterized by alteration in hepatic weight, total lipid content of the liver, and gross and microscopic changes in the liver.

rats revealed mild changes (mild steatosis, mild hydropic degeneration) in the liver that were not qualitatively different between the groups. The authors concluded that the concentration of carbon tetrachloride in the blood and liver are more important than the total amount of carbon tetrachloride absorbed.

Appelman et al. (1985) conducted a series of experiments in which groups of 10 male Wistar rats were exposed 6 h/day, 5 days/week for 4 weeks to carbon tetrachloride vapor. Daily exposure regimens varied and included: 6-h exposures (63 and 80 ppm), two 3-h exposures (63 and 80 ppm, with 1.5 h between exposures), two 3-h exposures (63 and 80 ppm, at 1.5 hr intervals) with 5-min peaks equivalent to six times the base exposure. Controls were exposed to fresh air. With the exception of body weight data that were taken at weekly intervals, data were available only at the end of the 4-week period. No overt signs of toxicity were detected in the treated rats. Serum enzyme activities (SGOT, SGPT) were significantly elevated (2- to 9-fold) in all treatment groups, and microsomal protein content and some microsomal enzyme activity levels were significantly reduced following treatment. The study showed measurable evidence of reversible toxic effects following various regimens of inhalation exposure to carbon tetrachloride at 63 or 80 ppm over a 4-week period. The available data were not appropriate for AEGL-specific time frames or for extrapolation to AEGL time frames.

TABLE 2-9 Effect of Exposure Protocol on Xanthine-Oxidase, SGPT, and SGOT Activity in Rats Exposed to Carbon Tetrachloride

Exposure	Xanthine Oxidase (% of control)	SGPT or SGOT (U/L or % of controls)
50 ppm for 4 h[a]	No effect	No effect
100 ppm for 4 h[a]	No effect	No effect
250 ppm for 4 h[a]	Males: marginal Females: 135%	Males: marginal Females: 250%
1,000 ppm for 4 h[a]	Males: 180% Females: 285%	Males: 275% Females: 800%
1,500 ppm for 4 h[a]	Males: 250% Females: 250%	Males: 750% Females: 750%
Controls[b]	NA	50
250 ppm for 72 min[b]	NA	60
50 ppm for 6 h[b]	NA	50
1,000 ppm for 18 min[b]	NA	95
1,000 ppm (six 3-min exposures at 1-h intervals)[b]	NA	40

Abbreviation: NA, not applicable (not examined); SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase.
[a]Cornish and Block 1960 (SGOT monitored).
[b]David et al. 1981 (SGPT monitored).

In an extensive study to evaluate the effect of exposure regimen on the distribution and toxicity of carbon tetrachloride, Paustenbach et al. (1986b) exposed groups of four male Sprague-Dawley rats to carbon tetrachloride at 100 ppm for 8 or 11.5 h/day for 1-10 days. For toxicity determination, serum sorbitol dehydrogenase (SDH) activity was measured. Results of the 1-day exposure showed that SDH was slightly higher ($p < 0.05$) in the 11.5-h group (14.8 ± 3.7 IU/ml) relative to those in the 8-h group (7.0 ± 1.5 IU/ml). SDH activity in control rats was 8.5 ± 2.0 IU/ml. SDH activity increased only about 2.5- to 3.5-fold (21.0 ± 3.3 IU/ml for 8 h/day; 29.0 ± 6.2 IU/ml for 11.5 r/day) with exposure durations of 3 days. Histopathologic evaluation was limited to 1- and 2-week exposures and were not available for the shorter exposures.

In studies to examine the effect of route and pattern of exposure on the pharmacokinetics and acute toxicity of carbon tetrachloride, Sanzgiri et al. (1995) exposed male Sprague-Dawley rats (325-375 g) to carbon tetrachloride at 100 or 1,000 ppm for 2 h. The total internal dose (systemically absorbed dose) over the 2-h exposure was 17.5 and 179 mg/kg, respectively. Relative to unexposed controls, a 2-h exposure at 100 ppm resulted in no biologically relevant alterations in SDH or serum alanine aminotransferase (ALT) activity but did significantly reduce hepatic microsomal P450 and glucose-6-phosphatase (G6Pase) levels. Following a 2-h exposure at 1,000 ppm, both serum SDH (87.9 ± 25.7 mU/ml vs 5.2 ± 1.0 mU/ml for controls; $p \leq 0.05$) and ALT activities (53.3 ± 14.7 mU/ml vs 24.4 ± 2.2 mU/ml for controls; $p \leq 0.05$) were significantly increased, microsomal P450 activity significantly decreased (0.61 ± 0.04 vs 0.81 ± 0.02 for controls), and G6Pase activity was unchanged.

Wang et al. (1997) studied the effects of dose and route of administration on the metabolism and toxicity of carbon tetrachloride. Groups of five Wistar rats were exposed to carbon tetrachloride at 50 or 500 ppm for 6 h. Chamber concentrations were monitored every 15 min by gas chromatography with a hydrogen flame ionization detector. As determined by SGOT and SGPT activity, carbon tetrachloride at 50 ppm resulted in no hepatic damage in rats, although exposure at 500 ppm resulted in statistically significant elevations indicative of minor hepatic injury (SGOT: 29, 33, and 57 IU/L for the control, 50-ppm, and 500-ppm groups, respectively; SGPT: 20, 20, and 38 IU/L for the control, 50-ppm, and 500-ppm groups, respectively). Rats pretreated with ethanol (2 g/day) for 3 weeks exhibited substantially greater evidence of hepatic damage as measured by SGOT and SGPT activity (SGOT: 31, 62, and 1,720 IU/L for the ethanol-control, 50-ppm, and 500-ppm groups, respectively; SGPT: 18, 41, and 870 IU/L for the ethanol-control, 50-ppm, and 500-ppm groups, respectively).

3.2.4. Mice

Gehring (1968) examined nonlethal end points of anesthesia and SGPT activity. At an exposure concentration of 8,500 ppm, an ECt_{50} of about 0.16 min

was determined for SGPT activity and about 21 min for anesthesia effects. Belyaev et al. (1992) conducted experiments to assess fibroblast growth in the livers of male A/He mice following carbon tetrachloride exposure. Centrilobular necrosis encompassing one-fifth to one-third of the lobule was observed at 24 h after a single 4-h exposure at 30 mg/L (30,000 mg/m^3 or 4,770 ppm). Continued biweekly exposures ultimately resulted in fibrosis and cirrhosis. No animal deaths were reported.

3.2.5 Rabbits

One study on the nonlethal effects of inhalation exposure of rabbits to carbon tetrachloride was available (Ugazio et al. 1995). The study involved a subchronic exposure for the development of a model for cirrhosis. Male New Zealand white rabbits were exposed to carbon tetrachloride for 2 h, twice per week, at concentrations that increase from 100 ppm to 600 ppm by week 23. Although results of daily exposure were not provided, none of the 12 rabbits died. By week 4, however, there was a 300% increase in hexobarbital sleeping time, implying a decrease in hepatic microsomal enzyme activity, and laparotomy revealed initial signs of hepatic fibrosis.

3.2.6 Cats

Wong and DiStefano (1966) conducted inhalation exposure experiments on anesthetized cats. Cats of both sexes were anesthetized with sodium pentobarbital, and were exposed by a tracheal cannula to carbon tetrachloride at 10,000 ppm for 15, 30, 60, or 240 min. Controls were treated similarly but with no carbon tetrachloride exposure. The kidney weight-to-body weight ratio was significantly increased ($p < 0.05$) following the 60- and 240-min exposures, and adrenal weight-to-body weight ratios were significantly increased ($p < 0.05$) for the 30-, 60-, and 240-min exposures. Liver weight-to-body weight ratios were unaffected by the treatment. Total lipid content in the renal cortex increased after 15 min of exposure but was not further increased with longer exposures. The elevated total lipids were still evident 12-h postexposure but were lower than baseline values at 24 h. Lipid content in the adrenal glands and liver were unaffected. With the exception of lipid accumulation, there were no significant histologic findings in the kidneys, and there were no histologic changes in the adrenal glands. Central necrosis was observed in the liver 12 h after the 240-min exposure; it became more prevalent 24-h postexposure. The results of the study affirm the liver and kidneys as target organs for carbon tetrachloride toxicity but also suggest that the kidneys may be affected earlier than the liver. It is uncertain whether the effects observed would have progressed to cause death.

3.2.7 Summary of Nonlethal Toxicity in Animals

Table 2-10 summarizes the nonlethal effects in animals following inhalation exposure to carbon tetrachloride. Although data pertaining to acute exposures is the primary focus, longer-term exposures with observations at 24 h or less are included as well as longer-term exposures that may provide useful perspective in assessing the effects of inhalation exposure to carbon tetrachloride. Generally, the concentration of carbon tetrachloride appears to be the driver for severity of effects. The liver and kidneys appear to be primary targets for toxicity. Serum enzyme activity levels are routinely employed as biochemical indices of toxicity and serve as reliable indicators of hepatic damage, although a progression of injury may occur after cessation of exposure. The toxic response to carbon tetrachloride among the various species tested appears to vary.

3.3 Developmental and Reproductive Toxicity

In a study by Schwetz et al. (1974), groups of pregnant Sprague-Dawley rats were exposed for 7 h/day on days 6-15 of gestation to carbon tetrachloride at nominal concentrations of 300 or 1,000 ppm (analytic concentration were 334 and 1,004 ppm, respectively). The two doses were tested in separate experiments, each with its own concurrent controls. Rats exhibited no overt signs of toxicity, but reduced food consumption (and consequent decreased body-weight gain) and signs of hepatotoxicity (increased SGPT activity, pale and mottled livers, and increased relative liver weight) were evidence of maternal toxicity in both exposure groups. Signs of maternal toxicity were resolved 6 days after exposure. Carbon tetrachloride had no effect on conception rate, number of implantations, or litter size. A summary of fetal anomalies is presented in Table 2-11. Relative to unexposed controls, the only statistically significant findings were total skeletal anomalies (300 ppm), sternebral anomalies (1,000 ppm), and subcutaneous edema (300 ppm). The investigators concluded that carbon tetrachloride was not teratogenic to the developing embryo under the conditions of the study. The authors stated that evidence of fetotoxicity (decreased crown-rump length and fetal body weight) was observed in the 300- and 1,000-ppm groups compared with the control groups. However, the experimental variability over the 3-fold dose range rendered these results inconclusive for identifying any fetal end points relevant to deriving AEGL values. For example, when compared with concurrent controls, the incidence of delayed sternebral ossification was statistically significant only at 1,000 ppm, with a substantially lower incidence in the concurrent control group; however, when the control data were combined, total skeletal abnormalities (predominantly delayed ossification) was significant only at 300 ppm. Similarly, compared with the combined controls, fetal subcutaneous edema (potentially pertinent to acute exposure scenarios) was only significant at 300 ppm; however, no significant increase in total soft-tissue

TABLE 2-10 Nonlethal Effects of Carbon Tetrachloride in Laboratory Species Following Inhalation Exposure

Species	Exposure	Effect	Reference
Rhesus monkey	200 ppm, 8 h/d, 5 d/wk for 10.5 mos	Transient hepatic injury.	Smyth et al. 1936
Dog	400 ppm, 7 h/d for 6 mos	Decreased body weight.	Mellon Institute 1947
Rat	1,500 ppm, varying exposure profiles all with Ct = 4,500 ppm-h	Hepatic vacuolation and individual cell necrosis which varied with exposure profile.	Van Stee et al. 1982
Rat	200 ppm, 8 h/d, 5 d/wk for 10.5 mos	No significant effects.	Smyth et al. 1936
Rat	50 ppm, 6 h for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	David et al. 1981
	250 ppm, 72 min for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	
	1,000 ppm, 18 min for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	
	1,000 ppm (six 3-min exposures with 1-hr intervals)	Minor increase in SGPT, minor histologic changes in the liver.	
Rat	63 ppm, 6 h/d, 5 d/wk for 4 wk	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	Appelman et al. 1985
	80 ppm 6 h/d, 5 d/wk for 4 wk	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	63 ppm (two 3-h exposures, 1.5 h intervals)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT	
	80 ppm (two 3-h exposures, 1.5 h intervals)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	63 ppm (two 3-h exposures, 1.5 h intervals, 5-min peaks of 6-fold baseline)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	80 ppm (two 3-h exposures, 1.5 h intervals, 5-min peaks of 6-fold baseline)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
Rat	100 ppm, 8 h	No significant effect on SDH.	Paustenbach et al. 1998b
	100 ppm, 11.5 h	Marginally increased SDH.	
Rat	180 ppm, 15 min	"Comatose"; increased ALT at 24 h postexposure.	Sakata et al. 1987
Rat	100 ppm, 2 h	No biologically relevant effect.	Sanzgiri et al. 1995
	1,000 ppm, 2 h	Increased ALT and SDH, decreased P-450.	

(Continued)

TABLE 2-10 Continued

Species	Exposure	Effect	Reference
Rat	50 ppm, 6 h	No effect.	Wang et al. 1997
	500 ppm, 6 hr	Minor increase in SGOT and SGOT.	
Rat	12,000 ppm, 3 min	Altered hepatic weight, total lipid content and/or gross or microscopic changes in the liver.	Adams et al. 1952
	3,000 ppm, 6 min	No effect.	
	3,000 ppm, 9 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.	
	800 ppm, 30 min	No effect.	
	800 ppm, 60 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver	
	400 ppm, 60 min	Altered liver weight, total lipid content and/or gross or microscopic changes in the liver	
	100 ppm, 420 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.	
	50 ppm, 420 min	No effect.	
Mouse	8,500 ppm, 0.16 min	ECt_{50} for SGPT activity.	Gehring 1968
	8,500 ppm, 21 min	ECt_{50} for anesthesia.	
Rabbit	100 ppm, 2 h/wk for 23 wk (increased to 600 ppm by 23 weeks)	Increased hexobarbital sleeping time; hepatic fibrosis.	Ugazio et al. 1995
Cat	10,000 ppm (via tracheal cannulation) for 15, 30, 60, or 240 min	Increased total lipids in renal cortex at 15 min; increased relative adrenal weight after 15 to 30 min; central necrosis in liver at 240 min.	Wong and DiStefano 1966

Abbreviations: ALT, alanine aminotransferase; ECt_{50}, effective concentration at which 50% of individuals exhibit a specific biologic effect; SDH, sorbitol dehydrogenase; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase.

TABLE 2-11 Effects of Carbon Tetrachloride During Gestation in Rats[a]

	Control	300 ppm	1,000 ppm
Maternal body weight, g (mean ± SD)			
Number of dams examined	43	22	23
Gestation day 6	283 ± 17	290 ± 21	275 ± 19
Gestation day 13	317 ± 18	281 ± 25[b]	253 ± 24[b]
Gestation day 21	397 ± 24	368 ± 33[b]	336 ± 57[b]
Fetal anomalies, % litters affected (number of litters)			
Number of litters examined	43	22	22
Gross anomalies	0 (0)	0 (0)	0 (0)
Skull anomalies (delayed ossification)	12 (5)	9 (2)	9 (2)
Lumbar ribs or spurs	24 (10)	41 (9)	27 (6)
Vertebral anomalies (bipartite centra)	21 (9)	27 (6)	14 (3)
Sternebral anomalies (bipartite, delayed ossification)	61 (14)	68 (15)	–
	11 (2)	–	59 (13)[c]
Subcutaneous edema	33 (14)	59 (13)[c]	50 (1)
Dilated ureters	12 (5)	14 (3)	5 (1)
Total soft tissue anomalies	51 (22)	68 (15)	59 (13)
Fetal growth			
Fetal body weight, g (mean ± SD)	5.64 ± 0.34	5.29 ± 0.34[d]	4.96 ± 0.68[d]
Fetal crown-rump length, mm (mean ± SD)	43.7 ± 1.0	42.2 ± 1.0[d]	41.8 ± 2.2[d]

[a]Carbon tetrachloride was administered by inhalation for 7 h/day on days 6-15 of gestation.
[b]Significantly different from control group ($p \leq 0.05$, by Dunnett's test).
[c]Significantly different from control group ($p < 0.05$, Fisher exact probability test)
[d]Significantly different from control group ($p < 0.05$, ANOVA and Dunnett's test).
Source: Adapted from Schwetz et al. 1974.

abnormalities was detected at either dose. Data on each set of concurrent controls and for individual litters were unavailable for further analysis. Furthermore, no gross abnormalities at either test concentration were found, and a clear dose-response relationship in skeletal and soft-tissue anomalies was lacking. Findings of lower fetal body weight and shorter crown-rump length are likely to be associated with the sustained lower maternal weight over gestation days 6-15.

3.4. Genotoxicity

Data on the genotoxicity of carbon tetrachloride are equivocal. Although DNA adducts have been identified in a variety of studies, no specific adducts were characterized (McGregor and Lang 1996). Using Chinese hamster ovary cells, carbon tetrachloride at 1,270 μg/ml was negative in sister-chromatid exchange and chromosomal-aberration tests both with and without activation (Loveday et al. 1990). Recombination effects have been reported in *Saccharomyces cerevisiae* and *Aspergillus nidulans* (reviewed in McGregor and Lang 1996). Reverse mutation tests using several strains of *Salmonella typhimurium* were negative (McGregor and Lang 1996).

Mirsalis and Butterworth (1980) reported no unscheduled DNA synthesis in hepatocytes from rats treated with carbon tetrachloride.

Studies of radiolabeled carbon tetrachloride indicated binding to DNA and rRNA in the liver of rats treated with 3-methylcholanthrene (Rocchi et al. 1973), and Sawada et al. (1989) reported that carbon tetrachloride (200 mg/kg) caused a 23-fold increase in replicative DNA synthesis at 48 h.

3.5 Carcinogenicity

Data on tumorigenic responses to carbon tetrachloride following inhalation exposure were limited. Costa et al. (1963) reported the occurrence of hepatic tumors in 30 rats (age, sex, strain not specified) after repeated inhalation exposure to carbon tetrachloride (concentration and daily exposure protocol not specified). The exposure duration was 7 months followed by a 3-9 month observation period. Ten of the rats exhibited lesions of the liver characterized histologically as adenocarcinomas, trabecular carcinomas, and anaplastic carcinomas accompanied by cirrhosis. The malignant nature of the tumors was affirmed by the invasion of hepatic veins by hepatoma cellular elements.

Liver tumors have been reported in rats and mice following subcutaneous injection (Reuber and Glover 1970) and gavage administration (Edwards 1941; Edwards and Dalton 1942; Edwards et al. 1942; Andervont 1958; Weisburger 1977). Because of the possible differences in metabolism and disposition for different routes of administration, and the resulting differences in target organ and tissue doses, the data are inappropriate for assessing carcinogenic potential from acute inhalation exposures.

In studies with rat liver microsomal preparations, Castro et al. (1997) reported that free radicals ($\cdot CCl_3$, $CCl_3O_2\cdot$, $\cdot OH$) were capable of altering the DNA bases, guanine, cytosine, and thymine. The authors contended that if these altered bases were formed and not adequately repaired before cell replication, liver DNA could be adversely affected and that such processes may be involved in carbon tetrachloride-induced carcinogenicity.

In a study by Nagano et al. (2007), groups of F344/DuCrj rats (50/sex/group) were exposed (whole-body) to carbon tetrachloride (99.8%) vapor at 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) for 6 h/day, 5 days/week for 104 weeks. The incidence of hepatocellular adenomas and carcinomas was statistically significantly increased in both sexes at 125 ppm. The study also examined the toxic responses of Crj:BDF1 mice (50/sex/group) exposed to carbon tetrachloride (99%) at 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) for 6 h/day, 5 days/week for 104 weeks. The incidences of hepatocellular adenomas and carcinomas were significantly increased in both sexes at concentrations of 25 ppm and greater. The incidence of liver adenomas in female mice (8/49 or 16%) in the 5-ppm group was statistically significantly higher than that of the concurrent control group and exceeded the historical control range (2-10%). The incidences of adrenal pheochromocytomaas were significantly increased in males at 25 ppm and in females at 125 ppm.

3.6 Summary

Animal toxicity data for inhaled carbon tetrachloride affirm hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points. The findings are consistent with those associated with human exposures, although carbon tetrachloride-induced nephrotoxicity appears to be more prevalent in humans than in laboratory species. The most sensitive end point for evaluating the hepatic toxicity of carbon tetrachloride in animals appears to be serum enzyme activities that reflect tissue damage. Results of a developmental-toxicity study were equivocal. Several studies have provided lethality data for various concentrations and exposure durations. Data on nonlethal effects are also available but are much more limited or come from studies that reported effects only after long-term exposures at low concentrations (generally less than 200 ppm).

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

Carbon tetrachloride is metabolized by the mixed function oxidases of the liver (Sipes et al. 1977) and other organs, such as the adrenal glands (Colby et al. 1994). Known metabolites include carbon dioxide, chloroform, free radicals, and possibly hexachloroethane (Recknagel 1967; Glende 1972; Paustenbach et al. 1988). Additional, unidentified metabolites are excreted in the feces and urine (McCollister et al. 1951; Paustenbach et al. 1986a).

On the basis of limited data on human subjects, Stewart et al. (1961) found that the elimination of carbon tetrachloride via expired air is inversely related to the duration of exposure.

The absorption, distribution, and excretion of [^{14}C]-carbon tetrachloride was studied in female Rhesus monkeys (McCollister et al. 1951). The monkeys breathed from bags containing [^{14}C]-carbon tetrachloride at 50 ppm and exhaled via a valve system into exhale bags; both types of bags were impermeable to air and carbon tetrachloride for the duration of the experiments. Exposure was for 139, 300, or 344 min. The average rate of absorption was 0.022 mg/kg/min, and the average absorption was 30% of the amount inhaled. Tissue analysis revealed that most of the carbon tetrachloride was in adipose tissue (tissue:blood ratio = 7.94). Radioactivity was found in the blood, exhaled carbon dioxide, urinary urea and carbonate, and feces. At least 51% of the absorbed radioactivity had been eliminated within 180 min of exposure. Test of dermal exposure to vapors of carbon tetrachloride (485 ppm for 240 min and 1,150 ppm for 270 min) revealed negligible absorption, as determined by radioactivity in the blood and expired air.

On the basis of limited data from humans, Lehmann and Schmidt-Kehl (1936) estimated pulmonary absorption to be about 60% for exposures at 50 ppm, or about twice that observed from nonhuman primates (McCollister et al. 1951).

Paustenbach et al. (1986a) reported differences in the distribution and elimination of inhaled carbon tetrachloride relative to exposure regimen. Sprague-Dawley rats were exposed to carbon tetrachloride at 100 ppm for either 8 h/day or 11.5 h/day. The daily exposure regimens were adjusted such that cumulative exposures were identical. Following the 2-week exposure using the 11.5-h/day regimen, ^{14}C-activity in expired air and feces represented 32% and 62% of the total dose, respectively. For the 8-h/day exposure regimen, ^{14}C-activity in expired air and feces represented 45% and 48% of the total dose, respectively, demonstrating that fecal excretion was greater after the 11.5-h exposure regimen. Regardless of the exposure schedule, urinary excretion and ventilatory elimination of $^{14}CO_2$ was minimal (8% and 2%, respectively). Results of the study indicated that over 60% of the inhaled dose was metabolized and that the 11.5-h/day schedule resulted in greater accumulation of carbon tetrachloride in the poorly perfused lipophilic depots, such as adipose tissue. Overall, the results suggest that relatively small changes in exposure regimens may influence the rate and route of elimination of carbon tetrachloride.

A physiologically-based pharmacokinetic (PBPK) model for inhaled carbon tetrachloride was developed by Paustenbach et al. (1988). Values for V_{max} (0.65 mg/kg/h) and K_m (0.25 mg/L) were determined on the basis of data from Sprague-Dawley rats exposed to carbon tetrachloride at 100 ppm. Metabolites were partitioned into three compartments: those excreted in the breath (CO_2 and possibly hexachloroethane), urine, and feces. Results of simulations with the model were consistent with the human data of Stewart et al. (1961) and the monkey data reported by McCollister et al. (1951).

Although McCollister et al. (1951) reported measurable amounts of radioactivity in the feces of monkeys exposed to [^{14}C]-carbon tetrachloride via inhalation and Paustenbach et al. (1986a) reported fecal excretion in rats, Page and Carlson (1994) found that fecal elimination of carbon tetrachloride (as parent compound) by Sprague-Dawley rats did not significantly contribute to overall elimination of carbon tetrachloride following single or repeated inhalation exposure. The authors contended it was more likely that the minimal fecal elimination represents a very slow elimination of a metabolite or catabolic product of a carbon tetrachloride-macromolecular adduct.

Kinetic parameters were estimated for rats exposed to carbon tetrachloride at 100 or 1,000 ppm for 2 h (Sanzgiri et al. 1995). There were no significant differences in the t_2 (162 and 166 min, respectively), or the apparent clearance (148 and 100 ml/min/kg, respectively). However, as would be expected, the area under the curve (AUC) was proportionately greater at 1,000 ppm (1,885 µg-min/ml) compared with that at 100 ppm (124 µg-min/ml), as was the C_{max} (1.0 and 12.8 µg/ml, respectively).

The effect of exposure route on the disposition of carbon tetrachloride in rats was examined by Sanzgiri et al. (1997). A comparison of uptake, distribution, and elimination of carbon tetrachloride following inhalation (1,000 ppm for 2 h) or oral exposure (179 mg/kg, single bolus or 2-h oral infusion) was conducted in male Sprague-Dawley rats. Carbon tetrachloride tissue concentrations were lower in the gastric infusion groups than in the oral bolus or inhalation exposure group. In fact, AUC data (0-24 h) indicated that liver accumulation (and accumulation in most tissues) of carbon tetrachloride was higher after inhalation (2,823 µg·min/ml) than after oral bolus (1,023 µg-min/ml) or oral infusion (149 µg-min/ml). As would be expected for a lipid-soluble chemical, the tissue-specific time courses for uptake and elimination were determined largely by the perfusion rate and lipid content of the tissue. The authors concluded that the most appropriate measure of internal dose for carbon tetrachloride-induced acute hepatotoxicity is the tissue-concentration versus time curve from 0 to 30 min.

4.2 Mechanism of Toxicity

Pulmonary, hepatic, cardiovascular, hematologic, and CNS effects have been documented in humans and laboratory animals exposed to carbon tetrachloride. However, the liver and kidneys appear to be the primary targets for carbon tetrachloride toxicity. The majority of research on mechanism of action has focused on hepatotoxic processes.

The mechanism of carbon tetrachloride hepatotoxicity has been extensively studied (e.g., reviews by Zimmerman 1978; Clawson, 1989). Because of the great volume of data available on this topic, an indepth discussion is beyond the scope of this chapter. Briefly, the metabolism of carbon tetrachloride is mediated by ethanol-inducible CYP2E1. The hepatotoxicity of carbon tetrachloride appears to be mediated by reactive metabolites. Several reactive metabolites

have been implicated in the mechanism(s) and include the trichloromethyl and chlorine free radicals (Rechnagel and Glende 1973), the trichloromethylperoxy free radical (Slater 1982), carbenes (Reiner and Uehleke 1971), and the carbon dioxide anion radical (LaCagnin et al. 1988). The trichloromethyl free radical, resulting from homolytic cleavage of the carbon-chlorine bond, is thought to react with fatty acids in the endoplasmic reticulum membranes which form secondary free radicals resulting in lipid peroxidation. The process rapidly becomes autocatalytic and results in further peroxidation thereby explaining the toxic potency of carbon tetrachloride. Rao and Recknagel (1969) showed that incorporation of ^{14}C from [^{14}C]-carbon tetrachloride into rat liver microsomal and mitochondrial lipids was rapid (about 5 min) following oral administration of carbon tetrachloride. Slater (1982) hypothesizes that the trichloromethylperoxy free radical, which is even more reactive, interacts with unsaturated membrane lipids resulting in lipid peroxidation. Ultimately, the lipid peroxidation from either of these mechanisms leads to cellular degeneration. Alternatively, the involvement of carbenes and their mediation of covalent binding of macromolecules has also been proposed, as has been involvement of the carbon dioxide anion radical. These processes ultimately result in centrilobular necrosis and fatty degeneration of the liver. Glende and Recknagel (1991) reported on the involvement of carbon tetrachloride-activated phospholipase A2 and the role of increased intracellular calcium in hepatocyte injury.

In addition to hepatotoxicity, carbon tetrachloride is also known to affect the CNS (Stevens and Forster 1953; Cohen 1957). The narcotic properties of carbon tetrachloride are well documented (ATSDR 2005) but the precise mechanism of action is unknown.

4.3 Structure-Activity Relationships

Assessment of structure-activity relationships were not instrumental is deriving AEGL values for carbon tetrachloride.

4.4 Other Relevant Information

4.4.1 Species and Individual Variability

Johnson and Simmons (1994) reported on the variable susceptibility to carbon tetrachloride-induced hepatotoxicity between Fischer-344 and Sprague-Dawley rats. Following gavage administration of carbon tetrachloride at 0.1 or 0.4 ml/kg, Sprague-Dawley rats appeared to be more resistant to carbon tetrachloride-induced hepatic necrosis than Fischer-344 rats.

It has also been reported that rats eliminate carbon tetrachloride faster than larger species (Andersen 1981), such as monkeys (McCollister et al. 1951) and humans (Stewart et al. 1961), and that rat studies may underestimate the accumulation of carbon tetrachlorie in tissues of humans.

One toxic end point that occurs consistently among species is hepatotoxicity. Mild signs of hepatotoxicity, such as elevated serum enzyme activities, have been reported in both humans and rodents. Interspecies comparisons of this end point can be made by examining the exposure associated with producing the effect in each species. The study by Stewart et al. (1961) reported minor enzymatic changes in two of six human subjects exposed at 49 ppm for 70 min. In contrast, rats exhibited mild elevations in serum enzyme activities following exposures at 250 ppm for 4 h (Cornish and Block 1960) and at 250 ppm for 70 min (David et al. 1981). Using these similar responses among species as a reference point, one can compare the relative susceptibility using exposures on a ppm-min or $ppm^{2.5}$-min basis (Table 2-12). For carbon tetrachloride, the appropriate exposure metric appears to be $ppm^{2.5}$-min. The range of human-to-rat variability is 5- to 200-fold for serum enzyme activity. That end point, however, is known to exhibit inherent variability.

As discussed earlier, the metabolism of carbon tetrachloride is mediated primarily by the mixed function oxidase, CYP2E1. Hepatotoxicity of carbon tetrachloride is mediated by reactive intermediates resulting from metabolism. Genetic polymorphisms in CYP enzymes have been proposed as a biomarker of susceptibility to environmental toxicants (Hong and Yang 1997). Substantial variation in human hepatic levels of CYP2E1 has been found, which may contribute to population variability in sensitivity to carbon tetrachloride. A 7-fold range in activity of CYP2E1 in liver samples collected from 23 subjects, and a 12-fold range in CYP2E1 protein content of liver samples from 40 liver donors has been reported (Lipscomb et al. 1997; Snawder and Lipscomb 2000). Furthermore, coexposure with CYP2E1 inducers, such as ethanol, isopropanol, and ketones, may increase susceptibility to carbon tetrachloride. In addition to genetic polymorphisms and exposure to CYP2E1 inducers, sensitive populations also include individuals with ketosis (diabetics, obese individuals, and people who are fasting). Bruckner et al. (2002) showed a circadian rhythmicity in carbon tetrachloride-induced hepatotoxicity in rats due to increased lipolysis and subsequent acetone production during overnight fasting associated with sleep cycles. Age-related variations in cytochrome-oxidase activity levels may also impact susceptibility to carbon tetrachloride. The reduction of cytochrome-oxidase activity associated with young age and older ages implies a decreased production

TABLE 2-12 Comparison of Exposures to Carbon Tetrachloride

Species	Exposure	C × t (ppm-min)	C × t ($ppm^{2.5}$-min)	Reference
Human	49 ppm, 70 min	3,430	1,176,490	Stewart et al. 1961
Rat	250 ppm, 4 h	60,000	237,170,824	Cornish and Block 1960
Rat	250 ppm, 70 min	17,500	10,249,085	David et al. 1981
Interspecies variability	–	5-17 fold	9-200 fold	

reactive intermediates and subsequent decrease in susceptibility of children and elderly individuals. Although age-related variations in cytochrome oxidsae activity imply decreased susceptibility to carbon tetrachloride toxicity, other age-related factors such as alterations in antioxidant activity are important in assessing overall susceptibility. Further, pathologic conditions such as cirrhosis and hepatitis may compromise hepatic function and reserve thereby increasing susceptibility to carbon tetrachloride. Although it is difficult to quantify the range of susceptibility, as indicated earlier in this report, human subjects have exhibited a wide range of response severity. More extensive discussion of factors affecting susceptibility to carbon tetrachloride are available in the reviews by Bruckner et al. (2008) and EPA (2010a).

Species variability in the metabolism and disposition of carbon tetrachloride has been addressed in several PBPK models and application of the models. The PBPK model of Paustenbach et al. (1988) predicted fat and venous-blood concentrations of carbon tetrachloride to be notably higher in rats than in humans at exposure concentrations of 5 ppm. Gargas et al. (1989) reported higher blood:air partition coefficients in rats than in humans. The greater respiratory rates and greater cardiac output/tissue perfusion rates in rodents in conjunction with the higher blood:air partition coefficients argues for a greater tissue dose in rodents than in humans when exposed at equivalent concentrations. Based on PBPK model predictions, Delic et al. (2000) showed that the ratio of rate and extent of metabolism in rats was greater than that in humans exposed at low concentrations (5 ppm [NOAEL] for rats and 2 ppm for humans [occupational exposure limit in the United Kingdom).

4.4.2 Concurrent Exposure Issues

The potentiation of carbon tetrachloride-induced hepatotoxicity by ethanol, aliphatic alcohols, and ketones has been well documented in animals and humans (Folland et al. 1976; reviewed by ATSDR2005; EPA 2010a; Plaa 2000; see also Section 2.2.1). Folland et al. (1976) reported on an individual who exhibited only a modest, transient increase in serum transaminase activity, but experienced renal failure following acute exposure to carbon tetrachloride. The individual was thought to have been preexposed to isopropanol, which induces CYP2E1 and thereby markedly potentiates acute carbon tetrachloride-induced cytotoxicity. Potentiation of carbon tetrachloride-induced toxicity in humans by ethanol has also been documented (Markham 1967; Manno and Rezzadore 1994; Manno et al. 1996). Although the precise mechanism of potentiation has not been elucidated for all interactions, the enhancement of metabolic processes resulting in increased production of reactive metabolites has been demonstrated. Because the toxicity of carbon tetrachloride is mediated by CYP2E1, it may be assumed that modulation of CYP2E1 expression by other chemicals (see reviews by Raucy 1995; EPA, 2010a) may alter the impact of carbon tetrachloride-initiated toxicity. In a study by Wang et al. (1997), it was shown that prior exposure of rats to ethanol (2 g/day) for 3 weeks resulted in an increase in the

hepatotoxicity (determined by serum enzyme activities) from carbon tetrachloride. The increase was 2-fold following a 6-h exposure at 50 ppm, and 20- to 30-fold after a 6-h exposure at 500 ppm.

Cornish and Adefuin (1967) reported on the effects of aliphatic alcohol pretreatment on the toxicity of carbon tetrachloride (1,000 ppm for 2 or 2.5 h) in male albino rats. Carbon tetrachloride had little effect on SGOT activity relative to unexposed controls (246 ± 20 vs 238 ± 8 units), but most of the alcohols studied resulted in notable increases in SGOT activity in combination with carbon tetrachloride relative to carbon tetrachloride alone (1,941 ± 558 vs 217 ± 17 units).

A remarkable potentiation of carbon tetrachloride-induced lethality by nontoxic concentrations of chlordecone has been documented in animal models (Mehendale 1994). Although such synergistic responses are often the result of altered metabolism, the chlordecone-potentiated carbon tetrachloride lethality appears to be the result of alterations in tissue-repair processes resulting in an amplification of the toxic insult rather than altered biotransformation (Mehendale 1990).

5. DATA ANALYSIS FOR AEGL-1

5.1 Human Data Relevant to AEGL-1

Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean concentrations of up to 4 ppm resulted in only minor alterations in serum enzyme activity. On the basis of estimated exposure concentrations and the responses of four individuals exposed under controlled conditions, Davis (1934) reported that no signs or symptoms of toxicity were observed at 158 ppm for 30 min or at 76 ppm for 2.5 or 4 h. At higher concentrations, CNS effects were observed. Six subjects exposed to a time-weighted average (TWA) concentration of 49 ppm for 70 min reported only odor detection and no irritation or symptoms of toxicity. Minor transient changes in serum iron, serum transaminases, and urinary urobilinogen were detected in two subjects exposed for 70 min (Stewart et al. 1961). In the same study, six subjects were exposed at a TWA concentration of 10.9 ppm for 180 min; no adverse effects were detected. In a report of an occupational exposure study, Smyth et al. (1936) concluded that exposure to carbon tetrachloride at 5-117 ppm (8-h TWA) resulted in minimal effects (restricted visual field and slightly elevated bilirubin), although actual daily exposures concentrations were unknown. However, Elkins (1942) noted that exposures to carbon tetrachloride at 20-85 ppm produced notable signs of toxicity (nausea, vomiting, and weight loss).

5.2 Animal Data Relevant to AEGL-1

Animal data defining no effect or minimal effects that are consistent with the derivation of AEGL-1 values are few and equivocal. Smyth et al. (1936) found no significant signs of toxicity in rats exposed to carbon tetrachloride at

200 ppm for 8 h/day, 5 days/week for 10.5 months. In contrast, Appelman et al. (1985), using a similar exposure protocol (6 h/day, 5 days/week), reported transient hepatic effects and elevated serum enzyme activities in rats exposed at 63 ppm for 4 weeks. Although Adams et al. (1952) reported no adverse effects in rats exposed at 3,000 ppm (6 min), 800 ppm (30 min), and 50 ppm (420 min), serum enzyme activities were not measured and, therefore, hepatotoxic effects may have been overlooked. Paustenbach et al. (1986b) reported no significant changes in SDH activity in rats exposed at 100 ppm for 8 h. David et al. (1981) noted minor changes in SGPT activity and minor histopathologic findings in rats exposed at 1,000 ppm for 18 min, 250 ppm for 72 min, 50 ppm for 6 h, or following six 3-min exposures (at 1-h intervals) at 1,000 ppm. Minor increases in activities of some serum enzymes were reported by Cornish and Block (1960) for rats exposed to carbon tetrachloride at 250, 1,000, or 1,500 ppm for 4 h, but not for rats exposed at 50 or 100 ppm for 4 h. Although several lethality studies (Mellon Institute 1947; Adams et al. 1952; Dow Chemical 1960) provided data showing no lethalities, those investigations did not assess other toxicity end points and, therefore, it cannot be assumed that the animals surviving the exposures were devoid of toxic effects above and beyond what would be considered for AEGL-1 assessments.

5.3 Derivation of AEGL-1 Values

Although the available data set of human studies on carbon tetrachloride was not robust, the data were considered for derivation of AEGL-1 values to eliminate the uncertainties inherent in extrapolating from animal data. Furthermore, the animal data on effects consistent with the definition of AEGL-1 are equivocal. Data reported by Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean exposures of up to 4 ppm resulted in only minor alterations in serum enzyme activity. However, the study involved long-term and repeated exposures to carbon tetrachloride, a regimen that was inappropriate for derivation of AEGL values. Reports by Davis (1934) and Stewart et al. (1961) also provided human exposure data, but they are not appropriate for derivation of AEGL-1 values. The Davis (1934) study was not used because the concentrations of carbon tetrachloride that produced no effects were also the no-effect levels for CNS effect (AEGL-2 level effects). The Stewart et al. (1961) study did not identify any irritation or clinically significant adverse effects; therefore, the study does not provide suitable data to derive AEGL-values. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1 Human Data Relevant to AEGL-2

Several reports provided data describing nonlethal effects of acute exposure of humans to carbon tetrachloride. Davis (1934) conducted experiments in

which three human subjects were exposed to carbon tetrachloride at 317 ppm (concentration calculated on the basis of room volume and amount of carbon tetrachloride) for 30 min. CNS effects, including nausea, vomiting, dizziness, and headaches, were reported by the subjects but clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure, and heart rate) remained normal for up to 48 h postexposure. Similar effects were reported by subjects exposed at 1,191 ppm for 15 min, with the exception that one of the four subjects found the exposure to be intolerable after 9 min. Exposures at 2,382 ppm for 3-7 min produced these effects in addition to dizziness and signs of anesthesia. The observed effects were apparently not long-lasting but may be considered severe enough to impair escape or normal function and, therefore, can be considered as a conservative end point for deriving AEGL-2 values. No effects were observed following exposure to carbon tetrachloride at 76 ppm for 2.5 or 4 h. Davis (1934) also reported notable renal effects in a worker experimentally exposed to carbon tetrachloride at 200 ppm for 8 h; renal function returned to near normal 2 months after exposure.

6.2 Animal Data Relevant to AEGL-2

Animal studies of carbon tetrachloride described effects indicative of hepatotoxicity following highly varied exposure regimens (Adams et al. 1952; David et al. 1981; Appleman et al. 1985; Belyaev et al. 1992). One report noted a "comatose" condition in rats following a 15-min exposure to carbon tetrachloride at 180 ppm (Sakata et al. 1987). Adams et al. (1952) characterized the severity of response of rats to various inhalation exposure protocols. Because the end points considered were responses characteristic of notable hepatic insult (change in hepatic weight, increased lipid content, and gross and microscopic changes), the adverse effects are considered to be consistent with AEGL-2 effects. Adverse effects were detected after exposures to carbon tetrachloride at 12,000 ppm for 3 min, 3,000 ppm for 9 min, 800 ppm for 60 min, and 400 ppm for 420 min. Minor changes in SGPT activity were reported by David et al. (1981) for rats exposed at 300 ppm-h under different exposure regimens; 1,000 ppm for 18 min; 250 ppm for 72 min; 50 ppm for 6 h; or after six 3-min exposures (at 1-h intervals) at 1,000 ppm. Four-week exposure of rats to carbon tetrachloride at 63 or 80 ppm for 6 h/day, 5 days/week, resulted in transient hepatic effects and 2- to 9-fold increases in serum enzyme concentrations. However, no data were provided relative to acute exposures. Mice exposed at 4,770 ppm for 4 h exhibited centrilobular necrosis in the liver (Belyaev et al. 1992). With the exception of the hepatic necrosis (Belyaev et al. 1992), the "comatose" effects reported in rats (Sakata et al. 1987), and the hepatic damage noted in rats (Adams et al. 1952), the available animal data do not suggest effects of a severity consistent with AEGL-2 effects. Furthermore, the liver is primarily affected by carbon tetrachloride in rodents, whereas hepatic injury is often relatively minor human poisoning cases, where renal damage predominates.

Schwetz et al. (1974) reported fetal toxicity (decreased fetal body weight and crown-rump length and) following exposures to carbon tetrachloride at 300 ppm (lowest concentration tested) or 1,000 ppm for 7 h/day on gestation days 6-15. Other reported effects included significant increases (relative to controls) in incidences of total skeletal anomalies (300 ppm), sternebral anomalies (1,000 ppm), and subcutaneous edema (300 ppm). Maternal toxicity (e.g., heptaotoxicity) was evident at both exposure concentrations. However, methodology issues compromised interpretation of the results. The tests of the two doses were conducted in separate experiments, each with its own concurrent controls. The experimental variability over the 3-fold dose range rendered these results inconclusive for identifying any fetal end points for deriving AEGL values. For example, when compared with concurrent controls, the incidence of delayed sternebral ossification was statistically significant only at 1,000 ppm, with a substantially lower incidence in the concurrent control group; however, when the control data were combined, total skeletal abnormalities (predominantly delayed ossification) was significant only at 300 ppm. Similarly, compared with the combined controls, fetal subcutaneous edema (potentially pertinent to acute exposure scenarios) was only significant at 300 ppm; however, no significant increase in total soft tissue abnormalities was detected at either dose. Data on each set of concurrent controls and for individual litters were unavailable for further analysis. Furthermore, no gross abnormalities at either test concentration were found, and a clear dose-response relationship in skeletal and soft-tissue anomalies was lacking. Findings of lower fetal body weight and shorter crown-rump length are likely to be associated with the sustained lower maternal weight over gestation days 6-15. Due to these uncertainties, the Schwetz et al. (1974) study is not suitable to serve as the basis for the AEGL-2 values.

6.3 Derivation of AEGL-2 Values

AEGL-2 values were derived on the basis of the highest no-effect level of 76 ppm for CNS effects in humans exposed carbon tetrachloride for 4 h (Davis 1934). An interspecies uncertainty factor of 1 was used because the study was conducted in humans. An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Temporal scaling was based on the equation $C^n \times t = k$ (ten Berge et al. (1986), where an empirical value for n of 2.5 was derived from rat lethality data. AEGL-2 values for carbon tetrachloride are presented in Table 2-13 and their derivations are presented in Appendix A.

TABLE 2-13 AEGL-2 Values for Carbon Tetrachloride

10 min	30 min	1 h	4 h	8 h
27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1 Human Data Relevant to AEGL-3

Although data on lethality in humans following acute exposures to carbon tetrachloride are available, exposure concentration and duration information are lacking. Norwood et al. (1950) provided the only quantitative exposure data regarding a human fatality in a heavy drinker following acute exposure to carbon tetrachloride. An exposure duration of 15 min was estimated in the study, but how it was estimated was not described in the report. Other uncertainties about the case included that the exposure concentration was estimated and may not have been an accurate estimate of the actual exposure of the individual; prior history of exposure to carbon tetrachloride could not be ruled out; dermal exposure to carbon tetrachloride could not be ruled out; the patient reported to work feeling unwell, so illness which may have contributed to higher vulnerability to carbon tetrachloride; and the patient was a heavy consumer of ethanol, which is known to potentiate the toxicity of carbon tetrachloride. Any or all of those factors could explain why the single fatality occurred, while two co-workers experienced minor symptoms of toxicity in association with exposures to carbon tetrachloride that were 16 times longer (4 h vs. 15 min).

Other studies have reported data that suggest that higher exposures to carbon tetrachloride are not lethal. As noted above, two co-workers of the worker that died continued mopping for 4 h and experienced mild headache and dizziness, which cleared after they stopped mopping. Davis (1934) reported that exposure of three individuals to carbon tetrachloride at 317 ppm for 30 min resulted in headache in one, nausea in two, and vomiting in one. Exposure at 1,191 ppm for up to 15 min resulted in headache, nausea, and vomiting in four adult subjects. Davis (1934) also reported that exposure to carbon tetrachloride at 2,382 ppm for up to 7 min resulted in headache, nausea, vomiting, dizziness, and "sleepiness" in three adult subjects. Given thse considerations, the Norwood et al. (1950) lethality case is considered to be an unreliable basis for deriving AEGL-3 values.

7.2 Animal Data Relevant to AEGL-3

Lethality data are available from studies of squirrel monkeys, dogs, rats, mice, and guinea pigs. The squirrel monkey and guinea pig data did not involve acute exposures, and the dog study involved only one animal. The most complete data sets are those of the Mellon Institute (1947), Adams et al. (1952), and Dow Chemical (1960) for rats exposed to carbon tetrachloride at concentrations of 1,000-20,000 ppm for durations of 0.1-10 h (these durations were not for all concentrations).

7.3 Derivation of AEGL-3 Values

Rat lethality data from the Adams et al. (1952) and Dow Chemical (1960) reports were used to derive AEGL-3 values for carbon tetrachloride. The method of Litchfield and Wilcoxon (1949) was used to obtain an estimate of a lethality threshold (LC_{01}) on the basis of 1-h lethality data. For durations other than 1 h, time scaling was performed using the equation $C^n \times t = k$, where n = 2.5. The value of the exponent n was determined empirically from rat lethality data (see Appendix B). With the exception of a 5-h exposure at 4,600 ppm (Adams et al. 1952), scaling was performed for durations of 0.5-2.2 h used in the study by Adams et al. The resulting 1-h LC_{01} of 5,153.5 ppm (see Appendix B) was used as the basis for scaling to other AEGL durations. PBPK model results predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans (Paustenbach et al. 1988). Delic et al. (2000) used PBPK model predictions to emphasize the greater metabolism of carbon tetrachloride by rats relative to humans. Overall, PBPK models affirm greater sensitivity of rodent species to carbon tetrachloride on the basis of metabolism and disposition considerations for carbon tetrachloride. PBPK models predict that at equal exposure concentrations, humans will have lower rates of production of reactive metabolites of carbon tetrachloride (human/rat = 0.5). O the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 (3 × 0.5 = 1.5). An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Due to the known variability in the metabolic disposition of carbon tetrachloride that may result in an altered toxic response, an uncertainty factor of 10 was retained for protection of susceptible individuals (see Section 4.4.1 for further discussion of variation in metabolism of carbon tetrachloride). Thus, the total uncertainty factor is 15.

Regression analysis of concentration-time relationships for rat lethality data (Mellon Institute 1947; Adams et al. 1952; Dow Chemical 1960), using the method of ten Berge et al. (1986), resulted in an n value of 2.5 (see Appendix B). That value is slightly lower than the n of 2.8 reported by ten Berge et al. (1986). The current analysis, however, used two additional data sets in addition to that of Adams et al. (1952), which was the study used by ten Berge. The AEGL-3 values for carbon tetrachloride are presented in Table 2-14, and their derivations are presented in Appendix A.

TABLE 2-14 AEGL-3 Values for Carbon Tetrachloride

10 min	30 min	1 h	4 h	8 h
700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)

8. SUMMARY OF AEGL VALUES

8.1 AEGL Values and Toxicity End Points

AEGL values for carbon tetrachloride are shown in Table 2-15. AEGL-1 values are not recommended, as available data relevant to AEGL-1 end points yield values that exceed the AEGL-2 values. AEGL-2 values are based on a no-effect level for CNS effects in humans (Davis 1934). The AEGL-3 values are based on an estimate lethality threshold in rats. Data from nonhuman primates indicate that chronic exposures to carbon tetrachloride at concentrations greater than the 8-h AEGL-3 value were not lethal.

Extrapolation of EPA's inhalation unit risk to AEGL-specific exposure durations yield 10^{-4} cancer risk estimates at exposure concentrations that are higher than AEGL-2 values (see Appendix C).

8.2 Standards and Guidelines for Carbon Tetrachloride

Exposure standards and guidelines for carbon tetrachloride have been established by several organizations (Table 2-16). The 8-h AEGL-2 of 5.8 ppm is similar to the threshold limit value–time-weighted average (TLV-TWA) concentration of the American Conference of Governmental Industrial Hygienists (ACGIH) of 5 ppm. The 10-min and 30-min AEGL-2 values of 27 ppm and 18 ppm, respectively, and are approximately 3-fold and 2-fold higher than the ACGIH short-term exposure limit (STEL) of 10 ppm. The AEGL-2 values are based on fetal toxicity in rats, whereas the TLV-TWA and STEL are based on hepatotoxicity observed in rats after repeated exposures. The STEL was based on the TLV-TWA; a PBPK model was used to adjust for duration.

8.3 Data Quality and Research Needs

The overall database on carbon tetrachloride was sufficient for developing AEGL-2 and AEGL-3 values. Although human data were considered for developing AEGL-1 values, the resulting values were higher than AEGL-2 values; therefore, AEGL-1 values are not recommended. AEGL-2 values are based on a no-effect level for CNS effects in humans. AEGL-3 values are based on animal lethality data sufficient to estimate a threshold. Metabolism and disposition data suggesting that rodents are more sensitive than humans to carbon tetrachloride was considered in the derivation of the AEGL-3 values. Metabolism data on carbon tetrachloride and the consequent ramifications of metabolism on the toxic response allowed for the identification of an important sensitive population (those with enhanced cytochrome P450 activity) and relevant adjustments to the AEGL values to account for this more sensitive group.

TABLE 2-15 AEGL Values for Carbon Tetrachloride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)
AEGL-3 (lethal)	700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)

[a]Not recommended. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

TABLE 2-16 Standards and Guidelines for Carbon Tetrachloride

Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm
AEGL-3	700 ppm	450 ppm	340 ppm	200 ppm	150 ppm
ERPG-1(AIHA)[b]	–	–	20 ppm	–	–
ERPG-2	–	–	100 ppm	–	–
ERPG-3	–	–	750 ppm	–	–
IDLH (NIOSH)[c]	–	200 ppm	–	–	–
TLV-TWA (ACGIH)[d]	–	–	–	–	5ppm
PEL-TWA (OSHA)[e]	–	–	–	–	10ppm
TLV-STEL (ACGIH)[f]	10ppm (15min)				
REL-STEL (NIOSH)[g]	–	–	2ppm	–	–
PEL-C (OSHA)[h]	25ppm	25ppm	25ppm	25ppm	25ppm
MAK (Germany)[i]	–	0.5 ppm	–	–	–

[a]NR: not recommended. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.
[b]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013).
ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.

ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[c]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[d]TLV-TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[f]TLV-STEL (threshold limit value - short term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[g]REL-STEL (recommended exposure limits - short term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.

[h]PEL-C (permissible exposure limit – ceiling, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is defined analogous to the ACGIH TLV-ceiling. Exposure to concentrations in excess of this value should not be permitted regardless of duration. For carbon tetrachloride, the acceptable maximum peak above the acceptable ceiling concentration for an 8-h shift is 200 ppm for 5 min in any 3-h period.

[i]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2000) is defined analogous to the ACGIH TLV-TWA.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. TLVs and BEIs Based on the Documentation of the Threshold Limit values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister, and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. AMA Arch. Ind. Hyg. Occup. Med. 6(1):50-66.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013 ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Andersen, M.E. 1981. Pharmacokinetics of inhaled gases and vapors. Neurobehav. Toxicol. Teratol. 3(4): 383-389.

Andervont, H.B. 1958. Induction of hepatomas in strain C3H mice with 4-o-tolyazoo-toluidine and carbon tetrachloride. J. Natl. Cancer Inst. 20(2):431-438.

Appelman, L.M., R.A. Woutersen, V.J. Feron, W.R.F. Notten, and M. Bogers. 1985. Fixed Versus Variable Levels of Exposure in Inhalation Toxicity Testing with Reference to Workplace: Studies with Acetaldehyde and Carbon Tetrachloride. Report no. V 84.382/140327. CIVO Institutes TNO, Zeist, The Netherlands. Submitted to EPA by Hoechst Celanese Corp., with cover letter dated December 3, 1991. EPA Document No. 86920000430. Microfiche No. OTS0534486.

Ashe, W.F., and S. Sailer. 1942. Fatal uremia following single exposure to carbon tetrachloride fumes. Ohio St. Med. J. 38(6):553-555.

ATSDR (Agency for Toxic Substances and Disease Registry). 2005. Toxicological Profile for Carbon Tetrachloride. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp30.pdf [accessed Mar. 25, 2014].

Barnes, R., and R.C. Jones. 1967. Carbon tetrachloride poisoning. Am. Ind. Hyg. Assoc. J. 28(6):557-560.

Belyaev, N.D., V.G. Budker, L. Deriy, I.A. Smolenskaya, and V.M. Subbotin. 1992. Liver plasma membrane - Associated fibroblast growth: Stimulatory and inhibitory activities during experimental cirrhosis. Hepatology 15(3):525-531.

Billings, C.E., and L.C. Jones. 1981. Odor thresholds in air as compared to threshold limit values. Am. Ind. Hyg. Assoc. J. 42(6):479-480.

Bruckner, J.V., R. Ramanathan, K. Lee, and S. Muralidhara. 2002. Mechanisms of circadian rhythmicity of carbon tetrachloride hepatotoxicity. J. Pharmacol. Exp. Ther. 300(1):273-281.

Bruckner, J.V., S.S. Anand, and D.A. Warren. 2008. Toxic effects of solvents and vapors. Pp. 981-1051 in Casarett and Doull's Toxicology: The Basic Science of Poisons, 7th Ed., C.D. Klaassen, ed. New York: McGraw Hill.

Castro, G.D., M.I. Díaz Gómez, and J.A. Castro. 1997. DNA bases attack by reactive metabolites produced during carbon tetrachloride biotransformation and promotion of liver microsomal lipid peroxidation. Res. Commun. Mol. Pathol. Pharmacol. 95(3):253-258.

Clawson, G.A. 1989. Mechanisms of carbon tetrachloride hepatotoxicity. Pathol. Immunopathol. Res. 8(2):104-112.

Cohen, M.M. 1957. Central nervous system in carbon tetrachloride intoxication. Neurology 7(4): 238-244.

Colby, H.D., H. Purcell, S. Kominami, S. Takemori, and D.C. Kossor. 1994. Adrenal activation of carbon tetrachloride: Role of microsomal P450 isozymes. Toxicology 94(1-3):31-40.

Cornish, H.H., and J. Adefuin. 1967. Potentiation of carbon tetrachloride toxicity by aliphatic alcohols. Arch. Environ. Health 14(3):447-449.

Cornish, H.H., and W.D. Block. 1960. A study of carbon tetrachloride. 1. The effect of carbon tetrachloride inhalation on rat serum enzymes. AMA Arch. Ind. Health 21:69-74.

Costa, A., G. Weber, O.F. Bartoloni, and G. Campana. 1963. Experimental cancerous cirrhosis from carbon tetrachloride in rats [in Italian]. Arch. De Vecchi Anat. Pathol. Med. Clin. 39:303-356.

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4(3):163-176.

David, A., E. Frantík, R. Holuša, and O. Novákova. 1981. Role of time and concentration on carbon tetrachloride toxicity in rats. Int. Arch. Occup. Environ. Health 48(1):49-60.

Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. JAMA 103(13):962-966.

Delic, J.I., P.D. Lilly, A.J. MacDonald, and G.D. Loizou. 2000. The utility of PBPK in the safety assessment of chloroform and carbon tetrachloride. Regul. Toxicol. Pharmacol. 32(2):144-155.

DFG (Deutsche Forschungsgemeinschaft). 2000. P. 36 in List of MAK and BAT Values 2000: Maximum Concentrations and Biological Tolerance Values at the Workplace. Report No. 36. Weinheim, Germany: Wiley-VCH.

Dow Chemical. 1960. Comparison of the Result of Exposure of Rats and Cavies to the Vapors of Carbon Tetrachloride and Bromochloromethane, June 11, 1960. Submitted to EPA by Dow Chemical with cover letter dated September 4, 1987. EPA Document No. 86870002363. Microfiche No. OTS0515887.

Edwards, J.E. 1941. Hepatomas in mice induced with carbon tetrachloride. J. Natl. Cancer Inst. 2(2):197-199.

Edwards, J.E., and A.J. Dalton. 1942. Induction of cirrhosis of the liver and of hepatomas in mice with carbon tetrachloride. J. Natl. Cancer Inst. 3(1):19-41.

Edwards, J.E., W.E. Heston, and A.J. Dalton. 1942. Induction of carbon tetrachloride hepatoma in strain L mice. J. Natl. Cancer Inst. 3:297-301.

Elkins, H.B. 1942. Maximal allowable concentrations. II. Carbon tetrachloride. J. Ind. Hyg. Toxicol. 24: 233-235.

EPA (U.S. Environmental Protection Agency). 2010a. Toxicological Review of Carbon Tetrachloride in Support of Summary on the Integrated Risk Information System (IRIS). EPA/635/R-08/005F. U.S. Environmental Protection Agency, Washington, DC [online]. Available: http://www.epa.gov/iris/toxreviews/0020tr.pdf [accessed Mar. 27, 2014].

EPA (U.S. Environmental Protection Agency). 2010b. Carbon tetrachloride (CASRN 56-23-5), Integrated Risk Information System, U.S. Environmental Protection Agency, Washington, DC [online]. Available: http://www.epa.gov/ncea/iris/subst/0020.htm [accessed Mar. 27, 2014].

Folland, D.S., W. Schaffner, H.E. Ginn, O.B. Crofford, and D.R. McMurray. 1976. Carbon tetrachloride toxicity potentiated by isopropyl alcohol. JAMA 236(16):1853-1856.

Gargas, M.L., R.J. Burgess, D.E. Voisard, G.H. Cason, and M.E. Andersen. 1989. Partition coefficients of low molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

Gehring, P.J. 1968. Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol. Appl. Pharmacol. 13(3):287-298.

Glende, E.A., Jr. 1972. On the mechanism of carbon tetrachloride toxicity-coincidence of loss of drug metabolizing activity with peroxidation of microsomal lipid. Biochem. Pharmacol. 21(15):2131-2138.

Glende, E.A., and R.O. Recknagel. 1991. An indirect method of demonstrating the CCl_4-dependent hepatocyte injury is linked to a rise in intracellular calcium ion concentration. Res. Commun. Chem. Pathol. Pharmacol. 73(1):41-52.

Gray, I. 1947. Carbon tetrachloride poisoning - Report of seven cases with two deaths. NY State J. Med. 47(21):2311-2315.

Guild, W.R., J.V. Young, and J.P. Merrill. 1958. Anuria due to carbon tetrachloride intoxication. Ann. Intern. Med. 48(6):1221-1227.

Hong, J., and C.S. Yang. 1997. Genetic polymorphism of cytochrome P450 as a biomarker of susceptibility to environmental toxicity. Environ. Health Perspect. 105(suppl. 4):754-762.

HSDB (Hazardous Substances Data Bank). 2005. Carbon tetrachloride. TOXNET Toxicology Data Network, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/. [accessed Jan. 13, 2013].

Jennings, R.B. 1955. Fatal fulminant acute carbon tetrachloride poisoning. AMA Arch. Pathol. 59(3):269-284.

Johnson, S.A., and J.E. Simmons. 1994. Examination of carbon tetrachloride hepatotoxicity in Fischer-344 and Sprague-Dawley rats [abstract]. Toxicologist 14:372.

Kazantzis, G., and R.R. Bomford. 1960. Dyspepsia due to inhalation of carbon tetrachloride vapor. Lancet 1(7120):360-362.

LaCagnin, L.B., H.D. Connor, R.P. Mason, and R.G. Thurman. 1988. The carbon dioxide anion radical adduct in the perfused rat liver: Relationship to halocarbon-induced toxicity. Mol. Pharmacol. 33(3):351-357.

Lehmann, K.B., and L. Schmidt-Kehl. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene [in German]. Arch. Hygiene 116:132-268.

Lipscomb, J.C., C.M. Garrett, and J.E. Snawder. 1997. Cytochrome P450-dependent metabolism of trichloroethylene: Interindividual differences in humans. Toxicol. Appl. Pharmacol. 142(2):311–318.

Litchfield, J.T., and F. Wilcoxon. 1949. Simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96(2):99-113.

Loveday, K.S., B.E. Anderson, M.A. Resnick, and E. Zeiger. 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V. Results with 46 chemicals. Environ. Mol. Mutagen. 16(4):272-303.

Manno, M., and M. Rezzadore. 1994. Critical role of ethanol abuse in carbon tetrachloride poisoning. Lancet 343(8891):232.

Manno, M., M. Rezzadore, M. Grossi, and C. Sbrana. 1996. Potentiation of occupational carbon tetrachloride toxicity by ethanol abuse. Hum. Exp. Toxicol. 15(4):294-300.

Markham, T.N. 1967. Renal failure due to carbon tetrachloride. Ann Arbor Case Reports. J. Occup. Med. 9(1):16-17.

McCollister, D.D., W.H. Beamer, G.J. Atchison, and H.C. Spencer. 1951. The absorption, distribution and elimination of radioactive carbon tetrachloride by monkeys upon exposure to low vapor concentrations. J. Pharmacol. Exp. Ther. 102(2):112-124.

McGregor, D., and M. Lang. 1996. Carbon tetrachloride: Genetic effects and other modes of action. Mutat. Res. 366(3):181-195.

Mehendale, H.M. 1990. Potentiation of halomethane hepatotoxicity by chlordecone: A hypothesis for the mechanism. Med. Hypotheses 33(4):289-299.

Mehendale, H.M. 1994. Amplified interactive toxicity of chemicals at nontoxic levels: Mechanistic considerations and implications to public health. Environ. Health Perspect. 102(suppl. 9):139-149.

Mellon Institute. 1947. Repeated Exposure of Rats and Dogs to Vapors of Eight Chlorinated Hydrocarbons. Mellon Institute of Industrial Research, University of Pittsburgh, January 13, 1947. Submitted to EPA BY Union Carbide with cover letter dated August 3, 1987. EPA Document No. 86-870001397. Microfiche No. OTS 0515559.

Merck (Merck and Co.). 1983. Acute response of Mice to Various Concentrations of Solvent Vapors, June 14, 1983. Submitted to EPA by DuPont, Wilmington, DE, February 4, 1983. EPA Document No. 878211692. Microfiche No. 205852.

Mirsalis, J.C., and B.E. Butterworth. 1980. Detection of unscheduled DNA synthesis in hepatocytes isolated from rats treated with genotoxic agents: An in vitro - in vivo assay for potential carcinogens and mutagens. Carcinogenesis 1(7):621-625.

Nagano, K., T. Sasaki, Y. Umeda, T. Nishizawa, N. Ikawa, H. Ohbayashi, H. Arito, S. Yamamoto, and S. Fukushima. 2007. Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal. Toxicol. 19(13):1089-1103.

New, P.S., G.D. Lubash, L. Scherr, and A.L. Rubin. 1962. Acute renal failure associated with carbon tetrachloride intoxication. JAMA 181:197-200.

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs): Carbon tetrachloride. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/56235.html.

Norwood, W.D., P.A. Fuque, and B.C. Scudder. 1950. Carbon tetrachloride poisoning: More regulation, more education needed. Arch. Ind. Hyg. Occup. Med. 1(1):90-100.

NRC (National Research Council), 1985. Hydrazine. Pp. 5-21 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

Page, D.A., and G.P. Carlson. 1994. The role of the intestinal tract in the elimination of carbon tetrachloride. Toxicol. Appl. Pharmacol. 124(2):268-274.

Paustenbach, D.J., G.P. Carlson, J.E. Christian, and G.S. Born. 1986a. A comparative study of the pharmacokinetics, of carbon tetrachloride in the rat following repeated inhalation exposures of 8 and 11.5 hr/day. Fundam. Appl. Toxicol. 6(3):484-497.

Paustenbach, D.J., J.E. Christian, G.P. Carlson, and G.S. Born. 1986b. The effect of an 11.5-hr/day exposure schedule on the distribution and toxicity of inhaled carbon tetrachloride in the rat. Fundam. Appl. Toxicol. 6(3):472-483.

Paustenbach, D.J., H.J. Clewell, III, M.L. Gargas, and M.E. Andersen. 1988. A physiologically based pharmacokinetic model for inhaled carbon tetrachloride. Toxicol. Appl. Pharmacol. 96(2):191-211.

Plaa, G.L. 2000. Chorinated methanes and liver injury: Highlights of the past 20 years. Annu. Rev. Pharmacol. Toxicol. 40:42-65.

Prendergast, J.A., R.A. Jones, L.J. Jenkins, Jr., and J. Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorofluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10(2):270-289.

Rao, K.S., and R.O. Recknagel. 1969. Early incorporation of carbon-labeled carbon tetrachloride into rat liver particulate lipids and proteins. Exp. Mol. Pathol. 10(2):219-228.

Raucy, J.L. 1995. Risk assessment: Toxicity from chemical exposure resulting from enhanced expression of CYP2E1. Toxicology 105(2-3): 217-223.

Recknagel, R.O. 1967. Carbon tetrachloride hepatotoxicity. Pharmacol. Rev. 19(2):145-208.

Recknagel, R.O., and E.A. Glende, Jr. 1973. Carbon tetrachloride hepatotoxicity: An example of lethal cleavage. CRC Crit. Rev. Toxicol. 2(3):263-297.

Reiner, O., and H. Uehleke. 1971. Binding of carbon tetrachloride to reduced microsomal cytochrome P-450 and to heme [in German]. Hoppe-Seylers Z. Physiol. Chem. 352(8):1048-1052.

Reuber, M.D., and E.L. Glover. 1970. Cirrhosis and carcinoma in the liver in male rats given subcutaneous carbon tetrachloride. J. Natl. Cancer. Inst. 44(2):419-427.

Rocchi, P., G. Prodi, S. Grilli, and A.M. Ferreri. 1973. In vivo and in vitro binding of carbon tetrachloride with nucleic acids and proteins in rat and mouse liver. Int. J. Cancer 11(2):419-425.

Ruprah, M., T.G. Mant, and R.J. Flanagan. 1985. Acute carbon tetrachloride poisoning in 19 patients: Implications for diagnosis and treatment. Lancet 1(8436): 1027-1029.

Ruth, H. 1989. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Sakata, T., A. Watanabe, N. Hobara, and H. Nagashima. 1987. Chronic liver injury in rats by carbon tetrachloride inhalation. Bull. Environ. Contam. Toxicol. 38(6):959-961.

Sanzgiri, U.Y., H.J. Kim, S. Muralidhara, C.E. Dallas, and J.V. Bruckner. 1995. Effect of route and pattern of exposure on the pharmacokinetics and acute hepatotoxicity of carbon tetrachloride. Fundam. Appl. Toxicol. 134(1):148-154.

Sanzgiri, U.Y., V. Srivitsan, S. Muralidhara, C.E. Dallas, and J.V. Bruckner. 1997. Uptake, distribution, and elimination of carbon tetrachloride in rat tissues following inhalation and ingestion exposures. Toxicol. Appl. Pharmacol. 143(1):120-129.

Schwetz, B.A., B.K. Leong, and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone on rats. Toxicol. Appl. Pharmacol. 28(3):452-464.

Sipes, I.G., G. Krishna, and J.R. Gillette. 1977. Bioactivation of carbon tetrachloride, chloroform and bromotrichloromethane: Role of cytochrome P-450. Life Sci. 20(9):1541-1548.

Slater, T.F. 1982. Free radicals as reactive intermediates in tissue injury. Pp. 575-589 in Biological Reactive Intermediates - II: Chemical Mechanisms and Biological Effects, R. Snyder, D.V. Parke, J.J. Kocsis, D.J. Jollow, G.G. Gibson, and C.M. Witmer, eds. New York: Plenum Press.

Smyth, H.F., H.F. Smyth, Jr., and C.P. Carpenter. 1936. The chronic toxicity of carbon tetrachloride; animal exposures and field studies. J. Ind. Hyg. Toxicol. 18:277-298.

Snawder, J.E., and J.C. Lipscomb. 2000. Interindividual variance of cytochrome P450 forms in human hepatic microsomes: Correlation of individual forms with xenobiotic metabolism and implications in risk assessment. Regul. Toxicol. Pharmacol. 32(2):200–209.

Stevens, H., and F.M. Forster. 1953. Effect of carbon tetrachloride on the nervous system. AMA Arch. Neurol. Psychiatry 70(5):635-649.

Stewart, R.D., H.H. Gay, D.S. Erley, C.L. Hake, and J.E. Petersen. 1961. Human exposure to carbon tetrachloride vapor. J. Occup. Med. 3:586-590.

Svirbaly, J.L., B. Highman, W.C. Alford, and W.F. von Oettingen. 1947. The toxicity and narcotic action of mono-chloro-mono-bromomethane with special reference to inorganic and volatile bromide in blood, urine, and brain. J. Ind. Hyg. 29(6):382-389.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Tomenson, J.A., C.E. Baron, J.J. O'Sullivan, J.C. Edwards, M.D. Stonard, R.J. Walker, and D.M. Fearnley. 1995. Hepatic function in workers occupationally exposed to carbon tetrachloride. Occup. Environ. Med. 52(8):508-514.

Tracey, J.P., and P. Sherlock. 1968. Hepatoma following carbon tetrachloride poisoning. NY State J. Med. 68(16):2202-2204.

Ugazio, G., S. Bosia, and E. Cornaglia. 1995. Experimental model of cirrhosis in rabbits exposed to carbon tetrachloride by inhalation. Res. Comm. Mol. Pathol. Pharmacol. 88(1):63-77.

Umiker, W., and J. Pearce. 1953. Nature and genesis of pulmonary alterations in carbon tetrachloride poisoning. AMA Arch. Pathol. 55(3): 203-217.

Van Stee, E.W., g.A. Boorman, M.P. Moorman, and R.A. Sloane. 1982. Time-varying concentration profile as a determinant of the inhalation toxicity of carbon tetrachloride. J. Toxicol. Environ. Health 10(4-5):785-795.

Walsh, D., ed. 1989. Carbon Tetrachloride. Pp. 38-41 in Chemical Safety Data Sheets. Vol. 1: Solvents. The Royal Society of Chemistry, The University of Nottingham, England.

Wang, P.Y., T. Kaneko, H. Tsukada, M. Nakano, and A. Sato. 1997. Dose- and route-dependent alterations in metabolism and toxicity of chemical compounds in ethanol-treated rats: Difference between highly (chloroform) and poorly (carbon tetrachloride) metabolized hepatotoxic compounds. Toxicol. Appl. Pharmacol. 142(1):13-21.

Weisburger, E.K. 1977. Carcinogenicity studies on halogenated hydrocarbons. Environ. Health Perspect. 21:7-16.

Wong, L.C.K., and V. DiStefano. 1966. Rapid accumulation of renal fat in cats after single inhalations of carbon tetrachloride. Toxicol. Appl. Pharmacol. 9(3):486-494.

Zimmerman, H.J. 1978. Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. New York: Appleton-Century Crofts.

APPENDIX A

DERIVATION OF AEGL VALUES FOR CARBON TETRACHLORIDE

Derivation of AEGL-1 Values

Data were inadequate for deriving AEGL-1 values for carbon tetrachloride. Attempts to use data from studies of human exposures to the chemical resulted in AEGL-1 values that exceeded AEGL-2 values. Thus, not values are recommended.

Derivation of AEGL-2 Values

Key study:	Davis 1934
Toxicity end point:	No-effect level for CNS effects in human volunteers, 76 ppm for 4 h
Scaling:	$C^{2.5} \times t = k$; n = 2.5 (see Appendix B for how the value for n was determined) $(76 \text{ ppm})^{2.5} \times 4 \text{ h} = 201{,}416 \text{ ppm-h}$
Uncertainty factors:	1 for interspecies differences 10 for intraspecies variability (e.g., variation in cytochrome P-450)
Modifying factors:	None
Calculations:	
10-min AEGL-2	$C^{2.5} \times 0.167 \text{ h} = 201{,}416 \text{ppm-h}$ C = 270 ppm 270 ppm ÷ 10 = 27 ppm (170 mg/m^3)
30-min AEGL-2:	$C^{2.5} \times 0.5 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 175 ppm 175 ppm ÷ 10 = 18 ppm (110 mg/m^3)
1-h AEGL-2:	$C^{2.5} \times 1 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 132 ppm 132 ppm ÷ 10 = 13 ppm (82 mg/m^3)
4-h AEGL-2:	$C^{2.5} \times 4.0 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 76 ppm 76 ppm ÷ 10 = 7,6 ppm (48 mg/m^3)
8-h AEGL-2:	$C^{2.5} \times 8.0 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 58 ppm 58 ppm ÷ 10 = 5.8 ppm (36 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Adams et al. 1952; Dow Chemical 1960
Toxicity end point:	Lethality in rats; estimated 1-h LC_{01} of 5,153.5 ppm (see Appendix B)
Time scaling:	$C^{2.5} \times t = k$ (ten Berge et al.1986) $(5{,}153.5 \text{ ppm})^{2.5} \times 1 \text{ h} = 1{,}906{,}582{,}933 \text{ ppm-h}$
Uncertainty factors:	1.5 for interspecies variability; results of PBPK models clearly indicate that the kinetics of carbon tetrachloride in rodents are markedly different from that in humans; rodents exhibit greater sensitivity in toxic responses. On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount produced in rodents. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 ($3 \times 0.5 = 1.5$). 10 for intraspecies variability (e.g., ethanol-induced P-450)
Calculations:	
10-min AEGL-3:	$C^{2.5} \times 0.167 \text{ h} = 1{,}906{,}582{,}933 \text{ ppm-h}$ $C = 10{,}544 \text{ ppm}$ 10,544 ppm ÷ 15 = 702.95 ppm, rounded to 700 ppm (4,400 mg/m^3)
30-min AEGL-3:	$C^{2.5} \times 0.5 \text{ h} = 1{,}906{,}582{,}933 \text{ ppm-h}$ $C = 6{,}800 \text{ ppm}$ 6,800 ppm ÷ 15 = 453.3 ppm, rounded to 450 ppm (2,800 mg/m^3)
1-h AEGL-3:	$C^{2.5} \times 1 \text{ h} = 1{,}906{,}582{,}933 \text{ ppm-h}$ $C = 5{,}153.5 \text{ ppm}$ 5,153.5 ppm ÷ 15 = 343.6 ppm, rounded to 340 ppm (2,100 mg/m^3)
4-h AEGL-3:	$C^{2.5} \times 4 \text{ h} = 1{,}906{,}582{,}933 \text{ ppm-h}$ $C = 2959.9 \text{ ppm}$ 2,959.9 ppm ÷ 15 = 197.3 ppm, rounded to 200 ppm (1,300 mg/m^3)

8-h AEGL-3:	$C^{2.5} \times 8$ h = 1,906,582,933 ppm-h C = 2,243 ppm 2,243 ppm ÷ 15 = 149.5 ppm, rounded to 150 ppm (940 mg/m^3)

APPENDIX B

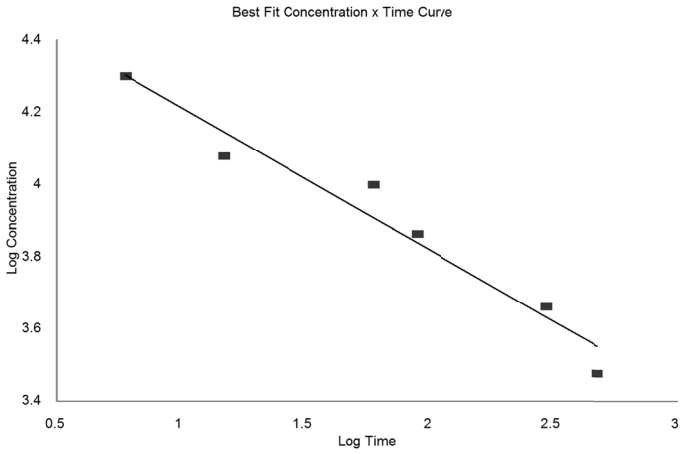
DERIVATION OF EXPONENTIAL FUNCTION FOR TEMPORAL SCALING AND DERIVATION OF LETHALITY THRESHOLD VALUE

Concentration-Time Mortality Response Relationship for Rats

Time	Concentration	Log Time	Log Concentration
6	20,000	0.7782	4.3010
15	12,000	1.1761	4.0792
60	10,000	1.7782	4.0000
90	7,300	1.9542	3.8633
300	4,600	2.4771	3.6628
480	3,000	2.6812	3.4771

Regression Output	
Intercept	4.6106
Slope	-0.3947
R Squared	0.9545
Correlation	-0.9770
Degrees of Freedom	4
Observation	6

n = 2.53
k = 4.813E+11



Data Sources: Adams et al. 1952; Dow Chemical 1960.

Estimation of Lethal Response by Rats to Carbon Tetrachloride

Dose	Mortality	Observed %	Expected %	Observed-Expected	Chi-Square
7,300.000	0/20	0 (7.20)	4.43	2.77	0.0181
8,750.000	0/20	0 (8.60)	9.30	-0.70	0.0006
10,000.000	0/5	0 (9.4)	15.54	-6.14	0.0287
11,760.000	0/5	0 (10.30)	27.23	-16.93	0.1446
12,000.000	3/10	30.00	29.02	0.98	0.0005
13,200.000	5/10	50.00	38.29	11.71	0.0580
15,150.000	8/10	80.00	53.14	26.85	0.2897
15,800.000	7/10	70.00	57.68	12.32	0.0621
19,000.000	9/19	47.37	75.35	-27.98	0.4215
26,000.000	20/20	100 (93.80)	92.35	1.45	0.0030

Values in parentheses are corrected for 0 or 100 percent Total = 1.0268

LD_{50} = 14,720.510 (12,841.527 – 16,874.428)*
Slope = 1.46 (1.26 - 1.69)*
*Values are 95 percent confidence limits

Total animals = 129
Total doses = 10
Animals/dose = 12.90
Chi-square = total chi-square × animals/dose = 13.2454
Table value for Chi-square with 8 Degrees of Freedom = 15.5100

Expected Lethal Dose Values:

$LD_{0.1}$	3,039.445
$LD_{1.0}$	5,153.488
$LD_{5.0}$	7,513.524
LD_{10}	8,911.792
LD_{25}	11,453.651
LD_{50}	14,720.510
LD_{75}	18,919.156
LD_{90}	24,315.358
LD_{99}	42,047.909

Data sources: Adams et al. 1952; Dow Chemical 1960.

APPENDIX C

CARCINOGENICITY ASSESSMENT FOR CARBON TETRACHLORIDE

Cancer Assessment of Carbon Tetrachloride

An inhalation unit risk of 6E-6 per μg/m^3 was derived by EPA (2010a, b) on the basis of pheochromocytomas in male mice. Carbon tetrachloride at a concentration of 17 μg/m^3 is associated with a risk level of 1 in 10,000 (EPA 2010b).

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

24-h exposure = d × 25,600; where d = 16.7 μg/m^3
16.7 μg/m^3 × 25,600 days
426,667 μg/m^3 (426.67 mg/m^3)

To account for uncertainty regarding the variability in the stage of the cancer process at which carbon tetrachloride or its metabolites may act, a multistage factor of 2.8 is applied (Crump and Howe 1984):

426.67mg/m^3 ÷ 2.8 = 152 mg/m^3

Therefore, on the basis of the potential carcinogenicity of carbon tetrachloride, an acceptable 24-h exposure would be 152 mg/m^3 (24.2 ppm) for a 10^{-4} risk.

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f × 24 h (NRC 1985). For a 10^{-4} risk:

24 h = 152mg/m^3 (24.2ppm)
8 h = 457mg/m^3 (72.6ppm)
4 h = 914mg/m^3 (145.3ppm)
1 h = 3,657mg/m^3 (581.2ppm)
0.5 h = 7,314mg/m^3 (1162 ppm)

Exposures relating to risk levels of 10^{-4}, 10^{-5}, and 10^{-6} are presented in Table C-1.

A comparison of the AEGL-2 and AEGL-3 values with the estimated concentration of carbon tetrachloride associated with a 10^{-4} cancer risk is presented in Table C-2. Estimated cancer risks for AEGL-2 and AEGL-3 values are also provided, obtained by assuming a linear relationship between exposure concentration and cancer risk. The cancer assessment is based on the EPA (1983) carcinogenicity assessment of carbon tetrachloride.

TABLE C-1 Potential Cancer Risk Associated with Acute Inhalation of Carbon Tetrachloride

	Exposure Duration				
Risk Level	0.5 h	1 h	4 h	8 h	24 h
1 in 10,000 (10^{-4})	1,200 ppm (7,500 mg/m^3)	580 ppm (3,600 mg/m^3)	140 ppm (880 mg/m^3)	73 ppm (460 mg/m^3)	24 ppm (150 mg/m^3)
1 in 100,000 (10^{-5})	120 ppm (750 mg/m^3)	58 ppm (360 mg/m^3)	14 ppm (88 mg/m^3)	7.3 ppm (46 mg/m^3)	2.4 ppm (15 mg/m^3)
1 in 1,000,000 (10^{-6})	12 ppm (75 mg/m^3)	5.8 ppm (36 mg/m^3)	1.5 ppm (9.4 mg/m^3)	0.73 ppm (4.6 mg/m^3)	0.24 ppm (1.5 mg/m^3)

TABLE C-2 Comparison of AEGL Values and Potential Cancer Risk Associated with Acute Inhalation of Carbon Tetrachloride

	Exposure Duration					
Value	10 min	30 min	1 h	4 h	8 h	24 h
Cancer risk (10^{-4})	–	1,200 ppm	580 ppm	140 ppm	73 ppm	24 ppm
AEGL-1 value:	NR	NR	NR	NR	NR	–
Estimated cancer risk:	–	–	–	–	–	–
AEGL-2 value:	27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm	–
Estimated cancer risk:	–	1.5×10^{-6}	2.2×10^{-6}	5.4×10^{-6}	7.9×10^{-6}	–
AEGL-3 value:	700 ppm	450 ppm	340 ppm	200 ppm	150 ppm	–
Estimated cancer risk:	–	3.8×10^{-5}	5.9×10^{-5}	1.4×10^{-4}	2.1×0^{-4}	–

Abbreviation: NR, not recommended. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR CARBON TETRACHLORIDE

Derivation Summary

AEGL-1 VALUES

Although human data on AEGL-1 effects from carbon tetrachloride are available, values derived on the basis of the data greater than the corresponding AEGL-2 values. Therefore, AEGL-1 values for carbon tetrachloride are not recommended.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm

Reference: Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. JAMA 103(13):962-966.

Test species/Strain/Number: Humans (gender not specified); ages 20-48 years; 3-4 per exposure group

Exposure route/Concentrations/Durations: Inhalation: 76 ppm for 2.5 or 4 h; 158 or 317 ppm for 30 min; 1,191 ppm for 15 min; 2,382 ppm for 3-7 min or ≤10 min; 5-117 ppm for 8 h.

Effects: CNS effects at concentrations >76 ppm
76 ppm for 2.5 h: no effects
76 ppm for 4 h: no effects
158 ppm for 0.5 h: nervousness in one subject; no effect in three subjects.
317 ppm for 0.5 h: slight nausea and vomiting, headache.
1,191 ppm for 0.25 h: nausea, vomiting, headache; intolerable for one subject (9-min exposure only)
2,382 ppm for 3-7 min: nausea, vomiting, dizziness, listlessness, headache, sleepiness.
2,382 ppm for ≤10 min: nausea, vomiting, headache, sleepiness.

Time scaling: $C^n \times t = k$; n = 2.5, on the basis of regression analysis of lethality data from Adams et al. (1952).

Concentration/Time Selection/Rationale: 76 ppm for 4 h; the highest no-effect level for CNS effects

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies:1, because the critical study was conducted in humans
Intraspecies:10, to protect sensitive individuals (e.g., variation in cytochrome P-450)

Modifying factor: none

Animal-to-human dosimetric adjustment: None

Data adequacy: Data are adequate to derive AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
700 ppm	450 ppm	340 ppm	200 ppm	150 ppm

References: Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister, and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. AMA Arch. Ind. Hyg. Occup. Med. 6(1):50-66.
Dow Chemical. 1960. Comparison of the Result of Exposure of Rats and Cavies to the Vapors of Carbon Tetrachloride and Bromochloromethane, June 11, 1960. Submitted to EPA by Dow Chemical with cover letter dated September 4, 1987. EPA Document No. 86870002363. Microfiche No. OTS0515887.

Test Species/Strain/Number: Rats; albino or not specified; 5-30 per group

Exposure route/Concentrations/Durations: Inhalation ; 3,000-20,000 ppm for 0.1-12 h.

Effects: Lethality in rats; estimated 1-h LC_{01} of 5,135.5 ppm.

Time scaling: $C^n \times t = k$; n = 2.5 on the basis of regression analysis of lethality data from Adams et al. (1952).

Concentration/Time selection/Rationale: Estimated 1-h LC_{01} of 5,153.5 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 15
Interspecies: 1.5, PBPK model results predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans, with greater metabolism of carbon tetrachloride by rats relative to humans (Paustenbach et al. 1988; Delic et al. 2000). PBPK models predict that, at equal exposure concentrations, humans will have lower rates of production of reactive CCl_4 metabolites (human/rat = 0.5). On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be expected to be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 ($3 \times 0.5 = 1.5$).
Intraspecies:10, to account for individual variability in the sensitivity to carbon tetrachloride-induced toxicity (e.g., alcohol-potentiated hepatotoxicity).

Modifying factor: None

Animal-to-human dosimetric adjustment: Insufficient data.

Data adequacy: The AEGL-3 values are supported by subchronic exposure studies in animals showing that exposures above the AEGL-3 values did not result in lethality. Potential dermal absorption of carbon tetrachloride is not addressed by the AEGL values.

APPENDIX E

CATEGORY PLOTS FOR CARBON TETRACHLORIDE

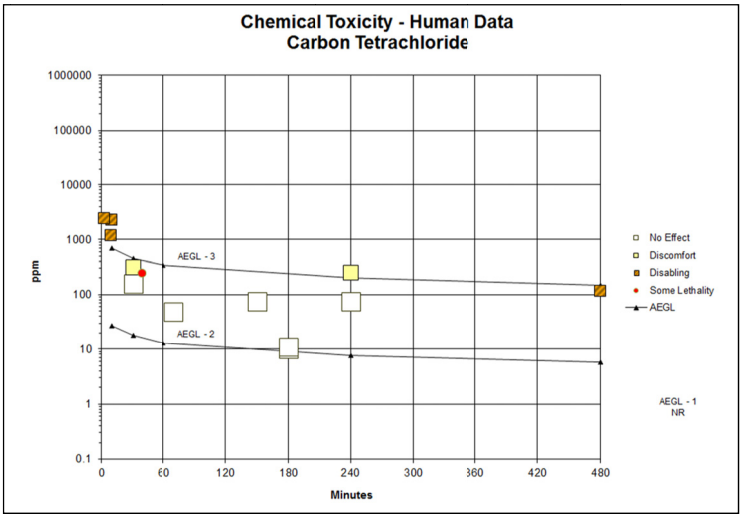


FIGURE E-1 Category plot of human toxicity data and AEGL values for carbon tetrachloride.

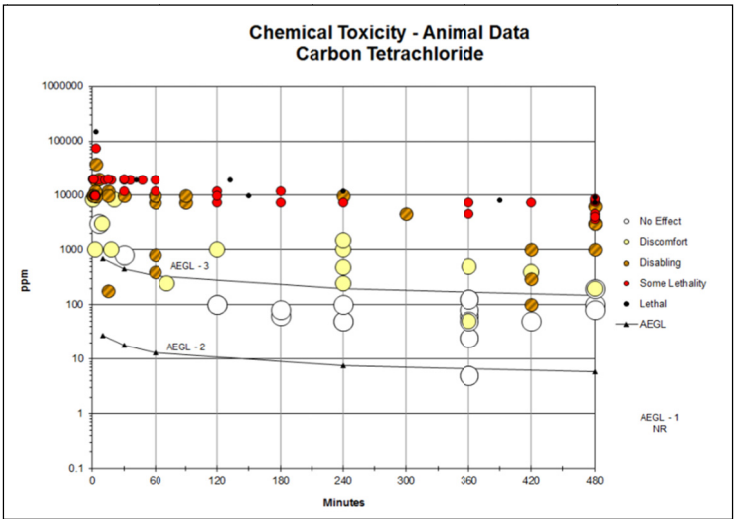


FIGURE E-2 Category plot of animal toxicity data and AEGL values for carbon tetrachloride.

TABLE E-1 Date Used in the Category Plots for Carbon Tetrachloride

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				27	10	AEGL	
AEGL-2				18	30	AEGL	
AEGL-2				13	60	AEGL	
AEGL-2				7.6	240	AEGL	
AEGL-2				5.8	480	AEGL	
AEGL-3				700	10	AEGL	
AEGL-3				450	30	AEGL	
AEGL-3				340	60	AEGL	
AEGL-3				200	240	AEGL	
AEGL-3				150	480	AEGL	
Davis 1934	Human		1	76	150	0	4 subjects, no adverse effects.
Davis 1934	Human		2	76	240	0	4 subjects, no adverse effects.
Davis 1934	Human		1	158	30	0	4 subjects, no adverse effects.
Davis 1934	Human		1	317	30	1	3 subjects: one experienced nausea, one had nausea and vomiting, and one complained of headache.
Davis 1934	Human		1	1,191	9	2	4/4 subjects experienced headache, nausea, vomiting, and tolerated exposures of 9 - 15 min.

Davis 1934	Human			2,300	10	2	3/3 subjects could not tolerate more than 10 min without becoming nauseated and sleepy. One experienced vomiting, dizziness, and a throbbing headache.
Davis 1934	Human		1	2,382	3	2	3/3 subjects experienced nausea, vomiting, dizziness, and listlessness or sleepiness and tolerated exposure for 3 - 7 min.
Norwood et al 1950	Human	M	1	250	15	SL	1/3 subjects experienced headache and dizziness, aches and pains, nausea and vomiting, renal failure and death, centrilobular necrosis of the liver and interstitial edema and tubular (loop of Henle and distal convoluted tubule) degeneration in the kidney.
Norwood et al 1950	Human		1	250	240	1	2/3 workers experienced mild headache and dizziness during exposure.
Smyth et al 1936	Human			117	480	2	Elevated bilirubin, restricted visual field (imprecise assessments for both).
Stewart et al. 1961	Human			10.1	180	0	6 subjects; no adverse effects.
Stewart et al. 1961	Human			10.9	180	0	6 subjects; no adverse effects.
Stewart et al. 1961	Human			49	70	0	6 subjects; no clinically significant effects; no irritation; odor detection; transient decline in serum iron 20-68 h postexposure; elevated urinary urobilinogen in one subject.
McCollister et al. 1951	Monkey		1	485	240	1	Negligible absorption as determined by radioactivity in the blood and expired air.
Dow Chemical 1960	Mouse	F	1	8,500	680	SL	LCt50
Gehring 1968	Mouse		1	8,500	0.16	1	ECt50 for SGPT activity
Gehring 1968	Mouse		1	8,500	21	1	ECt50 for anesthesia

(Continued)

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Merck 1983	Mouse		1	9,400	3.5	2	Mortality (0/5)
Merck 1983	Mouse		1	18,800	3.5	2	Mortality (0/5)
Merck 1983	Mouse		1	37,500	3.5	2	Mortality (0/5)
Merck 1983	Mouse		1	75,000	3.5	SL	Mortality (2/6)
Merck 1983	Mouse		1	150,000	3.5	3	Mortality (6/6)
Nagano et al. 2007	Mouse	B	520	5	360		
Nagano et al. 2007	Mouse	B	520	25	360		
Nagano et al. 2007	Mouse	B	520	125	360		
Svirbaly et al. 1947	Mouse		1	6,340	480	2	Mortality (0/20)
Svirbaly et al. 1947	Mouse		1	7,628	480	SL	Mortality (2/20)
Svirbaly et al. 1947	Mouse		1	8,088	480	SL	Mortality (19/20)
Svirbaly et al. 1947	Mouse		1	8,787	480	SL	Mortality (10/20)
Svirbaly et al. 1947	Mouse		1	9,327	480	3	Mortality (20/20)
Ugazio et al. 1995	Rabbit		23	100	120	0	Increased hexobarbital sleeping time; hepatic fibrosis.
Adams et al. 1952	Rat		1	50	420	0	No effects.
Adams et al. 1952	Rat		1	100	420	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	400	60	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	800	30	0	No effects.
Adams et al. 1952	Rat		1	800	60	2	Altered hepatic weight, total lipid content,

						and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat	1	3,000	6	0	No effects.
Adams et al 1952	Rat	1	3,000	9	1	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat	1	3,000	480	2	Mortality (0/20)
Adams et al. 1952	Rat	1	3,000	600	SL	Mortality (1/30)
Adams et al. 1952	Rat	1	3600	480	SL	Mortality (4/10)
Adams et al. 1952	Rat	1	3,600	720	SL	Mortality (1/10)
Adams et al. 1952	Rat	1	4,600	300	2	Mortality (0/20)
Adams et al. 1952	Rat	1	4,600	360	SL	Mortality (1/11)
Adams et al. 1952	Rat	1	4,600	480	SL	Mortality (2/10)
Adams et al. 1952	Rat	1	7,300	60	2	Mortality (0/20)
Adams et al. 1952	Rat	1	7,300	90	2	Mortality (0/20)
Adams et al. 1952	Rat	1	7,300	120	SL	Mortality (1/10)
Adams et al. 1952	Rat	1	7,300	180	SL	Mortality (1/10)
Adams et al. 1952	Rat	1	7,300	240	SL	Mortality (4/10)
Adams et al. 1952	Rat	1	7,300	360	SL	Mortality (6/10)
Adams et al. 1952	Rat	1	7,300	420	SL	Mortality (4/10)
Adams et al. 1952	Rat	1	7,300	480	3	Mortality (20/20)
Adams et al. 1952	Rat	1	12,000	3	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat	1	12,000	15	2	Mortality (0/20)
Adams et al. 1952	Rat	1	12,000	30	SL	Mortality (1/10)

(Continued)

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Adams et al. 1952	Rat		1	12,000	60	SL	Mortality (3/10)
Adams et al. 1952	Rat		1	12,000	120	SL	Mortality (7/10)
Adams et al. 1952	Rat		1	12,000	180	SL	Mortality (8/10)
Adams et al. 1952	Rat		1	12,000	240	3	Mortality (20/20)
Adams et al. 1952	Rat		1	19,000	6	SL	Mortality (1/10)
Adams et al. 1952	Rat		1	19,000	12	SL	Mortality (1/5)
Adams et al. 1952	Rat		1	19,000	18	SL	Mortality (3/5)
Adams et al. 1952	Rat		1	19,000	30	SL	Mortality (2/5)
Adams et al. 1952	Rat		1	19,000	36	SL	Mortality (14/15)
Adams et al. 1952	Rat		1	19,000	42	3	Mortality (5/5)
Adams et al. 1952	Rat		1	19,000	48	SL	Mortality (4/5)
Adams et al. 1952	Rat		1	19,000	60	SL	Morality (9/19)
Adams et al. 1952	Rat		1	19,000	132	3	Mortality (20/20)
Appelman et al. 1985	Rat		2	63	180	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		20	63	360	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		2	80	180	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		20	80	360	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Cornish and Block 1960	Rat	B	1	50	240	0	
Cornish and Block 1960	Rat	B	1	50	240	0	

Cornish and Block 1960	Rat		B	1	100	240	0	
Cornish and Block 1960	Rat		B	1	250	240	1	
Cornish and Block 1960	Rat		B	1	1,000	240	1	
Cornish and Block 1960	Rat		B	1	1,500	240	1	
David et al. 1981	Rat			13-18	50	360	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat			13-18	250	72	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat			13-18	1,000	3	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat			13-18	1,000	18	1	Minor increase in SGPT, minor histologic changes in the liver.
Dow Chemical 1960	Rat			1	10,000	60	2	Mortality (0/5)
Dow Chemical 1960	Rat			1	10,000	90	2	Mortality (0/5)
Dow Chemical 1960	Rat			1	10,000	120	SL	Mortality (5/10)
Dow Chemical 1960	Rat			1	10,000	150	3	Mortality (5/5)
Dow Chemical 1960	Rat			1	20,000	6	2	Mortality (0/10)
Dow Chemical 1960	Rat			1	20,000	15	SL	Mortality (5/10)
Dow Chemical 1960	Rat			1	20,000	30	SL	Mortality (8/10)
Nagano et al. 2007	Rat		B	520	5	360		
Nagano et al. 2007	Rat		B	520	25	360		
Nagano et al. 2007	Rat		B	520	125	360		Increased hepatocellular adenomas and carcinomas.
Paustenbach et al. 1986b	Rat			1	100	480	0	No significant effect on SDH.

(Continued)

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Paustenbach et al. 1986b	Rat		1	100	690	1	Marginally increased SDH.
Sakata et al. 1987	Rat		1	180	15	2	"Comatose"; increased ALT at 24-h postexposure.
Sanzgini et al. 1995	Rat		1	100	120	0	No effects.
Sanzgini et al. 1995	Rat		1	1,000	120	1	Increased ALT and SDH, decreased P-450.
Schwetz et al. 1974	Rat	F	10	300	420	2	Fetoxicity.
Schwetz et al. 1974	Rat	F	10	1,000	420	2	Fetoxicity.
Smyth et al. 1936	Rat		210	200	480	0	No significant effects.
Mellon Institute 1947	Rat		1	1,000	480	2	Mortality (0/12)
Mellon Institute 1947	Rat		1	3,000	480	2	Mortality (0/12)
Mellon Institute 1947	Rat		1	4,000	480	SL	Mortality (2/12)
Mellon Institute 1947	Rat		1	8,000	390	3	Mortality (12/12)
Van Stee et al. 1982	Rat		1				Hepatic vacuolation and individual cell necrosis which varied with exposure profile.
Wang et al. 1997	Rat		1	50	360	0	No effects.
Wang et al. 1997	Rat		1	500	360	1	Minor increase in SGOT and SGPT.
Smyth et al. 1936	Rhesus monkey		210	200	480	1	Transient hepatic injury.
Prendergast et al. 1967	Squirrel monkey		1	82	480	0	One of three monkeys died after the 7th exposure at 82 ppm (8h/day; 5d/wk for 6 wk).
Wong and DiStefano 1966	Cat		1	10,000	15	2	Increased total lipids in renal cortex.
Wong and DiStefano 1966	Cat		1	10,000	30	2	Increased relative adrenal weight.
Wong and DiStefano 1966	Cat		1	10,000	60	2	

Wong and DiStefano 1966	Cat	1	10,000	240	2	Central necrosis in liver.
Mellon Institute 1947	Dog	168	400	420	1	Decreased body weight.
Dow Chemical 1960	Guinea pig	1	10,000	0.25	2	Mortality (0/5)
Dow Chemical 1960	Guinea pig	1	10,000	1	2	Mortality (0/5)
Dow Chemical 1960	Guinea pig	1	10,000	1.5	SL	Mortality (1/10)
Dow Chemical 1960	Guinea pig	1	10,000	2	SL	Mortality (4/5)
Dow Chemical 1960	Guinea pig	1	10,000	2.5	SL	Mortality (1/5)
Dow Chemical 1960	Guinea pig	1	10,000	3	SL	Mortality (1/5)
Dow Chemical 1960	Guinea pig	1	20,000	0.5	SL	Mortality (2/5)
Dow Chemical 1960	Guinea pig	1	20,000	1	SL	Mortality (4/5)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal.

3

Cyanogen[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Glenn Leach (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Cyanogen is a colorless gas with a pungent, penetrating, almond-like odor (ACGIH 2001). It is generally prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper (II) sulfate or chloride. It may also be prepared from hydrocyanic acid by using copper oxide or from hydrocyanic acid and nitrogen dioxide. It is used as a gas for welding and cutting heat-resistant metals, as a rocket and missile propellant, and as a fumigant (HSDB 2009).

The hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as the AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If AEGL-1 values were derived on the basis of the cyanogen data, the no-observed-effect level for irritation in humans exposed to cyanogen for 6 min would be 8 ppm. Ocular and nasal irritation was reported at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be used because the study was conducted in humans. Thus, the threshold for irritation would be 2.7 ppm. Time scaling of this threshold would not be appropriate, because the critical effects (ocular and nasal irritation) are a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). How-

ever, because human data on exposures of durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective of both irritation and potential systemic cyanide effects.

In the absence of appropriate chemical-specific data to derive AEGL-2 values for cyanogen, the AEGL-3 values were divided by 3 to estimate the AEGL-2 values. That approach is justified by the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960).

Experimental concentrations causing no deaths in rats (McNerney and Schrenk 1960) were used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. Specifically, the concentration associated with 0% mortality after 10 min of exposure was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper. That approach estimated that no deaths would occur following a 10-min exposure at 1,530 ppm. The 30-min exposure at 500 ppm was used as the point-of-departure for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was used as the point-of-departure for the 1-h AEGL-3 value. An intraspecies uncertainty factor of 3 was applied and was considered sufficient due to the steep concentration-response curve evidenced in the mortality data from McNerney and Schrenk (1960), which implies limited intraindividual variability. An interspecies uncertainty factor of 3 was also applied. Although a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, and 4.3 ppm for 4 and 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects Lewis et al. [1984].) Therefore, the total uncertainty factor was 10.

The 4- and 8-h AEGL-3 values were derived by applying a modifying factor of 2 to the 1-h AEGL-3 value. That approach was used because time scaling using the equation $C^n \times t = k$, with a default value of $n = 1$, and yielded possible 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et

al. 1984). Rats exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.

AEGL values for cyanogen are presented in Table 3-1.

1. INTRODUCTION

Cyanogen is a colorless gas with a pungent, penetrating, almond-like odor (ACGIH 2001). It is generally prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper (II) sulfate or chloride. It may also be prepared from hydrocyanic acid by using copper oxide or from hydrocyanic acid and nitrogen dioxide. It is used as a gas for welding and cutting heat-resistant metals, as a rocket and missile propellant, and as a fumigant (HSDB 2009).

Selected chemical and physical properties of cyanogen are presented in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data on cyanogen were not found.

2.2. Nonlethal Toxicity

An odor threshold of 235 ppm (500 mg/m^3) and an irritating concentration of 15 ppm (32 mg/m^3) for cyanogen were reported by Ruth (1986).

TABLE 3-1 AEGL Values for Cyanogen

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)	AEGL-1 values for cyanide were adopted (NRC 2002).
AEGL-2 (disabling)	50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)	One-third the AEGL-3 values.
AEGL-3 (lethal)	150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)	Concentrations causing no lethality in rats (McNerney and Schrenk 1960)

TABLE 3-2 Chemical and Physical Data for Cyanogen

Parameter	Value	Reference
Synonyms	Carbon nitride; cyanogene; dicyan; dicyanogen; ethanedinitrile; nitroloacetonitrile; oxalic acid dinitrile; oxalonitrile; oxalyl cyanide	HSDB 2009
CAS registry no.	460-19-5	HSDB 2009
Chemical formula	C_2N_2	HSDB 2009
Molecular weight	52.03	HSDB 2009
Physical state	Colorless gas	HSDB 2009
Melting point	-27.83°C	HSDB 2009
Boiling point	-21.1°C	HSDB 2009
Density/Specific gravity	0.9537 g/m^3 at -21°C	HSDB 2009
Solubility in water	450 cc/100 mL at 20°C	HSDB 2009
Relative vapor density	1.8 (air = 1)	HSDB 2009
Vapor pressure	4,300 mm Hg at 25°C	HSDB 2009
Explosive limits	Upper: 42.6%; lower: 6.6%, by volume in air	IPCS 2012
Conversion factors in air	1 ppm = 2.1 mg/m^3 1 mg/m^3 = 0.47 ppm	NIOSH 2011

Seven human subjects (four men and 3 women; ages 21-65 years) were exposed to cyanogen at 8 or 16 ppm in three separate tests (McNerney and Schrenk 1960). The tests were performed in a 1,185-ft^3 sealed room. The cyanogen gas contained less than 0.5% contaminants such as nitrogen, chlorine, and cyanogen chloride. Cyanogen concentrations were obtained by measuring the required volume of gas over mercury in a graduated, gas sampling tube and introducing it into the exposure space by displacement of the mercury. In the first test, four men and three women were exposed to cyanogen at 8 ppm for 6 min; none of the subjects detected an odor, and no ocular or nasal irritation was reported by the subjects. In the second test, three men and two women were exposed at 16 ppm for 6 min; none of the subjects detected an odor, all subjects reported ocular irritation, and four subjects reported nasal irritation (the subject who did not experiencing nasal irritation had mild cold symptoms). In the third test, four men and three women were exposed to cyanogen at 16 ppm for 8 min; none of the subjects detected an odor, and all subjects reported ocular and nasal irritation. During the 16-ppm tests, ocular irritation was noted immediately when the desired test concentration was attained. Ocular irritation was perceived simultaneously with or slightly before the occurrence of nasal irritation. Both ocular and nasal irritation seemed to be transitory as signs persisted for several minutes following cessation of exposure. (There is a discrepancy in the description of the number of subjects for the first and second tests the report. The text suggests that the first test included five subjects and the second test included seven sub-

jects; however, the data table indicates that the first test had seven subjects and the second test had five subjects. It was assumed that the data table correctly lists the number of subjects in each test. In either case, the study results are unaffected.] Results are summarized in Table 3-3.

In an additional test (McNerney and Schrenk 1960), three men and one woman attempted to detect the odor of cyanogen drawn from a sampling tube connected to a chamber where concentrations of 50, 100, and 250 ppm were produced; none of the subjects detected any odor.

2.3. Case Reports

No case reports on cyanogen were found.

2.4. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of cyanogen in humans were not available.

2.5. Genotoxicity

No information regarding the genotoxicity of cyanogen in humans was available.

2.6. Carcinogenicity

No information regarding the carcinogenicity of cyanogen in humans was available.

2.7. Summary

Cyanogen inhalation data in humans are sparse. Cyanogen causes immediate ocular and nasal irritation at 16 ppm, but no irritation was noted at 8 ppm. No developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity data were available.

TABLE 3-3 Effects of Acute Cyanogen Exposure in Humans[a]

		Number per Group Experiencing Effects		
Concentration	Duration	Odor	Ocular Irritation	Nasal Irritation
8 ppm	6 min	0/7	0/7	0/7
16 ppm	6 min	0/5	5/5	4/5[b]
16 ppm	8 min	0/7	7/7	7/7

[a]Adapted from McNerney and Schrenk 1960.
[b]The subject without irritation had mild cold symptoms.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of six male albino rats were exposed to a total of six different concentrations of cyanogen for six different durations (McNerney and Schrenk, 1960). The tests were performed in a 2-ft^3 galvanized metal exposure chamber. A plexiglass door, bolted to the chamber, sealed the unit and allowed for observation of the rats during exposure. The cyanogen gas used contained less than 0.5% contaminants such as nitrogen, chlorine, and cyanogen chloride. Cyanogen concentrations were obtained by measuring the required volume of gas over mercury in a graduated, gas sampling tube and introducing it into the exposure space by displacement of the mercury. Experimental parameters and mortality incidence are summarized in Table 3-4. Observations during exposure included (in chronologic order) blinking, rubbing of forepaws over eyes and nose, huddling together with inactivity, slow gasping, tearing, yellow fluid from the nose and mouth, restlessness and "panic-type" movements, accentuated and poorly coordinated movements, bright pink coloration of the skin, labored breathing, deep and frequent gasping, tremors, sluggishness, prostration, shallow breathing, and death. All deaths occurred during or shortly after exposure except in the group exposed at 250 ppm for 120 min; two rats died during exposure, one died 7 h after exposure and exhibited signs of central nervous system damage starting at cessation of exposure through death, and one died 7 days after exposure and did not show any clinical signs. None of the rats showed any treatment-related gross lesions at necropsy.

TABLE 3-4 Mortality in Male Albino Rats after Acute Exposure to Cyanogen[a]

Concentration (ppm)	Duration (min)	Mortality Incidence
4,000	7.5	3/6
4,000	15	6/6
2,000	7.5	0/6
2,000	15	6/6
1,000	15	0/6
1,000	30	6/6
500	30	0/6
500	45	6/6
400	45	0/6
400	60	6/6
250	60	0/6
250	120	4/6

[a]Adapted from McNerney and Schrenk 1960.

3.1.2. Mice

Lethality was reported in mice exposed to cyanogen at 2,600 ppm for 12 min or 15,000 ppm for 1 min. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.3. Cats

Lethality was reported in cats exposed to cyanogen at 100 ppm for 2-3 h, at 200 ppm for 0.5 h, or 2,000 ppm for 13 min. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.4. Rabbits

Lethality was reported in rabbits exposed to cyanogen at 300 ppm for 3.5 h or 400 ppm for 1.8 h. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.5. Summary of Animal Lethality Data

Well-described animal lethality data are restricted to studies in rats. On the basis of signs of toxicity, cyanogen is similar to other cyanides. Signs of irritation are followed by central nervous system effects and eventually death.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of 30 male Charles River albino rats were exposed to cyanogen at 0, 11, or 25 ppm for 6 h/day, 5 days/week for up to 6 months, in 4.8-m^3 stainless steel and glass chambers (Lewis et al. 1984). Chambers had pyramidal top and bottom sections to obtain uniform dispersion of the test atmosphere. Cyanogen (99% pure) was introduced into the chamber from a compressed gas cylinder through a pressure regulator, metering valve, and flow meter. Breathing zone samples were taken two to six times per exposure period and analyzed by gas chromatography. Six rats per exposure group were killed after 2 days, 5 days, 1 month, 3 months, or 6 months of exposure. Serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were measured. Gross necropsies were performed, and lung tissue samples were collected for analysis of moisture content. Mean exposure concentrations of cyanogen over the 6-month period were 11.2 ppm (± 1.5 ppm) and 25.3 ppm (± 3.3 ppm). At the end of the 6-month exposure

period, the mean body weights of rats in the control, 11 ppm, and 25 ppm groups were 543 g, 589 g, and 470 g, respectively. The decrease in the 25-ppm group compared with controls was statistically significant ($p < 0.05$). Mean values for serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were unaffected by treatment. There were no treatment-related effects noted at necropsy.

3.2.2. Mice

It was reported that mice exposed to cyanogen at 235 ppm for 15 min "recovered". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.3. Rabbits

It was reported that rabbits exposed to cyanogen at 100 ppm for 4 h had "practically no effect" and rabbits exposed at 200 ppm for 4 h had "slight symptoms". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.4. Cats

It was reported that cats exposed to cyanogen at 50 ppm for 4 h had "severe symptoms but recovered". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.5. Monkeys

Groups of five male rhesus monkeys were exposed to cyanogen at 0, 11, or 25 ppm for 6 h/day, 5 days/week for up to 6 months in 4.8-m^3 stainless steel and glass chambers (Lewis et al. 1984). Chambers had pyramidal top and bottom sections to help attain uniform dispersion of the test atmosphere. Cyanogen (99% pure) was introduced into the chamber from a compressed gas cylinder through a pressure regulator, metering valve, and flow meter. Breathing zone samples were taken two to six times per exposure period and analyzed by gas chromatography. Behavioral tests involving lever pressing activity on a variable interval schedule of reinforcement were conducted daily after exposure and for 4 weeks following the end of the exposure period. Electrocardiograms were performed prior to exposure and immediately following the last exposure. Serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were measured throughout the course of exposure. Gross necropsies were performed, and lung tissue samples were collected for analysis of moisture content. Mean exposure concentrations over the 6-month period were 11.2 ppm (± 1.5 ppm) and 25.3 ppm (± 3.3 ppm).

Behavioral testing suggested an increase in response rate in all three groups during the exposure period compared with the baseline measurements. Mean increases were 20%, 14%, and 145% ($p = 0.06$) for the control, 11 ppm, and 25 ppm groups, respectively. The increase in the 25-ppm group was considered "marginal" and transitory, as the response rate returned to normal before the end of the study (Data were presented in averaged intervals such that no assessment of behavioral effects after a day of exposure was possible.) There were no treatment-related effects on electrocardiograms. Mean values for serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were unaffected by treatment. Total lung moisture content was lower in both the 11-ppm and 25-ppm groups compared with controls; however, because the effect was not significant ($p > 0.3$) and was not noted in the rats (see Section 3.2.1), the investigators found the effect to be of questionable toxicologic significance. There were no other treatment-related effects noted at necropsy.

3.2.6. Summary of Nonlethal Toxicity in Animals

Nonlethal acute inhalation toxicity data are sparse. Repeated-exposure experiments in both rats and monkeys suggest that exposure to cyanogen at 11 ppm for up to 6 months yielded no adverse treatment-related effects. Decreased body weight was noted in rats and marginal-transitory behavioral effects were noted in monkeys exposed to cyanogen at 25 ppm for up to 6 months.

3.3. Developmental and Reproductive Effects

No developmental or reproductive toxicity data in animals were found.

3.4. Genotoxicity

No genotoxicity data on cyanogen were found.

3.5. Carcinogenicity

No carcinogenicity data on cyanogen were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Definitive metabolism and disposition data for cyanogen in humans or animals were not available. Cyanogen is reportedly converted in the body partly to hydrogen cyanide and partly to cyanic acid (Flury and Zernik, 1931, as cited in Kopras 2012). It reportedly hydrolyzes to yield one mole of hydrogen cyanide

and one mole of cyanate (McNerney and Schrenk 1960). Clinical signs noted in cyanogen-exposed animals are similar to those noted in hydrogen cyanide-exposed animals.

4.2. Mechanism of Toxicity

The mechanism of toxicity of cyanogen is reportedly similar to that of hydrogen cyanide (Kopras 2012). Hydrogen cyanide is a systemic poison that acts on the central nervous system. It interrupts cellular respiration by inhibiting cytochrome oxidase, thus blocking electron transfer to oxygen (Rieders 1971). Tissue oxygen concentrations rise, resulting in increased tissue oxygen tension and a decreased unloading for oxyhemoglobin. As a consequence, oxidative metabolism may slow to a point where it cannot meet metabolic demands. That is particularly critical in the brainstem nuclei where lack of an energy source results in central respiratory arrest and death. Cyanide can inhibit many other enzymes, particularly those that contain iron or copper, but cytochrome oxidase appears to be the most sensitive enzyme (Rieders 1971). Cyanide also stimulates the chemoreceptors of the carotid and aortic bodies to produce a brief period of hyperpnea. Cardiac irregularities may occur, but death is due to respiratory arrest. Brain lesions have been associated with exposure of animals to hydrogen cyanide at high concentrations (NRC 2002).

4.3. Structure-Activity Relationships

Cyanogen is structurally similar to cyanide and other nitriles. At relatively low concentrations, cyanogen appears to be much more irritating than hydrogen cyanide. In human subjects exposed to cyanogen at 16 ppm for 6 or 8 min, ocular irritation was noted immediately. The ocular irritation was perceived simultaneously with or slightly before the occurrence of nasal irritation (McNerney and Schrenk 1960). In contrast, although signs of systemic cyanide poisoning (headache, vertigo, weakness, and numbness) were noted in humans occupationally exposed to hydrogen cyanide at concentrations of 5-75 ppm, no irritation was reported (NRC 2002).

Qualitatively, clinical signs in animals exposed to cyanogen are consistent with clinical signs associated with cyanide exposure. However, rat data suggest that cyanogen is less acutely toxic than hydrogen cyanide by a factor of 10 (McNerney and Schrenk 1960; ACGIH 2001). Analysis of available rat data suggests that this assumption may be true for very short exposure durations (up to approximately 15 min), but not for longer durations (30 min to 1 h). The 5-min rat LC_{50} values for hydrogen cyanide range from approximately 400-500 ppm (NRC 2002), and three of six rats died when exposed to cyanogen at 4,000 ppm for 7.5 min (McNerney and Schrenk 1960). A 15-min rat LC_{50} value for

hydrogen cyanide of 196 ppm was reported (NRC 2002), and no deaths occurred in six rats exposed to cyanogen at 1,000 ppm and six of six rats died when exposed to cyanogen at 2,000 ppm for 15 min (McNerney and Schrenk 1960). For 30-min exposures, rat LC_{50} values for hydrogen cyanide were 150-200 ppm (NRC 2002), and none of six rats exposed to cyanogen died when exposed at 500 ppm and six of six rats died when exposed at 1,000 ppm (McNerney and Schrenk, 1960). Finally, for 60-min exposures, rat LC_{50} values for hydrogen cyanide were 120-140 ppm (NRC 2002), and none of six rats died when exposed to cyanogen at 250 ppm and six of six died when exposed at 400 ppm (McNerney and Schrenk 1960) (see Table 3-5).

4.4. Species Variability

Data are insufficient to determine species variability for cyanogen.

4.5. Temporal Extrapolation

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). Because the data on cyanogen were insufficient for deriving an empirical value for n, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

TABLE 3-5 Comparison of Toxicity Data on Hydrogen Cyanide and Cyanogen in Rats

Concentration (ppm)	Duration (min)	Hydrogen Cyanide End Point	Cyanogen End Point
400-500	5	LC_{50}	–
4,000	7.5	LC_{50}	Mortality: 3/6
196	15	LC_{50}	–
1,000	15	LC_{50}	Mortality: 0/6
2,000	15	LC_{50}	Mortality: 6/6
150-200	30	LC_{50}	–
500	30	LC_{50}	Mortality: 0/6
1,000	30	LC_{50}	Mortality: 6/6
120-140	60	LC_{50}	–
250	60	LC_{50}	Mortality: 0/6
400	60	LC_{50}	Mortality: 6/6

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Immediate ocular and nasal irritation was found in humans exposed to cyanogen at 16 ppm for 6 or 8 min. Irritation persisted for several minutes following cessation of exposure. No irritation was noted in humans exposed at 8 ppm for 6 min (McNerney and Schrenk 1960).

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to derivation of AEGL-1 values for cyanogen were available.

5.3. Derivation of AEGL-1 Values

The hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If that study were used to derive AEGL-1 values, the no-observed-effect level for irritation in humans would be 8 ppm for 6 min. Ocular and nasal irritation was reported at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. This would yield a threshold for irritation of 2.7 ppm. An intraspecies factor would not be applied because the critical study was performed on humans. Time scaling would not be appropriate, because the critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because of the lack of human data on exposures to cyanogen for durations longer than 8 min and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values were adopted as the AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective of both irritation and potential systemic cyanide effects. The AEGL-1 values for cyanogen are presented in Table 3-6. Appendix D includes a summary of how the AEGL values for hydrogen cyanide were determined, provides a comparison of the AEGL values for hydrogen cyanide and cyanogen.

TABLE 3-6 AEGL-1 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values for cyanogen were found.

6.2. Animal Data Relevant to AEGL-2

No animal data relevant to derivation of AEGL-2 values for cyanogen were found.

6.3. Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data, the AEGL-2 values were derived by dividing the AEGL-3 values for cyanogen by 3. That approach is justified by the steep concentration-response curve for cyanogen (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960). The AEGL-2 values for cyanogen are presented in Table 3-7.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values for cyanogen were found.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats exposed to a total of six concentrations of cyanogen for six exposure durations (McNerney and Schrenk 1960). Durations were 7.5-120 min and concentrations of cyanogen were 250-4,000 ppm. Mortality incidences ranged from 0 to 100%, depending on concentration-duration pairings. The experimental parameters are summarized in Table 3-4. No death occurred in rats exposed to cyanogen at 2,000 ppm for 7.5 min, 1,000 ppm for 15 min, 500 ppm for 30 min, or 250 ppm for 60 min.

TABLE 3-7 AEGL-2 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm 9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)

7.3. Derivation of AEGL-3 Values

The experimental concentrations causing no deaths in rats (McNerney and Schrenk 1960) were used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. Specifically, the concentration associated with 0% mortality after 10 min of exposure was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper. That approach estimated that no deaths would occur following a 10-min exposure at 1,530 ppm. A point-of-departure of 1,530 ppm is supported by time scaling the empirical data for the 7.5-min exposure (no deaths at 2,000 ppm) to 10 min using the equation $C^n \times t = k$, with n = 1 (default value when extrapolating to longer durations), which results in a point-of-departure of 1,500 ppm. The 30-min exposure at 500 ppm was the point-of-departure for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was the point-of-departure for the 1-h AEGL-3 value. An intraspecies uncertainty factor of 3 was applied and was considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960), which implies limited intraindividual variability. An interspecies uncertainty factor of 3 was also be applied. Although a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, and 4.3 ppm for 4 and 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984].) Therefore, a total uncertainty factor of 10 was used.

The 4- and 8-h AEGL-3 values were determined by applying a modifying factor of 2 to the 1-h AEGL-3 value. That approach was used instead because

time scaling using the equation $C^n \times t = k$, with a default value of n = 1, yielded possible 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm. The AEGL-3 values for cyanogen are presented in Table 3-8, and their derivation is presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for cyanogen are presented in Table 3-9. AEGL-1 values for cyanogen were set equal to those established for hydrogen cyanide. AEGL-2 values were derived by dividing the AEGL-3 values by 3, and the AEGL-3 values are based on experimental concentrations of cyanogen causing no mortality in rats.

8.2. Other Standards and Guidelines

Other standards and guidelines for cyanogen are presented in Table 3-10.

TABLE 3-8 AEGL-3 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

TABLE 3-9 AEGL Values for Cyanogen

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)
AEGL-2 (disabling)	50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)
AEGL-3 (lethal)	150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

TABLE 3-10 Standards and Guidelines for Cyanogen

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
AEGL-2	50 ppm	17 ppm	8.3 ppm	4.3 ppm	4.3 ppm
AEGL-3	150 ppm	50 ppm	25 ppm	13 ppm	13 ppm
TLV-TWA (ACGIH)[a]	–	–	–	–	10 ppm
REL-TWA (NIOSH)[b]	–	–	–	–	10 ppm
MAK (Germany)[c]	–	–	–	–	5 ppm

[a]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The value was determined by analogy to cyanide, to prevent irritation and systemic effects.
[b]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health (NIOSH 2011) is defined as the time-weighted average concentration for up to a 10-h workday during a 40-h workweek.
[c]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (DFG 2007) is defined analogous to the ACGIH TLV-TWA. Skin notation.

8.3. Data Adequacy and Research Needs

Human and animal data on cyanogen are sparse. Acute exposure studies in animals other than rats would be helpful.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Cyanogen (CAS Reg. No. 460-19-5). Documentation of the Threshold Limit Values and Biological Exposure Indices. Cyanogen. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. Cyanogen (CAS Reg. No. 460-19-5). 2012 TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substance and Physical Agents. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

DFG (Deutsche Forschungsgemeinschaft). 2007. List of MAK and BAT Values. Maximum Concentrations and Biological Tolerance Value at the Workplace Report No. 43. Weinheim, Federal Republic of Germany: Wiley-VCH.

El Ghawabi, S.H., M.A. Gaafar, A.A. El-Saharti, S.H. Ahmed, K.K. Malash, and R. Fares. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br. J. Ind. Med. 32:215-219.

Flury, F., and F. Zernik. 1931. Schadliche Gase. Berlin: Springer (as cited in Kopras 2012).

Grabois, B. 1954. Exposure to hydrogen cyanide in processing of apricot kernels. Monthly Review NY Department of Labor 33:33-36.

Hardy, H.L., W.M. Jeffries, M.M. Wasserman, and W.R. Waddell. 1950. Thiocyanate effect following industrial cyanide exposure - report of two cases. New Engl. J. Med. 242:968-972.

HSDB (Hazardous Substances Data Bank). 2009. Cyanogen (CAS Reg. No. 460-19-5). TOXNET Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/ [accessed January 2013].

IPCS (International Programme on Chemical Safety). 2012. ICSC (International Chemical Safety Card): Cyanogen. ICSC 1390. International Programme on Chemical Safety/Commission of the European Union [online]. Available: http://www.inchem.org/documents/icsc/icsc/eics1390.htm [accessed January 2013].

Kopras, E..J. 2012. Cyanides and nitriles. Pp. 1-52 in Patty's Toxicology. New York: John Wiley & Sons.

Leeser, J.E., J.A. Tomenson, and D.D. Bryson. 1990. A Cross-sectional Study of the Health of Cyanide Salt Production Workers. Report No. OHS/R/2. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Lewis, T.R., W.K. Anger, and R.K. Te Vault. 1984. Toxicity evaluation of subchronic exposures to cyanogen in monkeys and rats. J. Environ. Pathol. Toxicol. Oncol. 5(4-5):151-163.

Maehly, A.C., and A. Swensson. 1970. Cyanide and thiocyanate levels in blood and urine of workers with low-grade exposure to cyanide. Int. Arch. Arbeitsmed. 27(3):195-209.

McNerney, J.M., and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 2(21):121-124.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard…. Occupational Exposure to Hydrogen Cyanide and Cyanide Salts (NaCN, KCN, and Ca(CN)2). U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/docs/1970/77-108.html [accessed Apr. 7, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Cyanogen. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0161.html [accessed Apr. 5, 2014].

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: The National Academies Press.

Rieders, F. 1971. Noxious gases and vapors. I: Carbon monoxide, cyanides, methemoglobin, and sulfhemoglobin. Pp. 1180-1205 in Drill's Pharmacology in Medicine, 4th Ed., J.R. DePalma, ed., New York: McGraw-Hill.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

APPENDIX A

DERIVATION OF AEGL VALUES FOR CYANOGEN

Derivation of AEGL-1 Values

The AEGL-1 values for hydrogen cyanide were adopted as AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). The no-observed effect level for irritation in humans was 8 ppm for 6 min. Ocular and nasal irritation was noted at the next highest concentration tested (16 ppm). If that study were used as the basis for deriving AEGL-1 values for cyanogen, the point-of-departure would be 8 ppm. An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be applied because the study was conducted in humans. Thus, the threshold for irritation would be 2.7 ppm. Time scaling of that concentration would not be appropriate, because the critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because human data on exposures to cyanogen for durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective for both irritation and potential systemic cyanide effects.

10-min AEGL-1:	2.5 ppm
30-min AEGL-1:	2.5 ppm
1-h AEGL-1:	2.0 ppm
4-h AEGL-1:	1.3 ppm
8-h AEGL-1:	1.0 ppm

Derivation of AEGL-2 Values

AEGL-2 values for cyanogen were derived by taking one-third of the respective AEGL-3 values (see below), because there were no data on cyanogen consistent with an AEGL-2 end point. That approach is justified by the steep concentration-response relationship (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]).

10-min AEGL-2:	150 ppm ÷ 3 = 50 ppm
30-min AEGL-2:	50 ppm ÷ 3 = 17 ppm
1-h AEGL-2:	25 ppm ÷ 3 = 8.3 ppm
4-h AEGL-2:	13 ppm ÷ 3 = 4.3 ppm
8-h AEGL-2:	13 ppm ÷ 3 = 4.3 ppm

Derivation of AEGL-3 Values

Key study:	McNerney, J.M., and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 2(21):121-124.
Toxicity end point:	Concentrations of cyanogen causing no deaths in rats is 1,530 ppm for 10 min (extrapolated from Figure 1 of paper by McNerney and Schrenk [1960]); 500 ppm for 30 min; and 250 ppm for 1 h.
Time scaling:	None
Uncertainty factors:	3 for interspecies differences; a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen. However, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, 4.3 ppm for 4 h, and 4.3 ppm for 8 h. Humans exposed at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984].) 3 for intraspecies variability; considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats

	exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]), which implies limited intraindividual variability.
Modifying factor:	2; applied to the 1-h AEGL-3 value to derive the 4- and 8-h AEGL-3 values. That approach was used because time scaling using the equation $C^n \times t = k$, with n = 1, would yield 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.
Calculations:	
10-min AEGL-3:	1,530 ppm ÷ 10 = 150 ppm
30-min AEGL-3:	500 ppm ÷ 10 = 50 ppm
1-h AEGL-3:	250 ppm ÷ 10 = 25 ppm
4-h AEGL-3:	25 ppm ÷ 2 = 13 ppm
8-h AEGL-3:	25 ppm ÷ 2 = 13 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CYANOGEN

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)

Data adequacy: The AEGL-1 values for hydrogen cyanide (NRC 2002) were adopted as the AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If AEGL-1 values were derived from the cyanogen data, the no-observed effect level for irritation in humans would be 8 ppm for 6 min. Ocular and nasal irritation was noted at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be applied because the study was conducted in humans. Thus, the threshold for irritation would have been 2.7 ppm. Time scaling of that concentration would not be appropriate, because the critical effects (ocular and nasal irritation) are a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because human data on exposures to cyanogen for durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective for both irritation and potential systemic cyanide effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)

Data adequacy: The data on cyanogen were inadequate for deriving AEGL-2 values, so the values were estimated by taking one-third of the AEGL-3 values. That approach is supported by steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min (McNerney and Schrenk1960).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

Reference: McNerney, J.M. and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 2(21):121-124.

Test species/Strain/Sex/Number: Rat; albino; male; 6/group

Exposure route/Concentrations/Durations: Inhalation, 250-4,000 ppm for 7.5-120 min.

Effects: Lethality

Concentration (ppm)	Duration (min)	Mortality
4,000	7.5	3/6
4,000	15	6/6
2,000	7.5	0/6
2,000	15	6/6
1,000	15	0/6
1,000	30	6/6
500	30	0/6
500	45	6/6
400	45	0/6
400	60	6/6
250	60	0/6
250	120	4/6

End point/Concentration/Rationale: Experimental concentrations causing no deaths in rats used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. The 10-min point-of-departure of 1,530 ppm was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper, the 30-min exposure at 500 ppm was the point-of-departure for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was the point-of-departure for the 1-h AEGL-3 value.

Uncertainty factors/Rationale: Total uncertainty factor was 10.
Interspecies: 3, a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen. However, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, 4.3 ppm for 4 h, and 4.3 ppm for 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984]).
Intraspecies: 3, considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]), which implies limited intraindividual variability.

Modifying factor: 2, applied to the 1-h AEGL-3 value to derive the 4- and 8-h AEGL-3 values. That approach was used because time scaling using the equation $C^n \times t = k$, with n = 1, would yield 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: Performed to determine the 10-min point-of-departure from a 7.5-min exposure at 2,000 ppm. Time scaling was performed using the equation $C^n \times t = k$ equation, with n = 1 (default value when extrapolating to longer durations) to derive a value protective of human health (NRC 2001).
Data adequacy: Sparse data set. Support from repeated-exposure studies.

APPENDIX C

CATEGORY PLOT FOR CYANOGEN

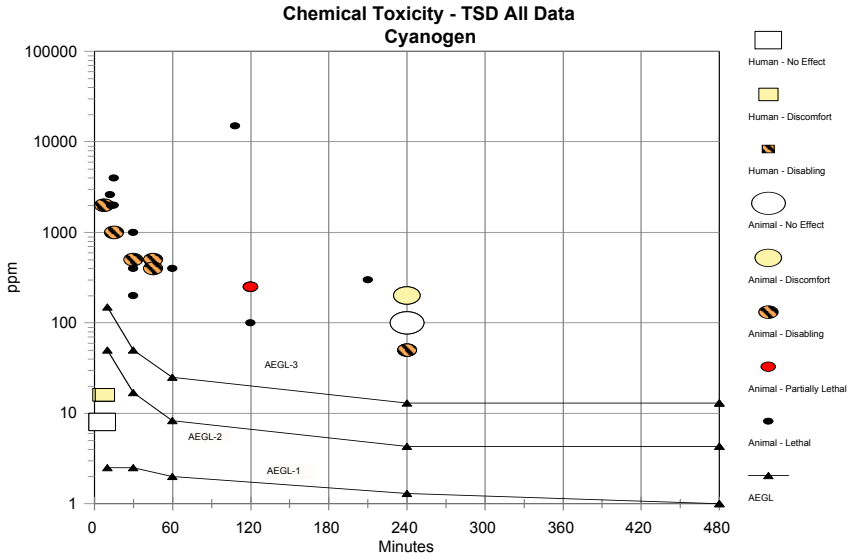


FIGURE C-1 Category plot of toxicity data and AEGL values for cyanogen.

TABLE C-1 Data Used in the Category Plot for Cyanogen

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				2.5	10	AEGL	
AEGL-1				2.5	30	AEGL	
AEGL-1				2.0	60	AEGL	
AEGL-1				1.3	240	AEGL	
AEGL-1				1.0	480	AEGL	
AEGL-2				50	10	AEGL	
AEGL-2				17	30	AEGL	
AEGL-2				8.3	60	AEGL	
AEGL-2				4.3	240	AEGL	
AEGL-2				4.3	480	AEGL	
AEGL-3				150	10	AEGL	
AEGL-3				50	30	AEGL	
AEGL-3				25	60	AEGL	
AEGL-3				13	240	AEGL	
AEGL-3				13	480	AEGL	
	Rat		1	4,000	7.5	PL	
	Rat		1	4,000	15	3	
	Rat		1	2,000	7.5	2	
	Rat		1	2,000	15	3	
	Rat		1	1,000	15	2	

Rat	1	1,000	30	3	
Rat	1	500	30	2	
Rat	1	500	45	2	
Rat	1	400	45	2	
Rat	1	400	60	3	
Rat	1	250	120	PL	
Mouse	1	2,600	12	3	Assumes all dead/worst case scenario.
Mouse	1	15,000	108	3	Assumes all dead/worst case scenario.
Cat	1	300	210	3	Assumes all dead/worst case scenario.
Cat	1	400	30	3	Assumes all dead/worst case scenario.
Rabbit	1	100	120	3	Assumes all dead/worst case scenario.
Rabbit	1	200	30	3	Assumes all dead/worst case scenario.
Rabbit	1	2,000	13	3	Assumes all dead/worst case scenario.
Rabbit	1	100	240	0	Questionable data point.
Rabbit	1	200	240	1	Questionable data point.
Cat	1	50	240	2	Questionable data point.
Human	1	8	6	0	
Human	1	16	6	1	
Human	1	16	8	1	

Categories: 0 = no effect, 1 = discomfort, 2 = disabling, PL = partial lethality, 3 = lethal.

APPENDIX D

DERIVATION OF HYDROGEN CYANIDE AEGL-1 VALUES AND COMPARISON OF HYDROGEN CYANIDE AND CYANOGEN AEGL VALUES

HYDROGEN CYANIDE AEGL-1 VALUES (NRC 2002)

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Key reference: Leeser, J.E., J.A. Tomenson, and D.D. Bryson. 1990. A cross-sectional study of the health of cyanide salt production workers. Report No. OHS/R/2, ICI Central Toxicology Laboratory, Alderley Park, Cheshire, U.K.
Supporting references:
(1) El Ghawabi, S.H., M.A. Gaafar, A.A. El-Saharti, S.H. Ahmed, K.K. Malash, and R. Fares. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br. J. Ind. Med. 32(3):215-219.
(2) Grabois, B. 1954. Exposure to hydrogen cyanide in processing of apricot kernels. Monthly Review NY Department of Labor 33:33-36.
(3) Maehly, A.C., and A. Swensson. 1970. Cyanide and thiocyanate levels in blood and urine of workers with low-grade exposure to cyanide. Int. Arch. Arbeitsmed. 27(3):195–209.
(4) Hardy, H.L., W.M. Jeffries, M.M. Wasserman, and W.R. Waddell. 1950. Thiocyanate effect following industrial cyanide exposure - report of two cases. New Engl. J. Med. 242: 968-972.

Test species/Strain/Number:
Occupational exposures/63 employees, mean age 44.7 (Leeser et al. 1990)
Occupational exposures/36 workers (El Ghawabi et al. 1975)
Occupational exposures/five factories (Grabois, 1954)
Occupational exposures/94 workers (Maehly and Swensson, 1970)
Occupational exposures/factories (Hardy et al. 1950)

Exposure route/Concentrations/Durations: Inhalation/geometric mean exposure of ≤1 ppm (range, 0.01-3.3 ppm; personal samplers), up to 6 ppm (area samples)/mean service years, 16.5 (Leeser et al. 1990); Inhalation/average exposure 8 ppm/5-15 years (El Ghawabi et al. 1975); Inhalation/5 ppm/unknown (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970).

Effects: No exposure related adverse symptoms or health effects (surveys and medical examinations taken in spring and fall of year) (Leeser et al. 1990); mild headache, other symptoms (El Ghawabi et al. 1975); no effects reported (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970).

End point/Concentration/Rationale: 8 ppm from the El Ghawabi et al. (1975) study; 5 ppm from the Hardy et al. (1950), Grabois (1954), and Maehly and Swensson (1970) studies; or 1 ppm from the Leeser (1990) study, were considered no-adverse-effect to mild effect concentrations for an 8-h work day. The NRC adjusted the chronic 8 ppm value of El Ghawabi et al. (1975) to a 1-h exposure for healthy adults.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable
Intraspecies: 3, no specific susceptible populations were identified in monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals including newborns. Application of the uncertainty factor to the El Ghawabi et al. (1975; as adjusted by the NRC) and Grabois (1954) data results in a value close to the 8-h 1 ppm concentration in the Leeser et al. (1990) study. The uncertainty factor was not applied to the Leeser et al. (1990) 1 ppm concentration as it is the lowest no-observed-adverse-effect level.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Because of the long-term exposure duration of the key studies, the conservative time-scaling value of n = 3 ($k = 480\ ppm^3$-min) was applied when scaling to shorter exposure durations. The starting point for time scaling was an 8-h concentration of 1 ppm.

Data adequacy: The preponderance of data from the key studies support an 8-h no effect concentration of 1 ppm. The Leeser et al. (1990) study encompassed subjective symptoms as well as extensive medical examinations. The occupational monitoring study of El Ghawabi et al. (1975) in which it is believed that workers inhaling a mean concentration of 8 ppm may suffer mild headaches support the safety of the derived values. The values are also supported by a NIOSH (1976) report in which 5 ppm was identified as a no-effect concentration in the Grabois et al. (1954) occupational study. Additional monitoring studies support the values.

COMPARISON OF AEGL VALUES FOR CYANOGEN AND HYDROGEN CYANIDE

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1					
Cyanogen	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
Hydrogen cyanide	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
AEGL-2					
Cyanogen	50 ppm	17 ppm	8.3 ppm	4.3 ppm	4.3 ppm
Hydrogen cyanide	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3					
Cyanogen	150 ppm	50 ppm	25 ppm	13 ppm	13 ppm
Hydrogen cyanide	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

4

Epichlorohydrin[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Kowetha Davidson (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Richard Thomas (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Epichlorohydrin is a colorless liquid at room temperature; its vapor is explosive when mixed with air. It has a sweet, pungent or chloroform-like odor. Epichlorohydrin has many uses, but it is used primarily in the manufacture of epoxy resins.

Most humans would not detect the odor of epichlorohydrin at concentrations below 10 ppm. The odor recognition level for epichlorohydrin is about 25 ppm; however, odor detection levels reported in the literature range from 0.08-25 ppm. The level of distinct odor awareness for epichlorohydrin is 46 ppm. No reports of human deaths from exposure to epichlorohydrin were found. Epichlorohydrin is irritating to mucous membranes, causing burning of the eyes, nose, and pharynx in humans. A few breaths or a 30-min exposure at high (unknown) concentrations have caused irritation to eyes, throat, and respiratory tract and gastrointestinal disturbances that may be delayed in onset. Irreversible respiratory and hepatic damage, but no renal damage, have been observed in humans. Humans exposed to epichlorohydrin at 20 ppm for 1 h experienced burning of the eyes and nose; 40 ppm for less than 2 h caused throat irritation, 68 ppm for 2 min was irritating to the pharynx, and 100 ppm was reported to be intolerable and potentially associated with pulmonary edema and renal damage. Exposure to epichlorohydrin at 136 ppm for 2 min was irritating to the eyes and pharynx and caused a cooling sensation in the eyes and mouth.

Inhalation exposure of laboratory animals (rats, mice, and hamsters) to epichlorohydrin causes effects similar to those reported for humans. In acute lethality studies, death was caused by effects on the respiratory center of the central nervous system and severe respiratory irritation manifested as pulmonary hemorrhage and edema. Death usually occurred a few hours or a few days after exposure. Before death, the animals showed signs of cyanosis, muscle relaxation of the extremities, gasping, labored breathing, depressed or increased respiration, lethargy, fine tremors, and clonic convulsions. In addition, animals showed degenerative lesions of the nasal epithelium and kidneys and damage to the lower respiratory tract. Evidence of nasal irritation and renal lesions also were seen after acute inhalation exposure to epichlorohydrin at nonlethal concentrations.

AEGL-1 values were derived from the no-effect level (17 ppm) for irritation in four subjects exposed to epichlorohydrin vapor for 2 min (Kobernick et al. 1983). The total uncertainty factor was 10; a factor of 10 was applied to account for intraspecies variability. Although mild irritation experienced by humans would most likely be confined to the nasal passages and eyes, a factor of 10 was used to provide sufficient protection for asthmatic individuals. Adjusting the point-of-departure by 10 yields an AEGL value of 1.7 ppm. That concentrations was used for all of the AEGL durations because the irritant effects of epichlorohydrin are not expected to become more severe with time at that concentration. The AEGL-1 value is below the level of odor recognition (25 ppm) and the level of odor awareness (46 ppm). Therefore, odor is not a factor for early warning of exposure to epichlorohydrin.

The available human and animal studies reporting nonlethal effects were not suitable for deriving AEGL-2 values. Therefore, AEGL-2 values were derived by reducing the AEGL-3 values by a factor of 3; that approach is used when a steep concentration-response curve is observed. The AEGL-2 value of 53 ppm for a 30-min exposure was also used for the 10-min exposure, because concentrations of 100 ppm or higher may cause pulmonary edema and renal damage.

The 10-min, 30-min, and 1-h AEGL-3 values were based on the 1-h rat LC_{01} (lethal concentration, 1% lethality) of 721 ppm (Dietz et al. 1985). A total uncertainty factor of 10 was applied. A factor of 3 was selected for interspecies differences on the basis of LC_{50} values for rats, mice, guinea pigs, and rabbits, which showed little variability among species. A factor of 3 was applied for intraspecies variability, on the basis of mechanistic information and information on occupational exposures. Epichlorohydrin is an epoxide and direct alkylating agent. These effects are likely involved in the observed irritation and systemic toxicity, and are not expected to vary considerably in the population. In addition, use of higher total uncertainty factor 30 would result in an 8-h AEGL-3 value of 6.6 ppm. That concentration is inconsistent with occupational data; exposures to epichlorohydrin at 15-54 ppm were apparently not life-threatening (Pet'ko et al. 1966 [as cited in NIOSH 1976]; de Jong et al. 1988). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 0.87. The

value of the exponent n was derived from rat LC_{50} (lethal concentration, 50% lethality) values for 1-, 4-, 6-, and 8-h exposures.

The 4- and 8-h AEGL-3 values were based on the 6-h rat LC_{01} of 274 ppm (Laskin et al. 1980). The same uncertainty factors and time-scaling method were the same as those used to derive the 10-min, 30-min, and 1-h AEGL-3 values.

Two inhalation studies in rats found squamous cell carcinomas of the nasal cavity after exposure to epichlorohydrin vapor. The studies showed that short-term exposure at high concentrations were more effective in inducing neoplasms than lifetime exposure at low concentrations. AEGL values calculated from the cancer unit risk for epichlorohydrin are 14,000, 4,500, 2,300, 560, and 280 ppm for 10-min, 30-min, 1-h, and 4-h, to 8-h exposures, respectively. Those values are for risks of 1 in 10,000 (10^{-4}), the level of risk most relevant for emergency exposure and response purposes. The concentrations greatly exceed values for AEGL-2 and AEGL-3. The AEGL values for epichlorohydrin are presented in Table 4-1.

1. INTRODUCTION

Epichlorohydrin is a colorless liquid at room temperature that is flammable (Berdasco and Waechter 2012). It is very reactive with metals such as zinc and aluminum, anhydrous metal halides, strong acids and bases, and alcohol-containing materials; it attacks steel in the presence of moisture (WHO 1984). Epichlorohydrin has a sweet, pungent or chloroform-like odor (Berdasco and Waechter 2012). Additional chemical and physical properties of epichlorohydrin are presented in Table 4-2.

Epichlorohydrin is manufactured at three sites in Louisiana and Texas. Epichlorohydrin is also manufactured in Thailand (ABC-Thailand, Ltd. 2013), France (Solvay 2011), and China (Alibaba 2013; ZSITC 2013). Epichlorohydrin is primarily used in the manufacture of epoxy and phenoxy resins (ACGIH 2001). It is also used in the synthesis of glycerol, and in the production of surface active agents, pharmaceuticals, insecticides, agricultural chemicals, textile chemicals, coatings, adhesives, ion-exchange resins, solvents, plasticizers, glycidyl esters, ethynyl-ethylenic alcohols, and fatty-acid derivatives. It is used as a solvent in the rubber and paper industries (Santodonato et al. 1980).

Epichlorohydrin is a bifunctional alkylating epoxide (Laskin et al. 1980). It causes severe irritation and sensitization when the liquid comes in contact with the skin (Berdasco and Waechter 2012); contact dermatitis has been reported after occupational exposure to epichlorohydrin (HSE 1991). Severe ocular irritation, skin irritation, and delayed contact skin sensitization have been found in animals after topical application of undiluted or diluted epichlorohydrin (Berdasco and Waechter 2012). Epichlorohydrin is moderately toxic by the oral route with LD_{50} (lethal dose, 50% lethality) values of 90-238 mg/kg in rats, guinea pigs, and mice (Berdasco and Waechter 2012).

The database that can be used to derive AEGL values for epichlorohydrin consists of acute and repeat-exposure inhalation studies in multiple species and a carcinogenicity study in rats.

TABLE 4-1 AEGL Values for Epichlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	No-effect level for irritation (Kobernick et al. 1983).
AEGL-2 (disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)	Three-fold reduction of AEGL-3 values, except for 10 min.
AEGL-3 (lethal)	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)	Lethality threshold (Dietz et al. 1985; Laskin et al. 1980)

TABLE 4-2 Physical and Chemical Data on Epichlorohydrin

Parameter	Value	Reference
Synonyms	2-(Chloromethyl) oxirane; 1-chloro-2,3-epoxypropane; 3-chloro-1,2-epoxypropane; α-epichlorohydrin	HSDB 2009
CAS registry no.	106-89-8	HSDB 2009
Chemical formula	C_3H_5ClO	HSDB 2009
Molecular weight	92.53	HSDB 2009
Physical state	Colorless liquid	HSDB 2009
Melting point	-25.6°C	HSDB 2009
Boiling point	117.9°C	HSDB 2009
Density (vapor)	3.29	HSDB 2009
Solubility	65.9 g/L of water at 25°C; miscible with ether, alcohol, chloroform, trichloroethylene, carbon tetrachloride	HSDB 2009
Vapor pressure	16.4 mm Hg at 25°C	HSDB 2009
Flammability limits	3.8% volume to 21% volume in air	HSDB 2009
Concentration in saturated air	1.7% at 25°C	HSDB 2009
Flash point (open cup)	40.6°C	Sienel et al. 2000
Log K_{ow}	0.45	HSDB 2009
Henry's Law constant	3.0×10^{-5} atm-m^3/mol at 25°C	HSDB 2009
Conversion factors	1ppm = 3.78 mg/m^3 1 mg/m^3 = 0.265 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available on the lethality of inhaled epichlorohydrin in humans.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

AIHA (1989) reported the range of odor threshold values for epichlorohydrin of 0.08-12 ppm, and Ruth (1986) reported a range of 50-80 mg/m^3 (13-21 ppm). Kobernick et al. (1983) reported that four subjects detected an at 17 ppm, and two identified the odor as epichlorohydrin. Amoore and Hautala (1983) reported an odor detection level of 0.93 ppm for humans. Berdasco and Waechter (2012) reported a mean odor threshold of 10 ppm and an odor recognition level of 25 ppm. The odor threshold during and after a 5-min exposure of unconditioned personnel to epichlorohydrin was 10-12 ppm for 50% of the subjects and 25 ppm for 100% of the subjects (Shell Oil Co. 1977). Shell Oil Co. (1977) also reported that epichlorohydrin is not detected by its odor at 5 ppm, the permissible exposure limit established by the Occupational Safety and Health Administration (29 CFR 1910.100 [2012]). The level of odor awareness determined by the method of Ruijten et al. (2009) for epichlorohydrin is 46 ppm.

2.2.2. Experimental Studies, Case Reports, and Anecdotal Data

Anecdotal information on effects of epichlorohydrin in humans has been reported in various sources. In a toxicology book, a chapter stated that humans exposed to epichlorohydrin vapor at 20 ppm for 1 h experienced burning of the eyes and nasal mucosa, that exposure at 40 ppm caused ocular and throat irritation that lasted about 48 h, and that 100 ppm was intolerable to man, with potential for pulmonary edema and renal lesions (Lefaux 1968). The statements were attributed to an individual (C.U. Dernehl) without a specific reference. Lefaux (1968) also indicated that chronic low-level exposure caused fatigue, gastrointestinal pain, conjunctivitis, and profuse nasal discharge, citing another individual (I. Sax). The anecdotal information was repeated in later references, including that of Wexler (1971). In another book chapter, Deichmann and Gerarde (1969) reported that humans exposed to epichlorohydrin at 40 ppm for less than 2 h experienced throat irritation; no data or citation was provided to support the statement. Enterline et al. (1990) reported that during the early years (assumed to be 1948-1955) of epichlorohydrin use and production, concentrations of the chemical at a Shell chemical facility were “sufficiently high to be a source of irritation (10-20 ppm)”; the publication did not specify whether exposure concentrations were measured in that range or assumed to be in that range on the

basis of worker reports of irritation. In another book chapter on epoxy compounds, Berdasco and Waechter (2012) reported that marked nasal and ocular irritation occurred only at epichlorohydrin concentrations exceeding 100 ppm; no background or reference for this statement was provided. In a toxicity and safety bulletin on epichlorohydrin (prepared in 1977 and submitted to the U.S. Environmental Protection Agency [EPA] under TSCA Section 8ECP in 1992), Shell Oil Co. (1977) reported that overexposure to epichlorohydrin vapor is manifested first by complaints of ocular, nasal, and throat irritation and possibly sneezing and bleeding of the nose in more serious cases. On the basis of industrial experience, Shell Oil Co. (1977) noted that no cases of serious pulmonary injury or systemic toxicity had been observed during the manufacture or handling of epichlorohydrin, and ocular conditions resulting from exposure to the vapor or contact with liquid epichlorohydrin were not serious and caused no loss of vision. No information on exposure conditions or concentrations was provided. In a summary of warning properties, the bulletin stated that "one report indicated eye and nose irritation only at levels exceeding 100 ppm while another stated that 40 ppm at the site of a spill caused immediate eye, nose, and throat irritation"; references were not provided for these statements.

Two case reports of accidental human exposure (Schultz 1964; NIOSH 1976) were identified in the available literature; neither included measurement or estimation of exposure concentrations. Schultz (1964) reported a case of irreversible hepatic and respiratory damage caused by accidental exposure of a worker to epichlorohydrin. A 39-year-old man took several deep breaths of a substance stored in a container under pressure that was later identified as epichlorohydrin. Initial symptoms included slight burning of the eyes and throat that increased in sensation along with a gradual swelling of the face, malaise, vomiting, and severe headache several hours later. He experienced shortness of breath and a feeling of suffocation the following night (probably more than 24 h after the accident). Clinical examination about 2 days after the accident showed inflammation of mucous membranes in the upper respiratory tract and a painfully enlarged liver, slight jaundice, increased serum bilirubin, and positive urine urobilinogen. Five and 8 months after the accident, clinical findings included bronchial changes in the right lung, elevated blood pressure, and evidence of abnormal liver function. Two years after the accident, the patient complained of nonspecific epigastric pain; a clinical examination showed pronounced fatty liver, abnormal liver function, and chronic asthmatic bronchitis. The fatty liver and chronic asthma-like bronchitis were attributed to exposure to epichlorohydrin because there were no preexisting conditions related to these findings. There was no evidence of renal damage.

NIOSH (1976) reported on a case of a 53-year-old worker exposed to a high but unknown concentration of epichlorohydrin for 30 min (written communication by Thoburn, May 1976, no additional citation information). Several hours after exposure he experienced burning of the nose and throat, cough, chest congestion, runny nose, eye tenderness, and headache followed by nausea. The man was hospitalized briefly, and the symptoms diminished within 3-4 days;

however, he reported more frequent upper-respiratory-tract infections followed by a productive cough. Clinical tests showed that the residual volume was increased by 40% (suggesting air trapping in the lungs) and arterial pO_2 of 77 mm Hg instead of 96 mm Hg. The report did not state how long after exposure these symptoms persisted.

NIOSH (1976) also reviewed a Russian study (Pet'ko et al. 1966, as cited in NIOSH 1976) of worker health in a facility producing epichlorohydrin. Workers were generally exposed at concentrations of 3.1-5.5 ppm, but concentrations during a mechanical failure reached about 55 ppm. NIOSH indicated that the study did not report the sampling method, and no further information on the sampling or analyses that resulted in these concentrations was provided by NIOSH (1976). Apart from two cases of dermatitis, Pet'ko et al. (1966, as cited in NIOSH 1976) concluded that medical examination of 49 men and 33 women in the epichlorohydrin-production areas showed no changes attributable to occupational exposure.

In the single controlled-exposure study, four human subjects were exposed to epichlorohydrin at concentrations of 17, 68, or 136 ppm for 2 min in a 6.5-ft^3 chamber (Kobernick et al. 1983). Three subjects exposed at 68 ppm reported no irritating effect, and one reported irritation to the pharynx. Two subjects exposed at 136 ppm reported a cooling sensation in the eyes and mouth and two reported irritation to the eyes or pharynx.

2.2.3. Epidemiologic Studies

Epidemiologic studies of epichlorohydrin have involved the analysis of mortality or morbidity data from two cohorts from the Shell Oil Company in its Texas and Louisiana facilities, both of which produced epichlorohydrin (Enterline et al. 1990; Tsai et al. 1990, 1996). Dow Chemical workers engaged in epichlorohydrin production also have been the subject of mortality studies (Olsen et al. 1994).

Tsai et al. (1990) conducted a study on the prevalence of morbidity among workers engaged in the manufacture of epichlorohydrin from January 1, 1981, to December 31, 1988. Morbidity included all illnesses resulting in work absence of more than 5 days. The only illness showing a significantly elevated standardized morbidity ratio involved skin and subcutaneous tissue, particularly in workers classified as having light to moderate exposure to epichlorohydrin. Light- and moderate-exposure categories (defined as the 95% upper confidence limit of the geometric mean of personal air samples) were >0.1 ppm but ≤0.5 ppm, and >0.5 ppm but ≤1.0, respectively. The investigators noted that skin conditions were more often associated with causes unrelated to epichlorohydrin exposure, such as physical trauma and poison ivy.

Although a concern existed for a possible association between exposure to epichlorohydrin and heart disease among workers engaged in the manufacture or use of epichlorohydrin, a statistically significant increase in the standard mor-

tality ratio (SMR) was not observed. However, Enterline et al. (1990) reported an increase in the SMR for heart disease among workers classified as having heavy exposure compared with workers in the low-exposure category. There was no significant increase compared with the reference population (local white males). Epichlorohydrin concentrations for the exposure categories were not reported, but concentrations during the early production years were high enough to cause irritation. In a subsequent study of the same cohort followed for an additional 10 years, Tsai et al. (1996) found a nonsignificant increase in the SMRs for heart disease among workers with moderate to heavy exposure to epichlorohydrin compared with those having no to light exposure.

Other epidemiologic studies have been conducted on workers with potential exposure to epichlorohydrin, but none demonstrated an association between epichlorohydrin and mortality experience due to any cause (Barbone et al. 1992, 1994; Olsen et al. 1994). Barbone et al. (1992, 1994) did not report exposure concentrations. Olsen et al. (1994) estimated that the 8-h time-weighted average (TWA) concentration of epichlorohydrin was below 1 ppm at an epoxy resin plant, and was 1-5 ppm at a glycerine department between 1957-1969; concentrations after 1970 were estimated to be less than 1 ppm. The publication did not report how the TWA estimates were derived, but did indicate that industrial hygiene records were reviewed.

2.3. Developmental and Reproductive Toxicity

Milby et al. (1981) investigated the association between fertility, as measured by sperm count and hormone concentrations, and potential exposure to epichlorohydrin at the two Shell chemical plants that produced epichlorohydrin. The control group consisted of workers from the same plant who had no known exposure to epichlorohydrin or any chemical known to be toxic to the testes. The investigators found no association between potential exposure to epichlorohydrin and sperm count or levels of testosterone, luteinizing hormone, or follicle stimulating hormone. Exposures in one of the plants (sampling for epichlorohydrin was conducted at only one) were categorized into four groups. Three of the four categories were exposures less than 1.0 ppm, and the fourth was 1.0 ppm or greater; no information on maximum exposure concentration was provided.

Venable et al. (1980) compared the fertility status, as measured by several sperm parameters (including sperm count/cc and percent normal forms) and hormone concentrations, in 64 men employed in the three-carbon production units at Dow Chemical (Texas Division) with 63 men who had not worked with chlorinated hydrocarbons for at least 5 years prior to the study. None of the parameters showed statistically significant differences that could be attributed to work environment or exposure to epichlorohydrin. The 8-h TWA exposures to epichlorohydrin were estimated to be less than 1 ppm in all groups; no further exposure information was provided.

2.4. Carcinogenicity

EPA's Integrated Risk Information System assessment of carcinogenicity for epichlorohydrin, which was revised in 1994, considered the human data to be inadequate for evaluating the carcinogenicity of epichlorohydrin and classified epichlorohydrin as a B2 carcinogen (probable human carcinogen) on the basis of sufficient evidence of carcinogenicity in animals (EPA 1994).

More recent epidemiologic studies than those evaluated by the EPA have been conducted on cohorts with potential exposure to epichlorohydrin during its manufacture or use. Barbone et al. (1994) reported an association between occupational exposure to epichlorohydrin, particularly acute exposure, and central nervous system neoplasms (in decedents and living). However, only four cases had potential exposure to epichlorohydrin and three of the four were also potentially exposed to anthraquinone dye intermediates or azo dyes. Other epidemiologic studies produced no convincing evidence of an association between potential occupational exposure to epichlorohydrin and cancer at any site including lung cancer (Enterline et al. 1990; Tsai et al. 1990, 1996; Barbone et al. 1992; Olsen et al. 1994).

IARC (1999) reviewed and evaluated the epidemiologic and supporting data on epichlorohydrin and concluded that human data were inadequate for evaluating carcinogenicity of the chemical. It classified epichlorohydrin as 2A, *probably carcinogenic in humans*, on the basis of adequate evidence of carcinogenicity in animals.

2.5. Genotoxicity

Kučerová et al. (1977) analyzed the peripheral lymphocytes of 35 workers occupationally exposed to epichlorohydrin for 1 or 2 years (exposure range was 0.13-1.32 ppm [0.5-5.0 mg/m^3]) and compared the frequency of chromosomal aberrations with the preemployment frequency. They observed that the overall percentage of chromosomal aberrations (chromatid and chromosome beaks and exchanges; gaps excluded) were statistically significantly increased after 1 year (1.91/100 cells) and 2 years of employment (2.96/100 cells) compared with the preemployment frequency (1.42/100 cells). The frequency of chromosome breaks in lymphocytes was 2.17/100 cells or 3.26/100 cells after employment for 1 or 2 years, respectively, compared with the preemployment frequency of 1.60/100 cells. The overall percentage of cells with aberrations was 1.91% or 2.69% after employment for 1 or 2 years, respectively, compared with 1.37% before employment.

Sram et al. (1980) conducted a follow-up analysis of peripheral lymphocytes in 28 workers (23 were previously analyzed by Kučerová et al. [1977]) occupationally exposed to epichlorohydrin for an additional 2 years (total exposure duration of 4 years). Matching subjects from the working and general population were analyzed as control groups. Sram et al. (1980) found 3.12% aberrant

cells (breaks and exchanges; gaps excluded) in exposed workers compared with 2.06% for the matching controls and 1.33% for the general population. All comparison groups were significantly different from each other including the two controls. The percentage of aberrant cells in the subgroup of 23 workers studied by Kučerová et al. (1977) was 3.02%. Sram et al. (1980) reported that the concentration of epichlorohydrin in the work environment was about 0.26 ppm (1 mg/m^3). Sram et al. (1983) conducted a follow-up study on the workers after an additional 4 years of exposure (total of 8 years); this group consisted of 33 workers and included the 28 previously analyzed by Sram and coworkers. The concentration of epichlorohydrin decreased from 0.26 ppm to 0.10 ppm. The percentage of aberrant cells in exposed workers decreased to 2.00%; the percentage in the matching controls was 1.68%. Chromatid and chromosome breaks were observed, but not exchanges.

Picciano (1979) compared the frequency of chromosome aberrations in peripheral lymphocytes from 93 workers occupationally exposed to epichlorohydrin with the frequency in 75 preemployment individuals (control). The frequencies of chromatid and chromosome breaks, marker chromosomes (rings, dicentrics, and translocations), severely damaged cells, and abnormal cells were increased in exposed workers. The greatest increases were in frequencies of cells with more than 12 chromatid breaks, cells with more than four chromosome breaks, the percent of individuals with more than 12 abnormal cells, and the percent of individuals with severely damaged cells. The investigators did not report the intensity or duration of exposure to epichlorohydrin.

de Jong et al. (1988) reported increased chromosome aberrations in the lymphocytes of workers involved in the manufacture of epichlorohydrin, ethylene oxide (ETO), and propylene oxide at one plant and epichlorohydrin and allyl chloride at another. They found increases in the percentage of aberrant cells (includes gaps) of 1.46% and 0.93% for the two worker groups, respectively, compared with 0.11% for a control population. The increase in the frequency of aberrations in exposed workers relative to the control population could not be attributed to epichlorohydrin alone.

Shell Oil Co. (1994) reported significant increases in the frequencies of sister chromatid exchanges, cells with high frequencies of sister chromatid exchanges, and chromosome aberrations and aberrant cells in workers exposed to epichlorohydrin. Worker exposures were measured to be 0.11-0.23 ppm for 11.15 h each day and higher concentrations of 0.19-2.57 ppm during three episodes of 15 min each per day (it is presumed that the authors intended to report 11.25, not 11.15 h, for a total duration of 12 h per day).

Giri (1997) reviewed data on chromosome aberrations in human cultured cells and noted that epichlorohydrin showed positive evidence of clastogenicity in different types of in vitro test systems.

2.6. Occupational Exposure

Concentrations of epichlorohydrin in the work environment of production facilities have ranged from TWA concentration of 0.01 ppm to 15 ppm (0.04 to 57 mg/m^3), as reported by WHO (1984). Citing a Dow Chemical Company monitoring report, NIOSH (1976) reported epichlorohydrin concentrations of 0.10-15.0 ppm for an epoxy-producing unit monitored in 1974, and concentrations of 0.01-4.69 ppm for a glycerin-producing unit monitored in 1975. de Jong et al. (1988) reported epichlorohydrin concentrations at two plants in a Shell petrochemical complex in the Netherlands. At one plant, the mean 4-8 h TWA concentration in 1977 was 6.6 ppm (25 mg/m^3), with a range of <0.03-54 ppm (<0.1-205 mg/m^3); in 1978, the mean was 1.3 ppm (5 mg/m^3), with a range of <0.03-3.17 ppm (<0.1-12 mg/m^3). In the second plant, the mean 4-8 h TWA concentration in 1977 was 1.6 ppm (6 mg/m^3), with a range of <0.03-2.9 ppm (<0.1-11 mg/m^3); in 1978, mean was 0.3 ppm (1 mg/m^3), with a range of <0.03-0.8 ppm (<0.1-3 mg/m^3) (de Jong et al. 1988). According to the National Occupational Exposure Survey (NOES), over 95,000 workers were potentially exposed to epichlorohydrin between 1981 and 1983 (NIOSH 2003). According to the International Information System on Occupational Exposure to Carcinogens (Carex), almost 48,000 workers in 15 European Union nations were exposed to epichlorohydrin between 1990 and 1993 (Kauppinen et al. 1998).

2.7. Summary

No lethality data in humans after acute exposure to epichlorohydrin were available, and data on acute nonlethal effects after acute exposure were limited. The odor detection levels reported in the literature ranged from 0.08 ppm to 25 ppm (Amoore and Hautala, 1983; Kobernick et al. 1983; AIHA 1989; Shell Oil Co. 1977; Berdasco and Waechter 2012).

Anecdotal reports suggest that epichlorohydrin may cause ocular and throat irritation at 10-20 ppm, prolonged ocular and throat irritation at 40 ppm, and pulmonary edema and renal lesions at concentrations greater than 100 ppm (Lefaux 1968; Deichmann and Gerarde 1969; Wexler 1971; Enterline et al. 1990). A more definitive study showed that epichlorohydrin at 68 ppm was irritating to the pharynx in one of four subjects after 2 min, and 138 ppm caused a cooling sensation in the eyes and mouth and irritation to the eyes and pharynx after 2 min (Kobernick et al. 1983). Exposure to epichlorohydrin may also cause sneezing and nosebleed (Shell Oil Co. 1977).

Two case reports of accidental exposure to epichlorohydrin provided evidence that exposure at high concentrations for only seconds (few breaths) or for 30 min caused irritation to the eyes, throat, and respiratory tract, gastrointestinal

disturbances, and irreversible liver damage in one case and irreversible damage to the respiratory tract in both cases (Schultz 1964; NIOSH 1976).

Genetic toxicity studies showed that workers exposed to epichlorohydrin at average concentrations of 0.26 ppm had higher frequencies of aberrant cells and chromosome aberrations in peripheral lymphocytes when compared with unexposed workers or the general population (Sram et al. 1980). However, the unexposed workers also had a higher frequency of chromosome aberrations than the general population (Sram et al. 1980). Occupational exposure to epichlorohydrin had no reproductive effects in human males as determined by sperm count and hormone concentrations (Venable et al. 1980; Milby et al. 1981).

Occupational exposure to epichlorohydrin also has not been associated with any other long-term clinical effects. Workers exposed chronically at low concentration of epichlorohydrin for various durations showed no excess in cause-specific morbidity or mortality due to nonneoplastic or neoplastic diseases (Enterline et al. 1990; Tsai et al. 1990, 1996; Barbone et al. 1992, 1994; Olsen et al. 1994). The epidemiologic data are inadequate for evaluating the carcinogenicity of epichlorohydrin in humans (EPA 1994; IARC 1999).

Taken as a whole, the data on human exposures to epichlorohydrin suggest that chronic exposure at concentrations greater than 10 ppm may be associated with irritation, but that concentrations up to 54 ppm over 4-8 h are unlikely to trigger life-threatening effects (Pet'ko et al. 1966, as cited in NIOSH 1976).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

The literature on the acute and short-term inhalation toxicity of epichlorohydrin is extensive, consisting of lethality data from studies of rats, mice, guinea pigs, rabbits, dogs, hamsters, and cats. In some studies, animals were exposed to epichlorohydrin vapor, whereas in others they were exposed to an aerosol. Exposure conditions were either dynamic or static. Concentrations of epichlorohydrin in the chamber atmospheres were determined analytically in some studies or were calculated on the basis of the flow rate and quantity of test substance delivered to the chamber in others. Single and repeat-exposure studies were considered in the evaluation.

3.1.1. Rats

Berdasco and Waechter (2012) reported 1-h LC_{50} values for epichlorohydrin in male and female rats of 2,165 and 3,617 ppm, respectively (geometric mean = 2,798 ppm). They also reported a 4-h LC_{50} of 500 ppm and 8-h LC_{50} 250 ppm for rats.

In an acute inhalation study by Kobernick et al. (1983), groups of six young male Carworth Farm-Wistar rats were exposed for 5, 10, or 15 min to "essentially saturated" vapor of epichlorohydrin in a dynamic 9-L glass chamber

and were observed for 14 days after exposure. The authors calculated the vapor concentration of epichlorohydrin from material loss and flow rate to be 23,400 ppm; analysis of the chamber concentrations was not undertaken. No rats exposed for only 5 min died within the specified time; five of six rats exposed for 10 min died within 2 days, and all six exposed for 15 min died within 12 h. Gasping was observed during exposure in all groups, and poor condition (indicative of narcosis) was observed in animals exposed for 10 or 15 min. Gross examination showed hemorrhage in the lungs, the severity of which increased with duration of exposure.

Dietz et al. (1985) exposed groups of six male and six female Fischer 344 rats to epichlorohydrin vapor at concentrations of 552, 1,008, 1,970, or 3,995 ppm for 1 h; additional groups of six male rats were exposed at 2,865 or 3,275 ppm for 1 h. The animals were exposed in 2.6-m^3 stainless-steel and glass Rochester-type inhalation chambers operated under dynamic conditions. Chamber concentrations were determined by gas chromatography seven times during each 1-h exposure. The animals were maintained for a 14-day observation period. Body weights were recorded at 2- to 3-day intervals. Necropsies were performed on all animals with special attention given to the eyes and nasal cavities. The mortality response is summarized in Table 4-3. No deaths occurred during exposure, but one female each died on days 2 and 3 after exposure at 1,970 ppm and all females exposed at 3,995 ppm died within 1 day of exposure. All males exposed at 3,995 ppm died 1-4 days after exposure. The LC_{50} values were 3,617 ppm for males, 2,165 ppm for females, and 2,369 ppm for the combined sexes. Clinical signs were observed in all exposure groups. During exposure at 552 and 1,008 ppm, the animals huddled in their cages and completely shut their eyes; no other signs were observed. At 1,970 ppm or higher, clinical signs included ocular and nasal irritation, respiratory difficulty, and secretion of a reddish, porphyrin-like material on the facial area. At 3,275 and 3,995 ppm, hyperactivity was observed during exposure followed by lethargy after exposure, and rats exposed at 3,995 ppm became cyanotic before the end of exposure.

TABLE 4-3 Mortality in Fisher 344 Rats Exposed to Epichlorohydrin Vapor by Inhalation

Concentration		Mortality		
ppm	mg/L	Male	Female	Male + Female
552	2.088	0/6	0/6	0/12
1,008	3.814	0/6	0/6	0/12
1,970	7.453	0/6	2/6	2/12
2,865	10.839	0/6	–	0/6
3,275	12.390	0/6	–	0/6
3,995	15.114	6/6	6/6	12/12

1-h LC_{50} = 3,617 ppm (male); 2,165 ppm (female); 2,369 ppm (combined sexes)

Source: Adapted from Dietz et al. 1985.

Grigorowa et al. (1974) exposed groups of 20 male albino rats to epichlorohydrin vapor at calculated concentrations of 0.190, 0.390, 0.855, 0.915, or 1.680 mg/L (50, 103, 226, 242, or 444 ppm, respectively) for 4 h in a dynamic exposure chamber. After exposure, one-half the rats were subjected to a temperature of 35°C and relative air humidity of 35-50% for 45 min and all animals were observed for an additional 72 h. The LC_{50}s for rats exposed to epichlorohydrin without and with heat treatment were 2.40 mg/L (635 ppm) and 2.20 mg/L (582 ppm), respectively. Marked hepatic damage, which was enhanced by heat, was observed in exposed animals. Microscopic lesions were observed in the kidneys (proximal tubules), adrenal glands (medulla), and thyroid gland (follicular epithelium); heat exacerbated the toxicity in the adrenal and thyroid glands. Hemorrhage, hyperemia, and edema were observed in the lungs, but subsequent heat treatment had no effect. The investigators did not report the concentrations at which the effects were observed. Data for other measures of toxicity were not presented in a manner meaningful for derivation of acute toxicity values.

In a study conducted by Kimmerle (1967), groups of 10 rats were exposed in a 400-L test chamber to epichlorohydrin evaporated from a petri dish and distributed around the chamber room with a fan. Complete evaporation of the material produced achieved concentrations (calculated) of 132, 331, 661, or 2,646 ppm (0.50, 1.25, 2.50, or 10.00 mg/L, respectively). Each group was exposed for 4 h and observed for 14 days. Five of 10 rats exposed at 661 ppm died within 2-4 days and all 10 rats exposed at 2,646 ppm died within 1-2 days. Symptoms of toxicity (not otherwise described) were observed in all rats at the two highest concentrations, moderate irritation to mucous membranes was observed at 661 ppm, and strong irritation occurred at 2,646 ppm. The 4-h LC_{50} for epichlorohydrin vapor was 741 ppm.

Kobernick et al. (1983) reported a study in which groups of six young or mature (not otherwise specified) Carworth Farm-Wistar rats were exposed to epichlorohydrin vapor at 290 or 580 ppm (calculated concentrations) for 4 h in a dynamic 9-L glass chamber and observed for 14 days. No young or mature rats died after exposure at 290 ppm. No signs of irritation were observed at 290 ppm; the mature females lost weight during the observation period, and slight pulmonary congestion and hemorrhage were observed in all animals. All rats except four mature females died within the first 24 h after exposure at 580 ppm, and the remaining rats died within 3-12 days. Gasping was observed in females exposed at 580 ppm. The LC_{50} was 411 ppm.

In another experiment by Kobernick et al. (1983), six different animal species including rats were exposed to epichlorohydrin vapor for 4 h and observed for 14 days. Male Carworth Farm-Wistar stock rats were exposed at 580 ppm (30 rats) or 1,160 ppm (six rats) in a 193-L hardboard chamber operated under dynamic conditions. Vapor concentrations were calculated from the amount of material used, the flow rate, and the ratio of analytic to nominal concentrations (1.16) determined from a repeat-exposure study. Fifteen of 30 rats died after exposure at 580 ppm and all six rats died after exposure at 1,160 ppm.

The LC_{50} was 580 ppm. Irritation of mucous membranes was observed in all animals, and increased respiration, lethargy, and labored breathing were observed in all animals that died. Gross examination showed hemorrhagic lungs in the animals that died and in a few survivors. The investigators described only a few specific effects for each species. The difference in the mortality response of rats exposed in the 9-L glass chamber and the 193-L hardboard chamber was attributed to the generation of heat by the rats and the smaller surface:volume ratio that prevented adequate heat loss in the smaller chamber.

Slott et al. (1990) observed no overt signs of toxicity in 48 male F344 rats during or after exposure to epichlorohydrin vapor at 100 ppm for 4 h. This was a reproduction study that showed a transient effect on sperm motility (see Section 3.3).

Groups of 20 Sprague-Dawley rats (8-week old males) were exposed to epichlorohydrin vapor in 128-L or 1.3-m^3 dynamic chambers at concentrations of 283, 303, 339, 369, 421, or 445 ppm for 6 h, and were observed for 14 days (Laskin et al. 1980). Chamber atmospheres were sampled every 30 min and analyzed by a spectrophotometric procedure. Acute respiratory irritation with hemorrhage and severe edema of the lungs along with elevated lung:body weight ratios occurred at concentrations of 339 ppm and higher. Mortality in each exposure group was 0/20, 1/20, 1/20, 15/20, 16/20, and 17/20, respectively; the LC_{50} reported was approximately 360 ppm.

Weil et al. (1963) reported that four of six rats (unspecified strain and sex) died after exposure to epichlorohydrin at 250 ppm for 8 h. No additional details were provided.

Groups of 20 male Wistar rats were exposed under dynamic conditions to atomized (aerosolized) epichlorohydrin in a mixture of lutrol (ethylene glycol) and alcohol (1:1) at epichlorohydrin concentrations of 296, 638, 1,038, or 1,440 mg/m^3 4 h, and were observed for 2 weeks (Kimmerle 1967). The concentrations of epichlorohydrin in the chamber atmospheres were determined spectrophotometrically on air samples reacted with hydroxylamine. The number of deaths and time-to-death were concentration related. One rat exposed at 638 mg/m^3 died on day 7, nine exposed at 1,038 mg/m^3 died on days 1 and 6, and all 20 exposed at 1,440 mg/m^3 died on days 1 and 4. Symptoms of toxicity were observed in all rats exposed to concentrations of 638 mg/m^3 or higher. The LC_{50} reported was 960 mg/m^3.

Groups of 10 or 20 rats inhaled epichlorohydrin aerosols for 1 h in a 2-m^3 chamber, and were observed for 14 days (Kimmerle 1967). Chamber concentrations were maintained by spraying epichlorohydrin dissolved in a mixture of lutrol (ethylene glycol) and alcohol (1:1) into the chamber every 30 min. Concentrations were analyzed by spectrophotometry of air samples collected through three consecutive U tubes cooled to -60°C. The average analytic concentrations were 70, 204, 324, 500, and 3,350 mg/m^3. The method for analyzing chamber atmospheres was not reported. The chamber also contained three rabbits, five guinea pigs, and 20 mice during each exposure. Eleven of 20 rats exposed at 3,350 mg/m^3 died 3-8

days after exposure. Symptoms of toxicity were observed at 324 and 3,350 mg/m^3, but not at 500 mg/m^3. The LC_{50} was 3,073 mg/m^3.

In the next series of studies, rats were repeatedly exposed to epichlorohydrin aerosols or vapor for different durations. Groups of 10 rats were exposed by inhalation to epichlorohydrin evaporated from a petri dish at concentrations of 66 and 661 ppm (250 or 2,500 mg/m^3, respectively), 4 h/day for 5 days (Kimmerle 1967). No rats died and no symptoms of toxicity were observed at 66 ppm, but nine of 10 rats died and symptoms of toxicity were observed in all rats exposed at 661 ppm. No signs of irritation of mucous membranes were reported.

Groups of young sexually mature male and female Carworth Farm-Wistar rats (23-32 per group) were exposed to calculated concentrations of epichlorohydrin vapor in 550-L hardboard chambers operated under negative pressure (Kobernick et al. 1983). Each group was exposed for 7 h/day, 5 days/week to epichlorohydrin at 0, 68, or 136 ppm for 45 exposures; 0, 17, or 43 ppm for 91 exposures; or 0, 5, or 8 ppm for 90 exposures. The incidences, severity, and types of effects increased as the exposure concentration increased from 5 ppm to 136 ppm. Repeated exposure to epichlorohydrin resulted in death only at 136 ppm (10 rats) and 68 ppm (5 rats). Reduced weight gain, renal toxicity, and urinary coproporphyrins were observed at 68 and 136 ppm. No definitive signs of renal toxicity occurred at less than 43 ppm; however, weight gain was depressed and coproporphyrins were found in the urine at 43 ppm.

In the another repeat-exposure study submitted by Kimmerle (1967), groups of 20 Wistar rats inhaled atomized epichlorohydrin in a mixture of lutrol (ethylene glycol) and alcohol (1:1) at epichlorohydrin concentrations of 32, 63, or 340 mg/m^3 for 4 h/day for 5 days, and were observed for 2 weeks. No animals died at 32 mg/m^3; two rats died at 63 mg/m^3, and four rats died at 340 mg/m^3. Symptoms of toxicity were observed in all rats exposed at 63 and 340 mg/m^3.

3.1.2. Mice

In 1941, Freuder and Leake reported the effects of inhaled epichlorohydrin on groups of 20-30 white mice exposed to epichlorohydrin vapors in a dynamic glass chamber at calculated concentrations of 8,300 or 16,600 ppm (0.35 or 0.70 mmol/L) for 30 min or at 2,370 ppm (0.10 mmol/L) for 60 min. All concentrations caused immediate signs of irritation to the nose and eyes, but the intensity was greater at 16,600 ppm. No additional signs were observed in mice exposed at 2,370 ppm for 1 h. Bristling of the hairs was observed almost immediately at 8,300 and 16,600 ppm and delirium (term not defined) was observed after 3 min at 16,600 ppm and after 14 min at 8,300 ppm. All animals exposed at 2,370 ppm for 60 min survived, but all mice exposed at 8,300 and 16,600 ppm for 30 min died within the first 24 h after exposure. Nno subsequent deaths occurred; however, the duration of the observation period was not reported. Before death, mice exhibited signs of cyanosis followed by muscular relaxation of the extremities, stiffening of the tail, fine tremors, depressed respiration, clonic convulsion, and finally respiratory arrest.

Grigorowa et al. (1974) exposed groups of 20 male albino mice to epichlorohydrin vapor at calculated concentrations of 50, 103, 226, 242, and 444 ppm (190, 390, 855, 915, or 1,680 mg/m^3, respectively) for 2 h in a dynamic exposure chamber as described for rats (see Section 3.1.1). The LC_{50}s for mice exposed to epichlorohydrin without and with subsequent heat treatment were 794 ppm and 1,058 ppm, respectively. Marked hepatic damage (enhanced by heat) and renal damage (not affected by heat) was observed in exposed animals. Hemorrhages, hyperemia, and edema were observed in the lungs; subsequent heat treatment had no effect on severity of the pulmonary lesions. The investigators did not report the concentrations at which the effects were observed.

In a study reported by Kobernick et al. (1983), groups of 6 or 11 male mice (strain and age not specified) were exposed to epichlorohydrin vapor at calculated concentrations of 290, 580, or 1,160 ppm for 4 h in 193-L hardboard chambers operated under dynamic conditions. The concentrations were verified in a repeat-exposure study and adjusted by the ratio of 1.16 for analytic:nominal concentrations. The mortality response was 0/11, 0/6, and 6/6 at 290, 580, and 1,160 ppm, respectively, resulting in an LC_{50} of 820 ppm. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of mucous membranes was observed in animals that survived.

In a study reported by Kimmerle (1967), groups of 20 male CF_1 mice were exposed for 4 h to epichlorohydrin vapor at 132, 331, 661, or 2,646 ppm. The vapor was generated by evaporation of epichlorohydrin from a petri dish as described for rats (see Section 3.1.1). No deaths, symptoms of toxicity (not otherwise described), or irritation of mucous membranes were observed at 132 and 331 ppm, but one death occurred at 661 ppm and 100% died after exposure at 2,646 ppm. Toxicity was observed in all mice exposed at 661 and 2,646 ppm, moderate irritation was observed at 661 ppm, and strong irritation occurred at 2,646 ppm. The LC_{50} was 1,153 ppm for the 4-h exposure.

All mice exposed by inhalation to epichlorohydrin at 687 ppm (10-min RC_{50}, see Section 3.2.3) for 6 h either died or were moribund within 72 h (Buckley et al. 1984). Groups of 16-24 (exact number per group not reported) male Swiss-Webster mice were exposed to epichlorohydrin vapor for 6 h. The chamber atmosphere was analyzed at least once per hour by infrared spectrophotometry. The mice were necropsied immediately or 72 h after exposure, and the heads and respiratory tracts were examined microscopically. At necropsy, a serous exudate was observed in the nose, and the abdomen was distended by gas probably caused by attempts to mouth breathe. Microscopic examination of the nasal tissue showed moderate exfoliation, erosion, ulceration, and necrosis along with minimal inflammation of the respiratory epithelium of the nose. Moderate ulceration and necrosis were observed in the olfactory epithelium. Mice exposed to epichlorohydrin vapor at 687 ppm also showed epithelial exfoliation, hyperplasia, and squamous metaplasia of the trachea and slight exfoliation of the bronchial epithelium with diffuse neutrophil infiltration.

Groups of 20 male CF_1 mice were exposed to epichlorohydrin aerosols for 1 h in a 2-m^3 chamber containing multiple species as described for rats in Section 3.1.1 (Kimmerle 1967). Chamber concentrations were maintained by spraying epichlorohydrin dissolved in a mixture of lutrol (ethylene glycol) and alcohol (1:1) into the chamber every 30 min. The average analytic concentrations were 70, 204, 324, 500, and 3,350 mg/m^3. One mouse exposed at 324 mg/m^3 and one exposed at 3,350 mg/m^3 died 7 days and 1 day, respectively, after exposure. Symptoms of toxicity were observed in 19 mice exposed at 324 mg/m^3 and all 20 mice exposed at 3,350 mg/m^3, but in none exposed at 500 mg/m^3.

Lawrence et al. (1972, 1974) calculated the LT_{50} (time to 50% lethality) for male ICR mice (number and age not reported) exposed to epichlorohydrin vapor in an 8.75-L glass chamber operated under dynamic conditions. Chamber concentrations of epichlorohydrin were calculated from the amount of material lost and the air flow. The LT_{50} was 9.13 min at a concentration of 71,890 mg/m^3. The study author presented little detail regarding experimental procedures.

Groups of 20 male CF_1 mice were exposed repeatedly to epichlorohydrin at 66 and 661 ppm (Kimmerle 1967). Epichlorohydrin was evaporated from a petri dish placed in a 400-L chamber as described for rats (see Section 3.1.1). The mice were exposed for 4 h/day for 5 days. No mice died after exposure at 66 ppm but 18 died after exposure at 661 ppm. Symptoms of toxicity were observed in all mice exposed at 661 ppm, but signs of irritation to mucous membranes were not observed in this group.

3.1.3. Guinea Pigs

Groups of four or six male guinea pigs (unspecified strain and age) inhaled epichlorohydrin vapor in a 193-L dynamic chamber at calculated concentrations of 290, 580, or 1,160 ppm for 4 h and were observed for 14 days (Kobernick et al. 1983). No deaths occurred at 290 ppm; two of six guinea pigs exposed at 580 ppm died and all four guinea pigs exposed at 1,160 ppm died. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of mucous membranes was observed in surviving animals. The LC_{50} was 651 ppm for the 4-h exposure.

Kimmerle (1967) reported on a study in which groups of five male Purlbright guinea pigs were exposed for 4 h to epichlorohydrin vapor at 132, 331, 661, or 2,646 ppm. Epichlorohydrin was evaporated from a petri dish as described for rats (see Section 3.1.1). All guinea pigs died after exposure at 2,646 ppm and four in each group died after exposure at 331 and 661 ppm. Moderate and strong irritation of mucous membranes was observed at 661 and 2,646 ppm, respectively, and symptoms of toxicity were observed at concentrations of 331 ppm and higher.

Groups of five male Purlbright guinea pigs were exposed to epichlorohydrin aerosols at concentrations of 70, 204, 324, 500, and 3,350 mg/m^3 for 1 h and at 171 and 498 mg/m^3 for 4 h in a 2-m^3 chamber containing multiple species as described for rats (see Section 3.1.1) (Kimmerle 1967). Two guinea pigs died

after exposure at 3,350 mg/m^3 for 1 h and three died after exposure at 498 mg/m^3 for 4 h. Symptoms of toxicity were observed in all guinea pigs exposed at 324 and 3,350 mg/m^3 for 1 h and at 498 mg/m^3 for 4 h, but no symptoms of toxicity were observed in the group exposed at 498 mg/m^3 for 1 h.

In a repeat-exposure study by Kimmerle (1967), groups of five male Purlbright guinea pigs were exposed by inhalation to epichlorohydrin vapor at concentrations of 66 and 661 ppm (250 or 2,500 mg/m^3) in a 400-L chamber as described for the single exposure studies. The guinea pigs were exposed for 4 h/day for 5 days. No deaths occurred at 66 ppm, but four deaths occurred at 661 ppm. Symptoms of toxicity or irritation to mucous membranes were observed in all five guinea pigs exposed at 661 ppm, but not those exposed at 66 ppm.

3.1.4. Rabbits

Groups of three male rabbits (unspecified strain and age) were exposed by inhalation to epichlorohydrin vapor at 290, 580, or 1,160 ppm for 4 h, as described for rats in Section 3.1.1 (Kobernick et al. 1983). Three rabbits exposed at 1,160 ppm and two exposed at 580 ppm died during the 14-day observation period. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of the mucous membranes was observed in surviving animals. The LC_{50} was 516 ppm for the 4-h exposure.

One rabbit each was exposed repeatedly to epichlorohydrin vapor at concentrations of 66 or 661 ppm (250 or 2,500 mg/m^3). The vapor was generated by evaporation of epichlorohydrin from a petri dish in a 400-L chamber (Kimmerle 1967). The rabbits were exposed for 4 h/day for 5 days. The rabbit exposed at 66 ppm survived and showed no symptoms of toxicity or irritation of the mucous membranes. The rabbit exposed at 661 ppm showed symptoms of toxicity and died 2 days after exposure.

Groups of 10 male New Zealand white rabbits were exposed to epichlorohydrin vapor at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (John et al. 1983b). The exposure was during the premating period for a reproduction study. Three rabbits died or were killed moribund during the 10-week exposure period, two at 50 ppm and one at 25 ppm. Suppurative rhinitis and diffuse pneumonia or pleuritis were observed during necropsy of the 50-ppm group and pulmonary abscesses were observed in the 25-ppm group. Surviving animals showed similar gross lesions, as well as microscopic evidence of inflammation and erosion of the nasal epithelium characterized by focal erosion and metaplasia at 50 ppm.

3.1.5. Dogs

In an acute inhalation study, one dog (male or female) per group inhaled epichlorohydrin vapor at concentrations of 72, 290, 580, or 1,160 ppm for 4 h, and were observed for 14 days (Kobernick et al. 1983). Two dogs (one male and one female) were exposed similarly at 145 ppm. Exposure conditions were as

described for rats in Section 3.1.1. The investigators noted that the dogs exposed at 145, 290, 580, or 1,160 ppm regurgitated a small dose of an herbicide (no explanation provided). The dogs exposed at 580 and 1,160 ppm developed a slightly hemorrhagic dura mater and died. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in animals that died (580 and 1,160 ppm) and mucous membrane irritation was observed in surviving animals (290 ppm and higher). Gross examination showed hemorrhagic lungs in animals that died.

3.1.6. Cat

One cat each was exposed repeatedly to epichlorohydrin vapor at concentrations of 66 and 661 ppm for 4 h/day for 5 days, and were observed for an unspecified period after the last exposure (Kimmerle 1967). The chamber atmospheres were generated by evaporation of the test substance in a 400-L chamber using a fan. The cat exposed at 66 ppm survived treatment and showed no symptoms of toxicity or irritation of mucous membranes, whereas the cat exposed at 661 ppm showed symptoms of toxicity and died the third day after exposure.

3.1.7. Summary of Lethality Data

Lethality data are summarized in Tables 4-4 and 4-5.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

One monkey (unspecified species) was exposed to epichlorohydrin at a concentration of 290 ppm for 4 h (Kobernick et al. 1983). The exposure conditions were the same as described for rats in Section 3.1.1. This animal survived the 14-day observation period; some mucous membrane irritation was observed. Gross examination revealed a blood clot in the midsagittal section of the brain. The monkey was suspected of having tuberculosis unrelated to treatment.

Two rhesus macaque monkeys exposed repeatedly to epichlorohydrin at 21 ppm for 7 h/day, 5 days/week for 90 exposures, had damage in the lungs and kidneys (Kobernick et al. 1983). The animals were exposed in a 550-L hardboard dynamic chamber. The chamber concentrations were determined by taking occasional air samples, analyzing the samples using a spectrophotometric procedure, and averaging all concentrations measured during exposure. Serum enzyme and hematologic parameters were not affected by exposure to epichlorohydrin. Microscopic findings in the lungs included bronchial irritation, mucous hypersecretion, subacute bronchitis, focal proliferation of alveolar septa, and hemosiderin deposits in the lungs. Microscopic findings in the kidneys included focal cloudy swelling of proximal convoluted tubules. A control group was not described.

TABLE 4-4 Summary of Acute Lethality Data in Laboratory Animals Exposed to Epichlorohydrin Vapor

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments	Reference
Rats/F344/males and females	1 h	3,617 ppm (males) 2,165 ppm (females) (552-3,995 ppm)	No deaths in males at ≤3,275 ppm or in females at ≤1,008 ppm.	Dietz et al. 1985
Rats/Sprague-Dawley/males	6 h	360 ppm (283-445 ppm)	LC_{Lo} = 303 ppm (1/20); respiratory irritation and severe lung edema at ≥339 ppm.	Laskin et al. 1980
Rats/Carworth Farm-Wistar/males and females	4 h	441 ppm (290-580 ppm)	Pulmonary irritation, but no deaths at 290 ppm; deaths at 580 ppm.	Kobernick et al. 1983
Rats/Carworth Farm-Wistar/males	4 h	580 ppm (580-1,160 ppm)	Deaths at both concentrations; irritation of mucous membranes (all animals) and lethargy, labored breathing, and hemorrhagic lungs in animals that died.	Kobernick et al. 1983
Rats/albino/males	4 h	635 ppm (50-444 ppm)	Toxicity in the liver, kidney, lungs, adrenal glands, thyroid gland (concentration not reported)	Grigorowa et al. 1974
Rats/Wistar/males	4 h	741 ppm (132-2,646 ppm)	Irritation at 661 and 2,646 ppm, other symptoms of toxicity not described.	Kimmerle 1967
Rats/Carworth Farm-Wistar/males	5, 10, or 15 min	NA (23,400 ppm)	No deaths after 5 min; 5/6 after 10 min and 6/6 after 15 min; gasping in all groups; hemorrhagic lungs after 10 and 15 min.	Kobernick et al. 1983
Mouse/Swiss-Webster/males	6 h	(RC_{50} = 687 ppm)	All animals dead or moribund within 72 h; moderate degeneration of nasal epithelium (respiratory and olfactory).	Buckley et al. 1984
Mouse/?/males	4 h	820 ppm (290-1,160 ppm)	Deaths only at 1,160 ppm; mucous membrane irritation at all concentrations, lethargy and labored breathing at 1,160 ppm.	Kobernick et al. 1983
Mouse/CF_1/male	4 h	1,153 ppm (132-2,646 ppm)	LC_{lo} = 661 ppm (1/20); moderate mucous membrane irritation, and symptoms of toxicity at ≥661 ppm.	Kimmerle 1967
Mouse/albino/males	2 h	794 ppm (50-444 ppm)	Toxicity in the liver, kidneys, and lungs (concentration not reported).	Grigorowa et al. 1974

(Continued)

TABLE 4-4 Continued

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments	Reference
Mouse/albino/?	1 h	(2,370 ppm)	Signs of irritation, no deaths (observation period not reported).	Freuder and Leake 1941
Mouse/albino/?	30 min	(8,300, 16,000 ppm)	8,300 ppm: 100% mortality (20/20) in 24 h.	Freuder and Leake 1941
Guinea pigs/?/males	4 h	651 ppm (290-1,160 ppm)	LC_{lo} = 580 ppm (2/6); mucous membrane irritation at all concentrations; labored breathing and lethargy in non-survivors.	Kobernick et al. 1983
Guinea pigs/ Purlbright/males	4 h	275 ppm (132-2,646 ppm)	Deaths and symptoms of toxicity at ≥331 ppm; moderate to strong irritation at ≥661 ppm.	Kimmerle 1967
Dogs/males and females	4 h	(72-1,160 ppm)	Death at 580 and 1,160 ppm.	Kobernick et al. 1983
Rabbit/?/males	4 h	516 ppm (290-1,160 ppm)	Deaths at 580 (2/3) and 1,160 ppm (3/3); mucous membrane irritation at all concentrations; labored breathing and lethargy in non-survivors.	Kobernick et al. 1983

TABLE 4-5 Summary of Acute Lethality Data in Laboratory Animals Exposed to Epichlorohydrin Atmospheres Generated from Aerosols

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments
Rats/Wistar/males	1 h	3,073 mg/m^3 (70-3,350 mg/m^3)[a]	No deaths at ≤500 mg/m^3; signs of toxicity at ≥324 and 3,350 mg/m^3.
Rats/Wistar/males	1 h	ND (825 or 1,375 mg/m^3)[a]	No deaths; signs of toxicity at 1,375 mg/m^3.
Rats/Wistar/males	4 h	960 mg/m^3 (296-1,440 mg/m^3)[a]	No deaths at 296 mg/m^3; signs of toxicity at ≥638 mg/m^3.
Rats/Wistar/males	4 h	ND (171 or 498 mg/m^3)[b]	No deaths or signs of toxicity.
Mouse/CF_1/males	1 h	ND (70-,350 mg/m^3)[a]	1 death (1/20) at 324 and 3,350 mg/m^3; signs of toxicity at ≥324 and 3,350 mg/m^3.
Guinea pig/males	1 h	ND (70-3,350 mg/m^3)[a]	2 deaths (2/6) at 3,350 mg/m^3; signs of toxicity at 324 and 3,350 mg/m^3.
Guinea pig/males	4 h	ND (171 or 498 mg/m^3)[a]	4 deaths (4/6) at 498 mg/m^3; signs of toxicity at 498 mg/m^3.

[a]Exposures generated by aerosolizing epichlorohydrin dissolved in a mixture of ethylene glycol and water (1:1, v:v). Concentrations analyzed by spectrophotometry of air samples collected through three consecutive U tubes cooled to -60°C.
[b]Exposures generated by aerosolizing epichlorohydrin without a solvent. Concentrations analyzed as described above.
Abbreviations: LD50, lethal concentration, 50% lethality; ND, not determined.
Source: Data from Kimmerle 1967.

3.2.2. Rats

Gardner et al. (1985) determined the concentration of inhaled epichlorohydrin that caused a 50% decrease in the respiratory rate (RD_{50}) of rats exposed to epichlorohydrin vapor; the study also was reported by Haskell Laboratory (1980). The RD_{50} model is based on stimulation of the trigeminal nerve upon contact with an airborne irritant followed by inhibition of respiration (Kane et al. 1979). Groups of four 8-week old male Crl-CD® rats were exposed head-only to epichlorohydrin vapor for 15 min, and time respiratory rates were determined using a plethysmograph. Exposure concentrations were 101.6, 363.2, 394.1, 642.7, 662.9, 913.7, and 1,963 ppm. Chamber atmospheres were sampled every 2-3 min and analyzed by gas chromatography. The maximum decrease in the respiratory rate occurred after the 15-min exposure; partial recovery was noted during the first 5 min postexposure. A clear nasal discharge was produced in rats

exposed at the highest concentration (1,963 ppm), and a slight weight loss occurred in all groups during the first 24 h postexposure. The authors did not report the duration of the postexposure observation period. The calculated RD_{50} for rats was 1,342 ppm. The maximum decrease in the respiratory rate at each concentration is presented in Table 4-6. A clear dose-response was not observed.

Robinson et al. (1995) found no histopathologic evidence of hepatic or renal damage in rats exposed to epichlorohydrin vapor at a concentration of 100 ppm for 4 h. Groups of male Fischer 344 rats were exposed to epichlorohydrin vapor in 422-L dynamic flow through inhalation chambers. The rats were either young adults (about 65 or 73 days old; six per group) or adults (96 days old; 11 per group). At least 14 grab samples per 4-h exposure period were taken from a single point near the geometric center of the chamber and analyzed for epichlorohydrin by infrared spectrophotometry. Controls were sham exposed. The study focused on various parameters of hepatic and renal damage on days 1, 2, and 3 postexposure. There was no evidence of hepatic damage in young rats as determined by organ weight, serum chemistry, or histopathologic examination. The only statistically significant change potentially relevant to renal toxicity was a 5% increase in relative kidney weight in exposed young adult rats on day 1 after exposure, which was not observed on days 2 or 3 after exposure, or at any time in adult rats. Furthermore, serum creatinine levels were unaffected by epichlorohydrin exposure in young or adult rats and blood urea nitrogen (BUN) levels decreased (15%) in adult rats on the day of exposure, but not at any other time (an increase in BUN would be indicative of possible renal toxicity). Collectively, the observations provide no consistent evidence of renal toxicity in young or adult rats. Robinson et al. (1995) did not conduct clinical observations of the rats during or after exposure.

Groups of 60 male white rats were exposed to epichlorohydrin vapors at concentrations of 1.9, 5.3, or 93 ppm (7, 20, or 350 mg/m^3) for 4 h, and they were evaluated on day 0 or 1 after exposure (Shumskaya et al. 1971). Exposure conditions (chamber size and mode of operation) and duration of the observation period were not reported by the investigators. The results showed increased hepatic and renal weights and decreased lung and spleen weights. Evaluation of urine showed increased production, decreased specific gravity, increased output of chlorides, and elevated excretion of protein at all concentrations. Bromosulfophthalein (BSP) removal from the blood was decreased at all three concentrations on the day of exposure. BSP was used to assess liver function, particularly biliary function, at the time this study was conducted.

TABLE 4-6 Reduction in Respiratory Rate of Rats Exposed to Epichlorohydrin

	Concentration (ppm)						
	101	363.2	394.1	642.7	662.9	913.7	1,963
Decease in respiratory rate, %	6 ± 15	33 ± 9	32 ± 7	52 ± 7	36 ± 19	54 ± 8	52 ± 21

In a 14-day inhalation toxicity study, groups or five male and five female Fischer rats were exposed to epichlorohydrin vapor at concentrations of 0, 10, 25, 50, 100, or 200 ppm for 6 h/day, 5 days/week, in an 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial Bio-Test Laboratories 1977a). The analytic concentrations were 0, 9.7, 23.0, 48.8, 97.3, and 209.8 ppm. Clinical signs observed after the first exposure are summarized in Table 4-7. No clinical signs attributed to epichlorohydrin exposure were observed at 10 and 25 ppm. Clinical signs at 50 ppm and higher involved primarily the eyes and respiratory tract. The number of different clinical signs increased as the exposure concentration increased from 50 ppm to 200 ppm. One male and three females died after repeated exposure at 200 ppm for 4-11 days. Gross findings at the end of the study included areas of consolidation in the lungs of two males, pale kidneys in three males and two females, extreme intestinal bloating in one male, and red oral and nasal discharge in one female at 200 ppm.

Groups of 20 male Wistar rats exposed to aerosolized epichlorohydrin (in a 1:1 mixture of alcohol and lutrol) at concentrations of 825 or 1,375 mg/m^3 for 1 h exhibited no symptoms of toxicity at 825 mg/^{3}, but symptoms of toxicity were observed in all rats exposed at 1,375 mg/m^3 (Kimmerle 1967). Symptoms of toxicity were not observed in groups of 10 male Wistar rats exposed to aerosolized epichlorohydrin (without alcohol and lutrol) at concentrations of 171 or 498 mg/m^3 for 4 h.

Ito et al. (1995) conducted a study to determine the biochemical and histopathologic effects of inhaled epichlorohydrin on the kidneys of Wistar rats (10 weeks old rats; sex and number per group not specified). Rats were exposed to epichlorohydrin vapor at 150 ppm for 1 h or 5 ppm for 2 h/day, 6 days/week for a total of 20 exposures. Chamber concentrations were monitored by gas chromatography (no other details provided). The effects in the experimental groups were compared with those of a control group. Body weight in the rat exposed repeatedly at 5 ppm was reduced throughout the exposure period. Pathologic lesions were observed in the kidney after single and repeat exposures. Exposure at 150 ppm caused severe damage to the proximal tubular epithelium of the kidneys. Severe microscopic changes also were observed in epithelial cells (apoptosis) in distal tubules in the kidneys of rats exposed at 150 ppm. Similar but less severe damage occurred after repeat exposures at 5 ppm.

Quast et al. (1979b) conducted a 12-day inhalation study using Fischer 344 and Sprague-Dawley rats (five males and five females per group) exposed to epichlorohydrin vapor at a concentration of 100 ppm for 7 h/day, 5 days/week for a total of nine exposures. The animals were exposed under dynamic conditions in a 4.3-m^3 Rochester-type chamber. Exposure concentrations were determined 3-7 times per day by gas chromatography. Control groups were not placed in a chamber. No signs of significant ocular or nasal irritation were observed during exposure; the animals, however, tended to huddle together and sleep. Transient moist nasal discharge, discoloration around the nasal orifice,

TABLE 4-7 Clinical Signs, Mortality, and Time of Onset in Fischer 344 Rats Exposed by Inhalation to Epichlorohydrin for 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)			
Clinical Signs	10 and 25	50	100	200
Squinting	–	+ (82 min)	+ (28 min)	+ (66 min)
Hypoactivity	–	+ (82 min)	+ (78 min)	+ (66 min)
Head shaking	–	–	+ (178 min)	–
Drooping eyelids	–	–	+ (223 min)	+ (126 min)
Irritated eyes	–	–	–	+ (136 min)
Gasping, intermittent	–	–	–	+ (171 min)
Red nasal discharge	–	–	–	+ (266 min)
Lacrimation	–	–	–	+ (336 min)
Mortality (earliest)	–	–	–	4/10 (4-11 d)

+ clinical signs observed; – no clinical signs observed
Source: Data from Industrial Bio-Test Laboratories 1977a.

sneezing, and rubbing of the nose were observed after each exposure and disappeared before the next exposure. Decreased body size (due to less filled abdominal region), food consumption, and fecal production observed after repeated exposures recovered somewhat over the weekend in the absence of exposures, but reappeared when another round of exposures was initiated. Effects at study termination attributed to epichlorohydrin included gross and histopathologic evidence of damage to nasal turbinates (degeneration, inflammation, hyperplasia, and squamous metaplasia), kidneys (increased weight and slight degeneration), and epididymis (slight change in contents). The kidneys were more affected in males than in females, and Sprague-Dawley rats were more affected than Fischer rats.

Groups of four male and four female albino Wistar rats were exposed under dynamic conditions to atomized epichlorohydrin (in propanol) diluted with air to achieve concentrations of 9, 17, 27, or 56 ppm (Gage 1959). Exposures were for 6 h/day, 5 days/week for 18 or 19 exposures or at 120 ppm repeatedly for 11 exposures. Labored breathing was observed 3 h after initiating the first exposure at 120 ppm. Profuse nasal discharge was observed at 120 ppm, lethargy and weight loss at 56 and 120 ppm, respiratory distress and nasal discharge at 56 ppm, poor general condition at 27-120 ppm, and signs of mild nasal irritation at 27 ppm. Gross and histopathologic evidence of leucocytosis and toxicity were observed in the lung, kidneys, and liver of rats exposed at 120 ppm and evidence of toxicity was found in the lungs at 27 ppm but not at 56 ppm. No rats died after only one exposure, but one rat died after 11 exposures at 120 ppm.

Groups of 30 male and 30 female Sprague-Dawley rats were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (John et al. 1983b). Weight gain was decreased slightly in male and female rats

exposed at 50 ppm. A slight potentiation of spontaneous renal damage and degenerative changes (inflammation, hyperplasia, and metaplasia) in the respiratory epithelium of the nasal cavity were observed at 25 and 50 ppm. The damage was minimal to moderate at 25 ppm and moderate to severe at 50 ppm. All nasal and renal damage was reversed during the 10-week postexposure period. The study was a reproduction study that showed marked transient decreases in fertility in male rats exposed at 25 and 50 ppm.

Groups of 20 male and 20 female Sprague-Dawley and Fischer 344 rats were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 3 months (Quast et al. 1979a). No effects were observed that could be attributed to a single exposure to epichlorohydrin. The most notable microscopic changes observed at the end of the study were inflammatory, degenerative, and reactive changes in the nasal turbinates of male and female rats of both strains exposed at 25 and 50 ppm. Other microscopic changes were observed in the liver and kidneys of males and females of both strains at 50 ppm and in the adrenal gland of males at 50 ppm.

3.2.3. Mice

Kane et al. (1979) determined the RD_{50} in groups of four specific pathogen free Swiss-Webster mice exposed to aerosolized epichlorohydrin head-only for 10 min at different concentrations. The respiratory rate was measured using a plethysmograph. Epichlorohydrin concentrations were determined spectrophotometrically after oxidation of epichlorohydrin with periodic acid. The RD_{50} was 687 ppm (95% confidence limits: 633-748 ppm). The concentrations were reported as ppm, although the exposure atmospheres were generated by aerosolizing epichlorohydrin. Presumably, the animals were actually exposed to vapor produced from the epichlorohydrin aerosol; however, that could not be confirmed from the report.

TABLE 4-8 Clinical Signs, Mortality, and Time of Onset in $B6C3F_1$ Mice Exposed by Inhalation to Epichlorohydrin for up to 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)			
Clinical Signs	10 and 25	50	100	200
Squinting	–	+ (66 min)	+ (78 min)	+ (66 min)
Hypoactivity	–	+ (217 min)	+ (178 min)	+ (126 min)
Drooping eyelids	–	–	+ (223 min)	+ (126 min)
Ruffed fur	–	–	–	+ (306 min)
Gasping	–	–	–	+ (381 min)
Mortality (earliest)	–	–	–	7/10 (6-12 d)

+ clinical signs observed; – no clinical signs observed.
Source: Data from Industrial Bio-Test Laboratories 1977b.

In a 14-day inhalation toxicity study, groups or five male and five female $B6C3F_1$ mice were exposed to epichlorohydrin vapor at concentrations of 0, 10, 25, 50, 100, or 200 ppm for 6 h/day, 5 days/week. The animals were exposed in an 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial Bio-Test Laboratories 1977b). The procedure for analysis of chamber atmospheres was not reported. The analytic concentrations were 0, 9.7, 23.0, 48.8, 97.3, and 209.8 ppm. Clinical signs observed after the first exposure are summarized in Table 4-8. No clinical signs attributed to epichlorohydrin were observed in the 10- and 25-ppm groups. The number of different clinical signs increased as the exposure concentration increased from 50 ppm to 200 ppm. A total of seven deaths occurred (all five females and two males) in the 200-ppm group after day 6. Gross findings were observed only at 200 ppm, and consisted of consolidation in the lungs of one male and two female mice.

Quast et al. (1979b) conducted a 12-day inhalation study using $B6C3F_1$ mice (five males) exposed to epichlorohydrin vapor at a concentration of 100 ppm for 7 h/day, 5 days/week for a total of nine exposures. The animals were exposed under dynamic conditions in a 4.3-m^3 Rochester-type chamber. Exposure concentrations were determined by gas chromatography 3-7 times each day. Five males serving as the control group were not placed in a chamber. No signs of significant ocular or nasal irritation were observed during exposure; the animals, however, tended to huddle together and sleep. Transient moist nasal discharge, sneezing, and rubbing of the nose were observed after exposure; the signs disappeared before the next exposure. Decreases in body size, food consumption, and fecal production observed during the weekday exposures showed recovery over the weekend (no exposures), but the same effects became readily apparent upon initiation of another round of exposures. Effects at study termination attributed directly to epichlorohydrin included gross and histopathologic damage to nasal turbinates (degeneration, inflammation, hyperplasia, and squamous metaplasia) but not to the kidneys or epididymis as observed in rats.

Groups of 20 male and 20 female $B6C3F_1$ mice were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 3 months (Quast et al. 1979a). No effects were observed that could be attributed to a single exposure to epichlorohydrin. The male and female mice, like the rats, had inflammatory, degenerative, and reactive changes in the nasal turbinates at 25 and 50 ppm. Other microscopic changes occurred only in the liver of males and females at 50 ppm.

In a continuous inhalation study, Formin (1966) exposed groups of 15 mice to epichlorohydrin at 0, 0.05, 0.53, or 5.3 ppm (0, 0.2, 2, or 20 mg/m^3) for 98 days. No details were provided regarding the exposure system or analysis of chamber atmospheres. Mice exposed at 0.05 ppm showed no adverse effects. On the first day of exposure, mice exposed at 5.3 ppm were noticeably excited, restless, and fairly active, and then became sluggish and somnolent before showing a gradual improvement. Body weight was 14-19% lower than that of controls by the end of exposure. Additional effects observed after repeated exposure to epichlorohydrin included increased latent reaction period of the motor defense

response to electrical stimulation (central nervous system effect) at 5.3 ppm, transient increase in the number of leukocytes with altered fluorescence at 0.53 and 5.3 ppm, decreased nucleic acids in blood at 0.53 and 5.3 ppm, and increased excretion of coproporphyrin in the urine at 5.3 ppm. Mice exposed at 5.3 ppm also had emphysema, bronchopneumonia, small edematous areas, and loosening and swelling of the adventitia of blood vessels in the lungs; foci of interstitial hemorrhages and venous congestion of the heart; cloudy swelling of the convoluted tubular epithelium of the kidney; and severe neuronal lesions in the medulla oblongata, cornu ammonis (hippocampus), and cerebellum of the central nervous system. No morphologic effects were seen in mice exposed at 0.05 and 0.53 ppm.

3.2.4. Hamsters

In a 14-day inhalation toxicity study, groups or five male and five female Syrian hamsters were exposed to epichlorohydrin vapor at concentrations of 0, 25, 50, 100, 200, or 400 ppm for 6 h/day, 5 days/week, in a 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial Bio-Test Laboratories 1977c). The procedure for analysis of chamber atmospheres was not reported. The analytic concentrations were 0, 23.0, 48.8, 97.3, 209.8, and 364.3 ppm. Clinical signs observed after the first exposure are summarized in Table 4-9. The number of different clinical signs observed in each group increased as the exposure concentration increased from 50 ppm to 400 ppm. Salivation was observed before exposure was initiated. A total of four males and all five females exposed at 200 ppm died between day 4 and termination of the study; all males and females exposed at 400 ppm died between day 3 and 6 of the study. Gross findings included areas of lung consolidation in four male hamsters and one female hamster, intestinal bloating in three females, and pale kidneys in one female.

3.2.5. Rabbits

Groups of three male and female rabbits were exposed under static conditions to atomized epichlorohydrin sprayed every 30 min into a 2-m^3 chamber for a single exposure of 1 or 4 h; the animals were observed for 14 days (Kimmerle 1967). Average exposure concentrations determined analytically were 70, 204, 324, 500, and 3,350 mg/m^3 for 1 h or 171 and 498 mg/m^3 for 4 h. Other species were housed in the same chamber. Symptoms of toxicity were observed only at 3,350 mg/m^3.

Gage (1959) exposed two New Zealand white rabbits to epichlorohydrin at 35 ppm or at 16 ppm reduced to 9 ppm after the second day. The animals were exposed daily for 6 h/day, 5 days/week for a total of 20 exposures. Signs of nasal irritation were observed at 35 and 16 ppm, but not at 9 ppm. Gross and histopathologic examinations showed no signs of toxicity.

TABLE 4-9 Clinical Signs, Mortality, and Time of Onset in Syrian Hamsters Exposed by Inhalation to Epichlorohydrin for up to 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)				
Clinical Signs	25	50	100	200	400
Squinting	–	+ (82 min)	+ (78 min)	+ 66 (min)	+ (40 min)
Hypoactivity	–	+ (262 min)	+ (178 min)	+ (126 min)	+ (100 min)
Drooping eyelids	–	–	+ (223 min)	+ (126 min)	+ (100 min)
Salivation	–	–	+ (268 min)	+ (126 min)	+ (-20 min)
Excitation, intermittent	–	–	–	+ (216 min)	+ (-30 min)
Gasping, intermittent	–	–	–	+ (381 min)	–
Gasping, not intermittent	–	–	–	+ (426 min)	+ (145 min)
Mouth pouches full or full of saliva	–	–	–	+ (306 min)	+ (240 min)
Very heavy labored breathing	–	–	–	–	+ (240 min)
Mortality (earliest)	–	–	–	9/10 (7-14 d)	2/10 (3-6 d)

+ clinical signs observed; – no clinical signs observed
Source: Data from Industrial Bio-Test Laboratories 1977c.

3.2.6. Dogs

Two dogs were exposed to epichlorohydrin vapor at a concentration of 21 ppm for 7 h/day, 5 days/week for 90 exposures (Kobernick et al 1983). The animals were exposed in 550-L hardboard chambers operated under dynamic conditions. The chamber atmosphere was sampled occasionally and analyzed using a spectrophotometric procedure. One dog lost a small amount of weight. Microscopic examination showed hemosiderin deposits and diffuse congestion of alveolar capillaries in both dogs, bronchial hypersecretion of mucus in one dog, focal interstitial nephritis in both dogs, diffuse cloudy swelling of the proximal convoluted tubules in one, and centrilobular cloudy swelling in the liver of one dog.

3.3. Developmental and Reproductive Toxicity

In developmental toxicity range finding studies, groups of five or six presumed pregnant rats and groups of five presumed pregnant rabbits were exposed to epichlorohydrin vapor under dynamic conditions at concentrations of 0, 25, 50, or 100 ppm for 7 h/day (Pilny et al. 1979). The rats were exposed on gestation days 6-15 and then killed on day 16, and the rabbits were exposed on gestation days 6-18 and then killed on day 19. At 50 and 100 ppm, female rats gained less weight and had decreased intraabdominal adipose tissue, decreased thymus size, and an increased incidence of pale liver. At 100 ppm, three of six rats had 100% resorptions, one had normal fetuses, and two had no evidence of being

pregnant (no implantation sites). Three rabbits exposed at 100 ppm and one exposed at 50 ppm died at an unknown time. Decreased body weight gain, respiratory tract irritation, pneumonia, and suppurative rhinitis were observed in all rabbits at 50 and 100 ppm. Severe pneumonia was confirmed at necropsy at 50 and 100 ppm and focal pneumonia in one rabbit at 25 ppm.

No maternal or developmental effects attributed to epichlorohydrin were observed in groups of 43-46 pregnant Sprague-Dawley rats exposed to epichlorohydrin vapor at concentrations of 0, 2.5, or 25 ppm for 7 h/day on gestation days 6-15 (John et al. 1983a). The animals were exposed in a 14.3-m^3 dynamic stainless-steel and glass chamber. Chamber atmospheres were sampled two to seven times per day and analyzed by gas chromatography. Analytic concentrations of epichlorohydrin were 2.5 and 24.6 ppm. Fetuses were harvested by Cesarean section on gestation day 21. Groups of 20-25 New Zealand white rabbits exposed on gestation days 6-18 under the same conditions as the rats and evaluated on gestation day 29 also had no maternal or developmental effects attributed to epichlorohydrin (John et al. 1983a).

John et al. (1983b) examined the effects of inhaled epichlorohydrin on fertility in groups of 30 male and 30 female Sprague-Dawley rats exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (about one spermatogenic cycle), followed by a 10-week postexposure period. A sialodacryadenitis infection (sialoacryadenitis virus is a coronavirus affecting the lacrimal and salivary glands, as well as upper and lower respiratory tracts, of rats) affected both control and exposed groups during weeks 1 and 2. Fertility was assessed during exposure (weeks 2, 4, 7, and 10) and postexposure (weeks 2, 5, and 10) in male rats mated with unexposed females. Fertility in the males of the 25- and 50-ppm groups was significantly reduced during exposure weeks 2-10, as assessed by the number of implantations per unexposed females mated with the exposed males, but was reduced only in the 50-ppm group, as assessed by the percentage of the exposed males impregnating unexposed females. Epichlorohydrin had no effect on the weight or histology of male reproductive organs. Fertility in exposed females was assessed by the ability of the females to produce viable litters after mating with unexposed males. Exposure to epichlorohydrin had no adverse effect on the estrous cycle, pregnancy rate, parturition, litter size, or pup viability. Renal damage and degenerative lesions in the nasal cavity were observed at 25 and 50 ppm (see Section 3.2.2).

Fertility and testicular function were evaluated in groups of 10 male New Zealand white rabbits exposed to epichlorohydrin at 0, 5, 25, or 50 ppm, as described for rats (John et al. 1983b). Semen evaluated prior to exposure, at weekly intervals from week 2 to termination of exposure, and biweekly during the postexposure period showed no effects on sperm motility, viability, concentration, or morphology. No adverse effects were observed on fertility assessed in unexposed does mated with the exposed males. Light microscopic examination of spermatozoa revealed no abnormalities. Death, pulmonary lesions, and nasal lesions occurred at 25 and 50 ppm (see Section 3.1.4).

Slott et al. (1990) evaluated the effect of inhaled epichlorohydrin on sperm motility and testicular function in male Fischer-344 rats. Groups of 48 rats (90 days old) were exposed to epichlorohydrin at 0 or 100 ppm for 4 h, and sperm motility and other parameters were evaluated immediately after exposure and on days 1, 2, 6, and 14 postexposure. The exposed rats showed no overt signs of toxicity. No adverse effects were observed on testicular or epididymal weight, caudal epididymal sperm counts, or testicular spermatid counts in rats exposed to epichlorohydrin. Evaluation of sperm motility showed transient decreases (-14% to -20% of control values) in progressive (straight line) and path (smoothed curvilinear) velocities of caudal epididymal sperm on day 1 postexposure only. The authors stated that the transient nature of the decrease and the small magnitude of the effect suggested that epichlorohydrin vapor at 100 ppm did not have a significant adverse effect on reproductive parameters.

3.4. Carcinogenicity

Only two inhalation carcinogenicity studies were found. Laskin et al. (1980) reported on studies in rats exposed to epichlorohydrin vapor for a total of 30 exposures or for their entire lifetime. In the first study, two groups of male Sprague-Dawley rats were exposed to epichlorohydrin vapor at 100 ppm for 6 h/day, 5 days/week for 30 exposures, and observed until death. One group had 40 rats and the other had 100 rats. In the second study, groups of 100 male Sprague-Dawley rats were exposed to epichlorohydrin vapor at 10 or 30 ppm for 6 h/day, 5 days/week until death. A total of 150 male rats served as controls; 100 were sham-exposed and 50 were untreated. It was unclear whether each study had separate control groups. Among the 140 animals exposed at 100 ppm for 30 days, 15 developed squamous cell carcinomas in the nasal cavity, two developed a nasal papilloma, and one developed a bronchial papilloma. The first tumor to appear was a carcinoma on day 330. After a lifetime exposure to epichlorohydrin at 30 ppm, one animal had a squamous cell carcinoma of the nasal cavity (at 752 days) and one had a nasal papilloma (at 402 days). No nasal neoplasms developed in animals exposed at 10 ppm. Nonneoplastic respiratory lesions in the 100-ppm group consisted of severe inflammation, suppuration, destruction of the mucous membrane, and mucosal metaplasia of the nasal cavity; severe inflammation in the larynx and trachea; and pulmonary edema, congestion, and pneumonia. Tubular degenerative changes in the kidney were also observed at 100 ppm. Rats exposed at 10 or 30 ppm over a lifetime developed pulmonary congestion, bronchiectasis, pneumonia, a very low incidence of mucosal metaplasia of the nasal cavity, and tubular degenerative changes in the kidney. These studies showed that: (1) epichlorohydrin is carcinogenic in rats; (2) the neoplastic response to inhaled epichlorohydrin occurs only at the site of contact; and (3) short-term intense exposure to epichlorohydrin is much more effective in inducing a neoplastic response than low-level long-term exposures (a dose-rate effect was observed [3,000 ppm-days [100 ppm × 30 days] vs. 8,700 ppm-days [30 ppm for lifetime] and 2,500 ppm-days [10 ppm for lifetime]).

Carcinogenicity studies have been conducted in rats exposed orally and topically to epichlorohydrin. Oral exposure to epichlorohydrin resulted in a dose-related increase in forestomach neoplasms (primarily squamous cell carcinomas) after gavage administration, and in papillomas after administration in drinking water. Skin tumors have been induced in mice receiving a single application of epichlorohydrin followed by repeated applications of phorbol myristate acetate (initiation/promotion protocol) (HSE 1991).

A quantitative assessment of single-exposure estimates for epichlorohydrin is presented in Appendix B.

3.5. Genotoxicity

In a review of the genetic toxicology of epichlorohydrin, Giri (1997) concluded that epichlorohydrin is a direct-acting mutagen in *Salmonella typhimurium, Escherichia coli*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Klebisella pneumoniae*. It is more effective as a mutagen in the absence of an exogenous metabolizing system. There is a reduction in mutagenic activity in the presence of an activation system. In vitro cytogenetic assays showed consistent positive clastogenic effects (chromosome aberrations) and sister chromatid exchanges in test systems using cultured animal cells.

In a study of mice and rats exposed to epichlorohydrin at concentrations of 1.3, 6.6, and 33 ppm (5, 25, or 125 mg/m^3) for 120 h, Sram et al. (1981) showed increased frequencies of chromosome aberrations in mouse bone marrow and spermatogonia and increased abnormal sperm in mice (unspecified strain) exposed by inhalation to concentrations of epichlorohydrin as low as 1.3 ppm. The abstract did not state whether the animals were exposed continuously or intermittently for 120 h The frequency of sister chromatid exchanges was not increased in bone marrow cells of mice, and the frequencies of chromosome aberrations in bone marrow cells and peripheral lymphocytes were not increased or were only slightly increased in rats after inhalation exposure to epichlorohydrin.

Another inhalation study showed a significant increase in the frequency of chromosome aberrations in spleen lymphocytes in CD-1 Swiss mice exposed to mixtures containing benzene, chloroprene, xylene, and epichlorohydrin at concentrations of 0, 0.1, 1.0, or 10 ppm (epichlorohydrin concentration was one-half that of the other components) for 3 or 6 weeks (Au et al. 1988). Exposure conditions are assumed to have been continuous. The effect could not be attributed to epichlorohydrin. Mixed results have been observed in oral and parenteral studies (Giri 1997).

3.6. Summary

Inhalation exposure to epichlorohydrin causes varying degrees of irritation of the mucous membranes of contact organs and effects on the central nervous system, kidneys, and liver. Acute lethality data are summarized in Table 4-3. LC_{50} values varied considerably depending on the exposure condition (dynamic

or static chambers) and the physical state (aerosol or vapor) of the epichlorohydrin (see discussion in Section 4.5). Acute LC_{50} values for epichlorohydrin vapor in rats were 2,165-3,617 ppm for a 1-h exposure, 471-635 ppm for a 4-h exposure, and 360 ppm for a 6-h exposure. LC_{50} values in other species were 794 ppm for a 2-h exposure and 820-1,153 ppm for a 4-h exposure in mice, 275-651 ppm for a 4-h exposure in guinea pigs; and 516 ppm for a 4-h exposure in rabbits. Deaths were due to effects on the respiratory center of the central nervous system and severe respiratory irritation manifested as pulmonary hemorrhage and edema. Before death occurred, the animals showed signs of cyanosis, muscle relaxation of the extremities, gasping, labored breathing, depressed or increased respiration, lethargy, fine tremors, and clonic convulsions. In addition, the animals had degenerative lesions of the nasal epithelium and kidneys and damage to the lower respiratory tract.

Inhalation exposure to nonlethal concentrations of epichlorohydrin resulted in systemic but mainly portal-of-entry effects. Data are summarized in Table 4-10. The RD_{50} is 1,342 ppm for a 15-min exposure of rats and 687 ppm (aerosol) for a 10-min exposure of mice. Clinical signs indicative of nasal irritation and sometimes ocular irritation have been observed in rats, mice, guinea pigs, hamsters, and rabbits exposed at nonlethal concentrations of epichlorohydrin. The nasal epithelium shows signs of degeneration similar to that described for lethal concentrations. Severe renal damage in rats exposed to epichlorohydrin vapor at 150 ppm for 1 h has been observed by light and electron microscopy (Ito et al. 1995) and functional changes in the kidney were noted after exposure at 93 ppm for 4 h (Shumskaya et al. 1971); however, no microscopic evidence of renal damage was found after exposure at 100 ppm for 4 h (Robinson et al. 1995). Renal damage was seen in rats, but not mice, exposed repeatedly to epichlorohydrin. Sprague-Dawley rats appeared to be more sensitive than Fischer 344 rats, and males were more severely affected than females (Quast et al. 1979a,b). Damage to the nasal epithelium was seen in both strains of rats and in mice, but the effect may be less severe in mice.

No developmental effects were observed in rats or rabbits exposed to epichlorohydrin at concentrations up to 25 ppm for 7 h/day during organogenesis (John et al. 1983a). A transient decrease in fertility was observed in male rats but not females exposed repeatedly to epichlorohydrin vapor at 25 or 50 ppm for 6 h/day for 2-10 weeks. Studies in rabbits exposed at concentrations up to 50 ppm for 6 h/day for up to 10 weeks showed no effects on sperm parameters (John et al. 1983b). However, decreases in sperm motility were observed in rats exposed at 100 ppm for 4 h (Slott et al. 1990).

Genetic toxicity studies showed that epichlorohydrin is mutagenic in bacteria and yeast without metabolic activation. In vivo studies in mice showed chromosome aberrations after exposure at concentrations as low as 1.3 ppm for 120 h (Sram et al. 1981). Carcinogenicity studies showed that 30 exposures (6-h exposures for 5 days/week) to epichlorohydrin vapor at 100 ppm followed by

TABLE 4-10 Nonlethal Effects in Animals Exposed to Epichlorohydrin by Inhalation

Species/Strain/Sex	Exposure Protocol	Effects	Reference
Single Exposures			
Rat/Crl-CD®/males	101-1,963 ppm × 15 min	6-54% decrease in respiration; RD_{50} = 1,342 ppm (50% decrease in respiratory rate).	Gardner et al. 1985
Rat/Wistar	150 ppm × 1 h	Severe renal damage.	Ito et al. 1995
Rat/F344	100 ppm × 4 h	Slight increase in renal weight in young rats; slight decrease in BUN in adult rats; no microscopic evidence of hepatic or renal damage.	Robinson et al. 1995
Rats	1.9, 5.3, or 93 ppm × 4 h	Increased hepatic and renal weight; decreased pulmonary and spleen weight; increased urinary protein and chlorides; decreased specific gravity and BSP removal from blood.	Shumskaya et al. 1971
Rat/F344/males and females	10 or 25 ppm × 6 h	No effect.	Industrial Bio-Test Laboratories 1977
	50 or 100 ppm × 28-223 min	Squinting, hypoactivity, head shaking, drooping eyelids.	
	200 ppm × 136-336 min	Same as at 100 ppm; plus irritated eyes, gasping, red nasal discharge, lacrimation.	
Mice/Swiss Webster	687 ppm × 10 min	RD_{50} (50% decrease in respiratory rate)	Kane et al. 1979
Mouse/B6C3F_1/males and females	10 or 25 ppm × 6 h	No effect.	Industrial Bio-Test Laboratories 1977b
	50, 100, or 200 ppm × 66-381 min	Squinting, hypoactivity, drooping eyelids, ruffed fur, gasping.	
Mouse	5.3 ppm × 24 h	Transient excitation, restlessness, sluggishness, somnolence.	Formin 1966
Hamster/Syrian/males and females	25 ppm × 6 h	No effects.	Industrial Bio-Test Laboratories 1977c
	50 or 100 ppm × 78-262 min	Salivation, hypoactivity, squinting, drooping eyelids.	
	200 ppm × 66-381 min	Same as at 100 ppm; plus excitation, gasping, full mouth pouch.	
	400 ppm × 20-240 min	Same as at 200 ppm; plus labored breathing.	

(Continued)

TABLE 4-10 Continued

Species/Strain/Sex	Exposure Protocol	Effects	Reference
Repeated Exposures			
Rat/Wistar	150 ppm × 1 h or 5 ppm × 2 h/day for 6 days/week for 20 exposures	Less severe renal damage than single 1-h exposure at 150 ppm.	Ito et al. 1995
Rats/Sprague-Dawley, F344/males and females	100 ppm × 7 h/day for 5 days/week for 9 exposures	Signs of nasal irritation after each exposure (discharge, sneezing, rubbing); nasal epithelial and renal degeneration after repeated exposures.	Quast et al. 1979b
Mouse/B6C3F_1/males	100 ppm ×7 h/day for 5 days/week for 9 exposures	Signs of nasal irritation after each exposure (discharge, sneezing, rubbing); nasal epithelial degeneration after repeated exposures.	Quast et al. 1979b

lifetime observation was very effective in inducing squamous cell carcinomas in the nasal cavity of rats, whereas lifetime exposure at 30 ppm (6 h/day, 5 days/week) was almost ineffective (Laskin et al. 1980). The study demonstrated that short-term exposure at high concentrations of epichlorohydrin are more effective than long-term exposure at low concentrations for nasal tumor induction; therefore, dose fractionation may not be effective for epichlorohydrin exposure.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

In a pharmacokinetic study, groups of three or four male Fischer 344 rats were exposed (head-only) to epichlorohydrin-1,3^{-14}C vapor at 1 or 100 ppm of for 6 h. About 72% of the dose was excreted in the first 24 h and about 83% was excreted within 72 h regardless of the concentration (Smith et al. 1979). About 46% and 54% of the radioactivity was recovered from urine, 34% and 27% in expired air, and 3% from feces after exposure at 1 and 100 ppm, respectively. Excretion of epichlorohydrin was biphasic; the half-life for the slower fraction was about 24 h. The half-life for elimination from plasma was 26 h, which was comparable to that for excretion. The uptake rates at 1 and 100 ppm were 15.48 and 1,394 µg/h and the total systemic doses were 0.37 and 33 mg/kg. The volume of distribution was 385 and 350 mL/kg, and was equivalent to 38.5 and 35% of the body weight. The investigators concluded that epichlorohydrin is not extensively sequestered in a deep compartment. Six metabolites were identified by chromatography of urine; the major metabolites recovered after exposure at 1 and 100 ppm were similar in type and proportion. The parent compound was not identified as a constituent of urine, indicating complete metabolic conversion of epichlorohydrin. Tissue distribution of radioactivity immediately after exposure showed that nasal turbinates (target organ) contained the largest fraction of epichlorohydrin when calculated on the basis of grams of tissue, followed by the lacrimal glands, large intestines, kidneys, liver, adrenal glands, erythrocytes, pancreas, and lungs. Except for the lacrimal glands, radioactivity decreased in all tissues over the first 24 h.

Stott and McKenna (1984) studied the absorption of epichlorohydrin in the isolated upper and isolated lower respiratory tract and the intact animal (male Fischer 344 rats). The animals were anesthetized and exposed to epichlorohydrin at 100 ppm by nose-only inhalation or via a one-way cephalad (upper respiratory tract) or endotracheal tube (lower respiratory tract, bypassing the nose) for about 2 h. Absorption reached a plateau in about 10-20 min and remained constant for the remaining exposure period. Absorption was 61% of available compound by the upper respiratory tract at a flow rate approximating the intact

breathing rate, 73% by the lower respiratory tract, and 51% by the intact respiratory tract. The authors explained some of the discrepancies in the percentages of absorption in the isolated upper and lower respiratory tract compared with the intact animal. Air flow through the isolated upper respiratory was unidirectional, which circumvented the loss of absorbed chemical due to significant back pressure during exhalation; the lower relative humidity may have altered blood flow and consequently chemical absorption by the isolated organ; and stimulation of the trigeminal nerve may have altered uptake by the lower respiratory tract. The authors further noted that absorption by the intact animal may have been underestimated because of unavoidable rebreathing of exhaled air, the effective dead-space in the upper respiratory tract causing less effective uptake, and fluctuating airflow during normal breathing patterns in the intact animals. Doubling the flow rate decreased the absorption fraction in the upper respiratory tract by about 17%. When absorption was calculated based on surface area, the dose received by the upper respiratory tract was estimated to be 5,000-6,000 times greater than that of the lower respiratory tract.

4.2. Mechanism of Toxicity

The mechanism by which epichlorohydrin causes toxicity is not known. Epichlorohydrin is a direct alkylating agent, which may account for some of its irritant properties.

Itoh et al. (1994) examined biochemical and histologic parameters in Wistar rats. Rats given a single inhalation exposure to epichlorohydrin at 20 ppm for 90 min or were exposed repeatedly to at 5 ppm for 6 h/day for a total of 30 exposures. Findings from the treatment groups were compared the results from those of a control group. The single exposure at 20 ppm caused an increase in urinary *N*-acetyl glucosaminidase activity, but had no effect on serum chemistry values. The erythrocyte count also was increased after a single exposure at 20 ppm. Glutathione (GSH) concentrations, along with glutathione peroxidase (GSH-Px) and glutathione-S-transferase activities, were decreased in the kidney.

Ito et al. (1995) reported that renal damage after exposure at a single to epichlorohydrin at 150 ppm for 1 h was accompanied by a pronounced reduction in GSH and a moderate reduction in GSH-Px. GSH showed greater than a three-fold increase (attributed to induction of tolerance to epichlorohydrin) and GSH-Px only a slight decrease after repeated exposure. The liver does not appear to be a primary target for epichlorohydrin in rodents, but there was a pronounced reduction in GSH in the liver after a single low-level exposure and no effect after repeated low-level exposures. GSH depletion is probably related to the extent of damage in the kidney. The authors stated that GSH caused cellular dysfunction because of the reduced capacity to process activated oxygen. The extent of damage was greater in the kidneys than in the liver, because of higher intracellular concentrations of epichlorohydrin in the kidney.

4.3. Structure-Activity Relationships

Structurally, epichlorohydrin can be related to either ETO or propylene oxide (either as chloromethyl ethylene oxide or as chlorinated propylene oxide) All three compounds are direct alkylating agents; however, the toxicity of epichlorohydrin is more like that of propylene oxide than ETO. Both epichlorohydrin and propylene oxide caused lesions in the upper respiratory tract after a single exposure and nasal tumors after repeated exposures. Unlike ETO, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant. Both compounds produce similar clinical signs. The 4-h LC_{50} values for epichlorohydrin and propylene oxide are 441-635 ppm and 4,000 ppm, respectively, in the rat, and 820-1,153 and 1,740 ppm, respectively, in the mouse. Values for propylene oxide were obtained from Berdasco and Waechter (2012). The data suggest that the rat is 5-10 times more sensitive to epichlorohydrin than propylene oxide, and the mouse is less than two times more sensitive to epichlorohydrin. Although the clinical signs were similar, the test concentrations eliciting clinical signs were much lower for epichlorohydrin than for propylene oxide. Therefore, epichlorohydrin is qualitatively similar but quantitatively different from propylene oxide.

4.4. Other Relevant Information

4.4.1. Species Variability

The range of LC_{50} values for inhalation exposure to epichlorohydrin vapor showed that the mouse is the least sensitive species, but that the values for the rat, guinea pig, and rabbit are within the same range. For nonlethal effects, the Industrial Bio-Test Laboratories (1977a,b,c) studies showed no difference in the lowest concentration eliciting clinical signs (50 ppm) and the type of sign observed (squinting, hypoactivity, and/or salivation) and very little difference in the time of onset. Humans exposed to epichlorohydrin experience effects similar to those observed in experimental animals: ocular and upper respiratory tract irritation. In a controlled exposure study (Kobernick et al. 1983), three of four human subjects experienced no irritation after exposure at 68 ppm for 2 min and two of four reported irritation of the eyes and pharynx after exposure at 136 ppm for 2 min. The data suggest that humans are slightly more sensitive than animals.

4.4.2. Susceptible Subpopulations

No data were available to identify populations more susceptible to epichlorohydrin. One report on exposure to ETO noted that an asthmatic worker experienced no effects after exposure for 4 h/day for 4 days at concentrations

detectable by its odor. Epichlorohydrin and ETO have similar structures. Direct alkylation may be involved in the irritant effects on the eyes and upper respiratory tract; this mechanism is not expected to vary considerably with individuals in the population. Systemic effects of epichlorohydrin may be modulated by metabolism (deactivation), which involves glutathione conjugation. Genetic polymorphism of the glutathione-S-transferase enzymes (Finell 1996) may result in some variations in human sensitivity within the population due to the slow versus rapid deactivation of epichlorohydrin.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). LC_{50} data from studies of the rat can be used to determine the relationship between concentration of epichlorohydrin and exposure duration. LC_{50} values for the rat are: 2,798 ppm (geometric mean of 3,617 ppm for males and 2,165 ppm for females) for a 1-h exposure, 580 and 635 ppm for 4-h exposures, 360 ppm for a 6-h exposure, and 250 ppm for an 8-h exposure. A linear log-log relationship was observed over the 1- to 8-h exposure durations. The calculated value of n was 0.87. The data are presented in Figure 4-1 (the LC_{50} on the plot for the 4-h diratopm is the midpoint [608 ppm] between the reported values of 580 and 635 ppm).

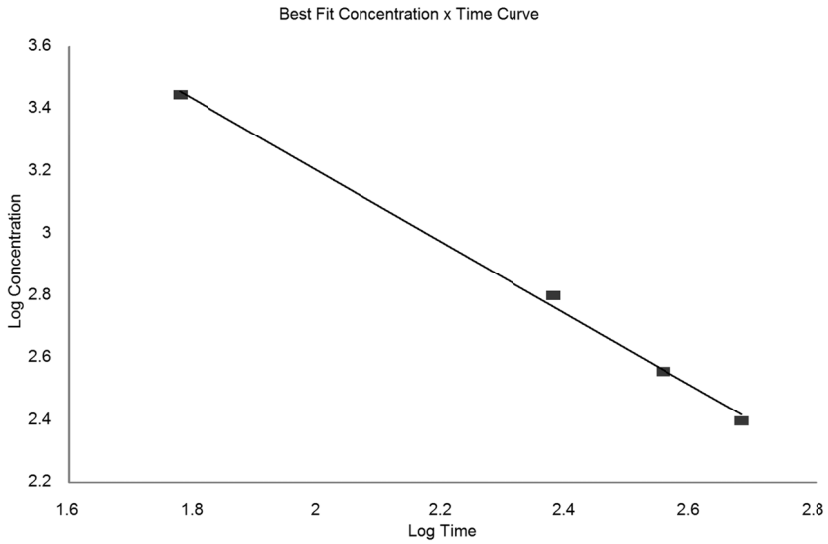


FIGURE 4-1 Concentration-time curve of LC_{50} values for epichlorohydrin in the rat.

4.5. Vapor and Aerosol Exposures

AEGL values were derived for epichlorohydrin on the basis of studies in which animals were exposed only to vapor for several reasons. First, epichlorohydrin will produce vapor when liquid epichlorohydrin or aerosolized epichlorohydrin is exposed to air (vapor pressure = 13 mm Hg at 20°C). Thus, in studies that exposed animals to epichlorohydrin aerosols, animals would have inhaled epichlorohydrin both as an aerosol and as a vapor. Second, studies using aerosols generally did not indicate whether exposure concentrations were measured and were reported as total epichlorohydrin (the sum of aerosol and vapor); thus, the nature of the actual exposure in these studies is not known. Third, aerosol studies frequently used a solvent or other stabilizing agent for which control exposures are not reported; the role of these coexposures in the observed toxicity cannot be evaluated. Finally, there are adequate data available from studies in which animals were exposed to epichlorohydrin vapor, so the aerosol data are not needed to fill any data gaps. In summary, given the uncertainties in the aerosol studies and the availability of adequate studies of epichlorohydrin administered as a vapor, aerosol studies were not used in the derivation of AEGL values.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Epichlorohydrin has a sweet, pungent or chloroform-like odor. Odor perception of epichlorohydrin by human subjects occurs in the range of 0.08-25 ppm (Amoore and Hautala 1983; Kobernick et al. 1983; AIHA 1989; Shell Oil Co. 1977; Berdasco and Waechter 2012). Kobernick et al. (1983) reported that two of four subjects exposed at 17 ppm for 2 min noted the odor of epichlorohydrin but experienced no irritation, one of four subjects exposed at 68 ppm for 2 min experienced pharyngeal irritation, and two of four subjects exposed at 135 ppm for 2 min experienced ocular and pharyngeal irritation. The odor of epichlorohydrin was detected but irritation was not reported by subjects exposed at 25 ppm for 5 min (Shell Oil Co. 1977). Lefaux (1968) and Wexler (1971) reported that humans exposed at 20 ppm for an extended period experienced burning of the eyes and nasal mucosa and that those exposed at 40 ppm for 1 h experienced throat irritation; however, no direct evidence for this conclusion was provided.

5.2. Animal Data Relevant to AEGL-1

Several datasets are relevant for deriving AEGL-1 values from animal studies. Studies of animals exposed under static conditions are considered inferior to studies in which exposures were under dynamic conditions, and were not used as basis for AEGL values. As discussed in Section 4.5, AEGL values were

derived for epichlorohydrin vapor on the basis of studies in which animals were exposed to vapor, and aerosol studies were not used. Exposure to epichlorohydrin at 101 ppm for 15 min caused a 6% decrease in the respiratory rate in rats (Gardner et al. 1985). The only evidence of possible hepatic or renal toxicity in male rats exposed to epichlorohydrin vapor at 100 ppm for 4 h was a transient 5% increase in renal weight 1 day after exposure and a transient 15% decrease in blood urea nitrogen (BUN) on the day of exposure, which were not consistently observed in young adult and adult rats (Robinson et al. 1995); neither parameter is considered sufficient evidence of toxicity. The investigators did not indicate whether they observed the animals for clinical signs. In the studies by Industrial Bio-Test Laboratories (1977a,b,c), rats, mice, and hamsters showed clinical signs, such as squinting, hypoactivity, and salivation, after a single exposure to epichlorohydrin at 50 ppm for 66-217 min. Squinting of the eyes was considered separately from ocular irritation, which occurred in rats exposed at 200 ppm for 136 min. In addition, drooping eyelids or head shaking was observed in rats, mice, and hamsters exposed at 100 ppm for at least 178 min. In a repeat inhalation study, Quast et al. (1979b) reported no clinical signs in two strains of rats and one strain of mice during exposure to epichlorohydrin vapor at 100 ppm for 7 h, but after exposure the animals showed signs of nasal irritation that disappeared before the next exposure. John et al. (1983b) reported no clinical signs of toxicity after the first exposure of rats to epichlorohydrin vapor at 5-50 ppm for 6 h.

5.3. Derivation of AEGL-1 Values

Because irritation is the most sensitive effect experienced by humans exposed to epichlorohydrin at low concentrations, that end point was used to derive AEGL-1 values. The point-of-departure was a no-effect level for irritation of 17 ppm for a 2 min exposure (Kobernick et al. 1983). The total uncertainty factor of 10 was applied, which represented uncertainties associated with intraspecies variability. Mild irritation experienced by humans (e.g., at 17 ppm) would most likely be confined to the nasal passage and eyes. Variability in pharmacokinetics would not be expected to contribute to variability in dose-response relationships for chemicals acting at the portal of entry. However, to provide sufficient protection for asthmatic individuals, a factor of 10 was used. Applying the total uncertainty factor of 10 to the point-of-departure yields an AEGL value of 1.7 ppm. That value was applied to all the AEGL exposure durations because epichlorohydrin is an irritant and the irritation is not expected to become more severe with increasing exposure duration at that concentration. The AEGL-1 values for epichlorohydrin are presented in Table 4-11. The AEGL-1 values are below the level of odor recognition (25 ppm) and the level of odor awareness (46 ppm). Therefore, odor is not a factor for early warning of exposure to epichlorohydrin.

TABLE 4-11 AEGL-1 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are few human data relevant to AEGL-2 derivation. Irreversible hepatic and respiratory-tract damage occurred in a worker who took a few breaths of epichlorohydrin at a very high (unknown) concentration (Shultz 1964). Anecdotal information (Lefaux 1968; Deichmann and Gerarde 1969; Wexler 1971; Enterline et al. 1990; Berdasco and Waechter 2012) has suggested that exposure to epichlorohydrin at 20 ppm for 1 h caused burning to the eyes and nose, 40 ppm caused throat irritation lasting for about 48 h, and 100 ppm could not be tolerated and may be associated with pulmonary edema and renal damage. No data were provided to support these conclusions. A report by Kobernick et al. (1983) stated that one of four subjects experienced irritation of the pharynx after a 2-min exposure to epichlorohydrin vapor at 68 ppm, and two subjects experienced eye or pharyngeal irritation after a 2-min exposure at 136 ppm. Epidemiologic studies did not provide evidence of a causal association between exposure to epichlorohydrin and morbidity, including skin diseases (Tsai et al. 1990).

6.2. Animal Data Relevant to AEGL-2

A relatively large animal database was available for evaluating nonlethal toxicity of epichlorohydrin (see Table 4-9). However, the available data were not suitable for defining a point-of-departure for AEGL-2 derivation, as discussed below.

The study using the monkey is not adequate because the animals had tuberculosis, only one animal was exposed, and no other primate data were available (Kobernick et al. 1983). Two RD_{50} studies were available in rodents. One study showed that the respiration rate in rats was decreased by 33-36% during a 150-min inhalation exposures to epichlorohydrin vapor at 363, 394, and 663 ppm and by about 50% at 643, 914, and 1,963 ppm; the RD_{50} was 1,332 ppm (Gardner et al. 1985). In an aerosol study, the RD_{50} for male Swiss-Webster mice was 687 ppm for a 10-min exposure (Kane et al. 1979). The mouse RD_{50} has been used for AEGL-2 derivation (see NRC 2004) on the basis of its correlation with a human irritation threshold (Schaper 1993). However, the mouse RD_{50} data for epichlorohydrin are not suitable for AEGL-2 derivation because the data are from an aerosol study. In addition, there are no data supporting an association between rat RD_{50} values and human irritation.

Ito et al. (1995) observed severe renal toxicity in rats exposed to epichlorohydrin vapor at 150 ppm for 1 h. This effect exceeds the threshold for an AEGL-2 effect, and no other exposure concentrations were tested; therefore, a no-effect level could not be determined. Robinson et al. (1995) reported no histopathologic evidence of hepatic or renal damage in F344 rats exposed to epichlorohydrin at 100 ppm for 4 h; the result appears to conflict with information reported by Ito et al. (1995).

In a series of studies using rats, mice, and hamsters exposed repeatedly to epichlorohydrin at concentrations ranging from 10 to 400 ppm for 6 h/day for 14 days, the investigators provided detailed information on clinical signs after each exposure (Industrial Bio-Test Laboratories 1977a,b,c). Clinical signs related to AEGL-2 derivation included gasping, irritated eyes, excitation, and labored breathing. Signs were not seen at 100 ppm in any species, but were observed at 200 ppm in rats and mice and 200 and 400 ppm in hamsters. The concentration of 100 ppm may be a no-observed-effect level for clinical effects that may impair escape; however, mortality was seen in all three species at 200 ppm, and evaluation of the kidneys was limited to gross examination at study termination (findings included lung consolidation and/or intestinal bloating and pale kidneys at 200 ppm and higher in all species). In a repeated inhalation study using two strains of rats (Fischer 344 and Sprague-Dawley) and B6C3F_1 mice (Quast et al. 1979b), the animals huddled together and slept during exposure to epichlorohydrin at 100 ppm for 7 h/day. Transient signs of nasal irritation were the only clinical findings seen after each individual exposure. Exposure to epichlorohydrin for 5 days/week for 9 days resulted in histopathologic evidence of damage to nasal turbinates, kidneys, and epididymis; the findings are considered to be above the threshold for AEGL-2 effects.

On the first day of a continuous-exposure study, mice showed excitation and restlessness followed by sluggishness and somnolence and gradual recovery at 5.3 ppm (Formin 1966). The study provided no information on exposure conditions or analytic measurements and was not considered for use in deriving AEGL-2 values. The study in rabbits exposed to epichlorohydrin at 19-886 ppm for 1 h or at 45 and 132 ppm for 4 h was conducted using a static chamber (Kimmerle 1967) and atomized epichlorohydrin, and is not considered reliable for purposes of AEGL derivation.

Several developmental and reproductive toxicity studies were available; inhalation exposure to epichlorohydrin at concentrations of 2.5 or 25 ppm did not induce developmental effects in rats or rabbits exposed during organogenesis (John et al. 1983a). Transient infertility was induced in male rats exposed to epichlorohydrin at concentrations of 25 or 50 ppm for 6 h/day, 5 days/week for 2-10 weeks (one spermatogenic cycle), but no effects were observed on fertility when exposed females were mated with unexposed males (John et al. 1983b). No reproductive effects were observed in male rabbits exposed under conditions similar to those used for the rats (John et al. 1983b). Slott et al. (1990) reported altered sperm motility in male rabbits exposed to epichlorohydrin at 100 ppm for

4 h; the effect is not considered to be irreversible nor of sufficient severity to reflect an AEGL-2 effect.

Finally, as discussed in Section 4.5, AEGL values were derived for epichlorohydrin vapor based on studies in which animals were exposed to vapor. Aerosol studies (e.g., Gage 1959; Kane et al. 1979; Kimmerle 1967) were not used to derive AEGL values.

6.3. Derivation of AEGL-2 Values

The human and animal data showed that exposure to epichlorohydrin is associated with various degrees of ocular and respiratory-tract irritation. Adequate data were not available for deriving AEGL-2 values from studies with humans or animals, as discussed above in Sections 6.1 and 6.2. Therefore, AEGL-2 values were estimated by reducing the AEGL-3 values by a factor of 3. That approach is used in cases of a steep-concentration-response curve (NRC 2001); the steep concentration-response curve is seen in a 1-h study of rats in which no deaths occurred among six rats exposed to epichlorohydrin at 3,275 ppm epichlorohydrin, and all 12 rats exposed at 3,995 ppm died (Dietz et al. 1985).

Reducing the 10-min AEGL-3 value by a factor of 3 yields a10-min AEGL-2 value of 188 ppm. Anecdotal information provided by Lefaux (1968) suggested that concentrations greater than 100 ppm for short intervals might result in pulmonary edema and renal damage. Although the information is anecdotal, support for the effects comes from a study of rats exposed to epichlorohydrin at 150 ppm for 1 h that exhibited evidence of severe renal damage (Ito et al. 1995). Therefore, t

The 30-min AEGL-2 value of 53 ppm was applied to the 10-min exposure to be protective of the lungs and kidneys. AEGL-2 values are presented in Table 4-12.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data are available on the lethal effects of single inhalation exposures to epichlorohydrin.

7.2. Animal Data Relevant to AEGL-3

A large number of lethality studies are available for deriving AEGL-3 values. Studies of animals exposed under static conditions are considered inferior to studies in which exposures were under dynamic conditions, and were not used as basis for AEGL values. As discussed in Section 4.5, AEGLs were derived for epichlorohydrin vapor on the basis of studies in which animals were exposed to vapor, and aerosol studies were not used.

TABLE 4-12 AEGL-2 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm 91 (mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)

Animals exposed at lethal concentrations of epichlorohydrin vapor showed signs of cyanosis, muscle relaxation, lethargy, tremors, increased or decreased respiration, labored breathing, clonic convulsions, and respiratory arrest. Microscopic examination of the respiratory tract showed exfoliation, erosion, ulceration, and necrosis of the nasal epithelium and hemorrhage, congestion, edema, or pneumonia in the lower respiratory tract. Systemic effects may include severe renal or hepatic damage. Six studies provided data that could be used to derive AEGL-3 values; they include rat studies by Dietz et al. (1985), Kobernick et al. (1983), and Laskin et al. (1980) and mouse, guinea pig, and rabbit studies by Kobernick et al. (1983). The studies were conducted using dynamic chambers, whereas in the other lethality studies, the animals were exposed to vapor in static chambers or they were exposed to aerosolized epichlorohydrin as discussed in Section 3.1.

7.3. Derivation of AEGL-3 Values

The LC_{50} values, and the corresponding estimates for the threshold for lethality (LC_{01} values), derived by probit analysis of the mortality data from five studies are presented in Table 4-13. The best datasets are obtained from the rat studies by Laskin et al. (1980) and Dietz et al. (1985). Although all the studies were conducted in dynamic chambers, Laskin et al. (1980) and Dietz et al. (1985) measured chamber concentrations analytically, whereas Kobernick et al. (1983) calculated the nominal chamber concentrations. Therefore, AEGL-3 values are calculated from the Laskin et al. (1980) and Dietz et al. (1985) data.

The 10-min, 30-min, and 1-h AEGL-3 values are based on the 1-h rat LC_{01} of 721 ppm (Dietz et al. 1985). A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences. The 4-h LC_{50} values for rats, mice, guinea pigs, and rabbits ranged from 573 to 820 ppm; thus, showing very little variability among the species. Although limited, the data suggest humans are more sensitive than animals to inhaled epichlorohydrin but are within a factor of about 2.5. Epichlorohydrin at 50 ppm for 66-262 min caused squinting, hypoactivity, and salivation in animals, whereas 20 ppm for 1 h caused burning of eyes and nose in humans. In addition, epichlorohydrin is an epoxide and direct alkylating agent, similar in structure to ETO; a factor of 3 was also used for ETO (NRC 2010). A factor of 3 was applied for intraspecies variability. Epichlorohydrin is an epoxide and direct alkylating agent. The irritation and systemic toxicity caused by epichlorohydrin are likely to involve its alkylating activity. Therefore, the concentrations causing severe pulmonary irri-

tation are not expected to vary considerably in the population. The systemic toxicity may be modulated by the detoxification enzymes, most likely epoxide hydrolase and glutathione-S-transferase activity. The structural similarity of epichlorohydrin to ETO suggests that metabolism involving the glutathione-S-transferase enzyme system, which is genetically polymorphic in human, may be similar. This similarity in structure provides additional support for an intraspecies factor of 3. A factor of 3 is also supported by human data. Use of higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value of 6.6 ppm; however, occupational exposures as high as 15-54 ppm have occurred (Pet'ko et al. 1966 [as cited in NIOSH 1976]; de Jong et al. 1988) and were apparently not life-threatening. Time scaling was performed using he equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 0.87. An empirical value for the exponent n was derived from rat LC_{50} values for 1-, 4-, 6-, and 8-h exposures.

The 4- and 8-h AEGL-3 values were based on the 6-h rat LC_{01} of 274 ppm (Laskin et al. 1980). The uncertainty factors and time-scaling method were the same as those used to derive the AEGL-3 values for the 10-min, 30-min, and 1-h durations. The 8-h AEGL-3 of 20 ppm is supported by a chronic exposure study in rats, in which exposure to epichlorohydrin at 30 ppm for 6 h/day for a lifetime did not result in any mortality. AEGL-3 values for epichlorohydrin are presented in Table 4-14.

TABLE 4-13 LC_{50} Values and Lethality Thresholds (LC_{01}) for Animals Exposed to Epichlorohydrin Vapor

Species/Sex	Exposure Duration (min)	LC_{50}[a] (ppm)	LC_{01}[a] (ppm)	Reference
Rat/male	360	373	274 ± 13.1[b]	Laskin et al. 1980
Rat/male	240	580	182 ± 125	Kobernick et al. 1983
Rat/male, female combined	60	2,369	721 ± 225	Dietz et al. 1985
Mouse/male	240	820	468 ± 116	Kobernick et al. 1983
Guinea pig/male	240	666	170 ± 115	Kobernick et al. 1983
Rabbit/male	240	573	100 ±112	Kobernick et al. 1983

[a]Values derived by probit analysis (Number Cruncher Statistical System: Survival Analysis, Version 5.5).
[b]±Standard error.

TABLE 4-14 AEGL-3 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for epichlorohydrin are presented in Table 4-15. The AEGL-1 value was derived from a no-effect level for irritation in humans. The AEGL-2 values were derived by reducing the AEGL-3 values by a factor of 3 and retaining the 30-min value for the 10-min value. AEGL-3 values for the 10-min, 30-min, and 1-h exposures were derived from a 1-h lethality study in rats; the 4- and 8-h values were derived from a 6-h lethality study in rats.

8.2. Other Standards and Guidelines for Epichlorohydrin

Standards and guidelines established for epichlorohydrin are presented in Table 4-16. The AEGL-1 value of 1.7 ppm is lower than the emergency response planning guideline 1 (ERPG-1) value of 5 ppm. The ERPG-1 value is based on an irritation threshold of 10 ppm (AIHA 2013). The ERPG documentation cites Diechmann and Gerarde (1969) as the source of the threshold, but the citation appears to be in error because that publication makes no mention of effects or lack of effects at 10 ppm.

The AEGL-2 value of 24 ppm for 1 h is similar to the ERPG-2 value of 20 ppm for 1 h. The ERPG-2 value (AIHA 2013) was based on the observation that epichlorohydrin at 20 ppm for 1 h resulted in burning of eyes and nose that was not expected to impair escape; it appears that this observation is based on the anecdotal information in Wexler (1971 [originally reported by Lefaux 1968]). As noted in Section 2.2.2, data supporting these anecdotal statements were not found in the available literature, so this information was not considered adequate to serve as the basis for AEGL values.

TABLE 4-15 AEGL Values for Epichlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)
AEGL-2 (disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)
AEGL-3 (lethal)	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

TABLE 4-16 Standards and Guidelines for Epichlorohydrin

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)
AEGL-2	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)
AEGL-3	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)
ERPG-1 (AIHA)[a]	–	–	5.0 ppm (7.6 mg/m^3)	–	–
ERPG-2 (AIHA)	–	–	20 ppm (76 mg/m^3)	–	–
ERPG-3 (AIHA)	–	–	100 ppm (380 mg/m^3)	–	–
IDLH (NIOSH)[b]	–	75 ppm (280 mg/m^3)	–	–	–
TLV-TWA (ACGIH)[c]	–	–	–	–	0.5 ppm (1.9 mg/m^3)
PEL-TWA (OSHA)[d]	–	–	–	–	5 ppm (19 mg/m^3)
MAC-TGG (The Netherlands)[e]	–	–	–	–	0.5 ppm (1.9 mg/m^3)

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[b]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. NIOSH considers epichlorohydrin to be a potential occupational carcinogen.

[c]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The TLV for epichlorohydrin includes a skin notation.

[d]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29CFR Part 1910.1000 [2012]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week. The PEL for epichlorohydrin includes a skin designation.
[e]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

The 1-h AEGL-3 value of 72 ppm is in the same range as the ERPG-3 value of 100 ppm. The ERPG-3 derivation used an LC_{50} estimate of about 2,000 ppm in multiple species (citing Gage 1959; Kimmerle 1967; and Dietz et al. 1985) as the starting point to derive the guideline of 100 ppm; no further information was given on how the guideline was derived.

The immediately dangerous to life for health (IDLH) value of 75 ppm (NIOSH 1994) is based in part on the statements of Lefaux (1968 [repeated by NIOSH 1976]) that 100 ppm is intolerable and potentially causes pulmonary edema and renal lesions, and on a Russian study (Pet'ko et al. 1966 [cited in NIOSH 1976]) reporting no apparent adverse effects in workers exposed to epichlorohydrin at 4.9-54.9 ppm. Animal data were also referenced to support the IDLH value.

The AEGL-1 value of 1.7 ppm is higher than the American Conference of Governmental Industrial Hygienists threshold limit value–time-weighted average (TLV-TWA) of 0.5 ppm (ACGIH 2001). That value is based on a NOAEL of 5 ppm for fertility in male rats exposed for 10 weeks (John et al. 1983b), as well as a NOAEL of 9 ppm for upper respiratory tract irritation (the LOAEL was 16 ppm in rabbits and 17 ppm in rats) in a repeated exposure study (Gage 1959). The 8-h AEGL-1 of 1.7 ppm is intended to protect against discomfort from a single exposure.

The Occupation Safety and Health Administration permissible exposure limit–time-weighted average (PEL-TWA) for epichlorohydrin is 5 ppm. The Netherlands has established a maximal accepted concentration of 0.5 ppm for epichlorohydrin. German MAK values have not been established for epichlorohydrin; however, Germany has a skin designation for this compound.

8.3. Data Quality and Research Needs

A robust animal toxicity database was available for deriving AEGL values for epichlorohydrin. However, many animal studies were conducted in a static environment using epichlorohydrin aerosols generated with the use of other substances (alcohol and lutrol). Data were not available for corroborating the nonlethal effects observed in humans. Only studies conducted with epichlorohydrin vapor in which animals were exposed in a dynamic chamber were considered suitable for deriving AEGL values. There are a number of uncertainties concerning some of the AEGL values derived, particularly the 8-h value for AEGL-3.

The time-frame extrapolation procedure seems to break down after 4 h, suggesting that dose fractionation may not be applicable for the longer inhalation exposure durations. Additional studies to investigate dose fractionation for acute exposure would be helpful for relating exposure concentration and duration with toxic effects. It was not possible to ascertain the relative thresholds for respiratory tract irritation and systemic toxicity (renal or hepatic damage) from the available studies. Therefore, additional animal studies in which clinical signs and gross and histopathologic changes in the respiratory tract and systemic organs are evaluated in the same animals would provide helpful information to determine the most sensitive end point.

9. REFERENCES

ABC-Thailand (Aditya Birla Chemicals Thailand, Ltd). 2013. Epichlorohydrin [online]. Available: http://www.adityabirlachemicals.com/products/chlorine_derivatives/epichlorohydrin.html [accessed April 4, 2014].

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Epichlorohydrin (CAS Reg. No. 106-89-8). Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists .

ACGIH (American Conference of Governmental Hygienists). 2012. Epichlorohydrin (CAS Reg. No. 106-89-8). P. 29 in TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

AIHA (American Industrial Hygiene Association). 1989. P. 18 in Odor Thresholds for Chemicals with Established Occupational Health Standards. Fairfax, VA: AIHA.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013 ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Alibaba. 2013. Epochlorohydrin [online]. Available: http://www.alibaba.com/countrysearch/CN-suppliers/Epichlorohydrin_Manufacturers.html [accessed June 17, 2013].

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-290.

Au, W.W., J.B. Ward, Jr., V.M.S. Ramanujam, B.L. Harper, M.T. Moslen, and M.S. Legator. 1988. Genotoxic effects of a sub-acute low-level inhalation exposure to a mixture of carcinogenic chemicals. Mutat. Res. 203(2):103-115.

Barbone, F., E. Delzell, H. Austin, and P. Cole. 1992. A case-control study of lung cancer at a dye and resin manufacturing plant. Am. J. Ind. Med. 22(6):835-849.

Barbone, F., E. Delzell, H. Austin, and P. Cole. 1994. Exposure to epichlorohydrin and central nervous system neoplasms at a resin and dye manufacturing plant. Arch. Environ. Health 49(5):355-358.

Berdasco, N.A.M., and J.M. Waechter. 2012. Epoxy compounds: Aromatic diglycidyl ethers, polyglycidyl ethers, glycidyl esters, and miscellaneous epoxy compounds.

Pp. 491-528 in Patty's Industrial Hygiene and Toxicology[online]. Available: http://onlinelibrary.wiley.com/doi/10.1002/0471435139.tox083.pub2/abstract [accessed Apr. 4, 2014].

Buckley, L.A., X.Z. Jiang, R.A. James, K.T. Morgan, and C.S. Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. Toxicol. Appl. Pharmacol. 74(3):417-429.

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4(3):163-176.

Deichmann, W.B., and H.W. Gerarde, eds. 1969. Epichlorohydrin. P. 241 in Toxicology of Drugs and Chemicals. New York: Academic Press.

de Jong, G., N.J. van Sittert, and A.T. Natarajan. 1988. Cytogenetic monitoring of industrial populations potentially exposed to genotoxic chemicals and of control populations. Mutat. Res. 204(3):451-464.

Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC_{50} Determination in Fischer-344 Rats. Lake Jackson Research Center, Health and Environmental Sciences - Texas, Dow Chemical, Freeport, TX.

Enterline, P.E., V. Henderson, and G. Marsh. 1990. Mortality of workers potentially exposed to epichlorohydrin. Br. J. Ind. Med. 47(4):269-276.

EPA (U.S. Environmental Protection Agency). 1994. Epichlorohydrin (CAS Reg. No. 106-89-8). Carcinogenicity Assessment. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC [online]. Available: http://www.epa.gov/iris/subst/0050.htm [accessed June 2013].

Finell, T.R. 1996. Biomarkers of exposure and susceptibility: Application to ethylene oxide. CIIT Activities 16:2-6.

Formin, A.P. 1966. Biological effects of epichlorohydrin and its hygienic significance as an atmospheric pollutant. Hyg. Sanit. 31(9):357-363.

Freuder, E., and C.D. Leake. 1941. The toxicity of epichlorohydrin. U. Calif. Publ. Pharmacol. 2(5):69-78.

Gage, J.C. 1959. The toxicity of epichlorohydrin vapour. Br. J. Ind. Med. 16(1):11-14.

Gardner, R.J., B.A. Burgess, and G.L. Kennedy, Jr. 1985. Sensory irritation potential of selected nasal tumorigens in the rat. Food Chem. Toxicol. 23(1):87-92.

Giri, A.K. 1997. Genetic toxicology of epichlorohydrin: A review. Mutat. Res. 386(1):25-38.

Grigorowa, R., G.M. Muller, R. Rothe, and R. Gholke. 1974. Combined action of epichlorohydrin and elevated ambient temperature in acute and subacute animal experiments [in German]. Int. Arch. Arbeitsmed. 33(4):297-314.

Haskell Laboratory. 1980. Rat Sensory Irritation Study using Epichlorohydrin. Submitted to EPA, Washington, DC, by Du Pont de Nemours & Co., Wilmington, DE with Cover Letter Dated December 3, 1982. EPA Document No. 878220379. Microfiche No.OTS0215158.

HSDB (Hazardous Substance Data Bank). 2009. Epichlorohydrin (CAS Reg. No. 106-89-8). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov [accessed May, 2013].

HSE (Health and Safety Executive). 1991. Toxicity Review 24, Part 2. 1-Chloro-2,3-epoxypropane (Epichlorohydrin). Sheffield: Health and Safety Executive.

IARC (International Agency for Research on Cancer). 1999. Epichlorohydrin. Pp. 603-628 in Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans, Vol. 71 (Part

2). Lyon, France: IARC Press. [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-26.pdf [accessed April 2, 2014].

Industrial Bio-Test Laboratories. 1977a. Repeated Dose Inhalation Study with Alpha-Epichlorohydrin (CO7001) in F344 Rats, October 13, 1977. Submitted to EPA, Washington, DC, by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. EPA Document No. 878211476. Microfiche No. OTS0206230.

Industrial Bio-Test Laboratories. 1977b. Repeated Dose Inhalation Study with Alpha-Epichlorohydrin (CO7001) in $B6C3F_{1,}$ October 13, 1977. Submitted to EPA, Washington, DC by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. Document No. 878211478. Microfiche No. OTS0206230.

Industrial Bio-Test Laboratories. 1977c. Repeated Dose Inhalation Study with Alpha-Epichlorohydrin (CO7001) in Golden Syrian Hamsters, October 13, 1977. Submitted to EPA, Washington, DC by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. EPA Document No. 878211477. Microfiche No. OTS0206230.

Ito, A., K. Ito, M. Hoshida, M. Watabe, and F.Y. Qiu. 1995. Experimental studies and renal lesions induced by epichlorohydrin inhalation exposure: Glutathione metabolism and apoptosis. Toho Igakkai Zasshi 42(4):321-330.

Itoh, A., T. Oguchi, M. Watabe, and M. Shimada. 1994. Toxicity profile of epichlorohydrin. Hochudoku 12(2):148-149.

John, J.A., T.S. Gushow, J.A. Ayres, T.R. Hanley, J.F. Quast, and K.S. Rao. 1983a. Teratologic evaluation of inhaled epichlorohydrin and allyl chloride in rats and rabbits. Fundam. Appl. Toxicol. 3(5):437-442.

John, J.A., J.F. Quast, F.J. Murray, L.G. Calhoun, and R.E. Staples. 1983b. Inhalation toxicity of epichlorohydrin: Effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68(3):415-423.

Kane, L.E., C.S. Barrow, and Y. Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40(3):207-229.

Kauppinen, T., J. Toikkanen, D. Pedersen, R. Young, M. Kogevinas, W. Ahrens, P. Boffetta, J. Hansen, H. Kromhout, J.M. Blasco, D. Mirabelli, V. de la Orden-Rivera, N. Plato, B. Pannett, A. Savela, H. Veulemans, and R. Vincent. 1998. Occupational Exposure to Carcinogens in the European Union in 1990-93. Carex. International Information System on Occupational Exposure to Carcinogens. Finnish Institute of Occupational Health, Helsinki [online]. Available: http://www.ttl.fi/en/chemical_safety/carex/countries/pages/default.aspx [accessed February 12, 2012].

Kimmerle, G. 1967. Toxicological Studies with Epichlorohydrin, October 20, 1967. Report No. 479/7. Farbenfabriken Bayer AC, Wuppertal-Elberfeld, Germany. Submitted to EPA, Washington, DC, by Mobay Chemical Corporation, Stilwell, KS with Cover Letter Dated January 28, 1983. EPA Document No. 878211473. Microfiche No. OTS0206022.

Kobernick, J.L., J.H. Nair, III, U.C. Pozzani, L.D. Roger, Jr., and J.S. West. 1983. Epichlorohydrin: Repeated Inhalation Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983. Document No. 878212138. Microfiche No. OTS0206066.

Kučerová, M., V.S. Zhurkov, Z. Polívková, and J.E. Ivanova. 1977. Mutagenic effect of epichlorohydrin. II. Analysis of chromosomal aberrations in lymphocytes of persons occupationally exposed to epichlorohydrin. Mutat. Res. 48(3-4):355-360.

Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.

Lawrence, W.H., M. Malik, J.E. Turner, and J. Autian. 1972. Toxicity profile of epichlorohydrin. J. Pharm. Sci. 61(11):1712-1717.

Lawrence, W.H., M. Malik, and J. Autian. 1974. Development of a toxicity evaluation program for dental materials and products. II. Screening for systemic toxicity. J. Biomed. Mater. Res. 8(1):11-34.

Lefaux, R. 1968. Epichlorohydrin. P. 108 in Practical Toxicology of Plastics, P.P. Hopf, ed. Cleveland, OH: CRC Press.

Milby, T.H., M.D. Whorton, H.A. Stubbs, C.E. Ross, R.E. Joyner, and R.I. Lipshultz. 1981. Testicular function among epichlorohydrin workers. Br. J. Ind. Med. 38(4):372-377.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Jan. 3, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard. Occupational Exposure to Epichlorohydrin. NIOSH 76-206. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health, Atlanta, GA [online]. Available: http://www.cdc.gov/niosh/docs/1970/76-206.html [accessed on February 9, 2012].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs): Epichlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/106898.html [accessed July 2013].

NIOSH (National Institute for Occupational Safety and Health). 2003. National Occupational Exposure Survey (NOES) Conducted from 1981-1983 [online]. Available: http://www.cdc.gov/noes/ [accessed July 2013].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Epichlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0254.html [accessed May, 2013].

NRC (National Research Council). 1986. EEGLS for carcinogens. Pp. 25-27 in Criteria and Methods for preparing Emergency Exposure Guidance Level (EEGL), Short-term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010. Ethylene oxide. Pp. 46-135 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

Olsen, G.W., S.E. Lacy, S.R. Chamberlin, D.L. Albert, T.G. Arceneaux, L.F. Bullard, B.A. Stafford, and J.M. Boswell. 1994. Retrospective cohort mortality study of workers with potential exposure to epichlorohydrin and allyl chloride. Am. J. Ind. Med. 25(2):205-218.

Pet'ko, L.I., E.S. Gronsberg, L.N. Chernova, and V.I. Filina. 1966. Some data on the conditions of work and status of health of workers in the production of epichlorohydrin [in Russian]. Gig. Tr. Prof. Zabol. 10(11):52-54.

Picciano, D. 1979. Cytogenetic investigation of occupational exposure to epichlorohydrin. Mutat. Res. 66(2):169-173.

Pilny, M.K., T.S. Lederer, J.S. Murray, M.S. Deacon, R.R. Hanley, J.F. Quast, and J.A. John. 1979. Epichlorohydrin B Subchronic Studies. IV. The Effects of Maternally Inhaled Epichlorohydrin on Rat and Rabbit Embryonic and Fetal Development. Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No. 878210751. Microfiche No. OTS0206139.

Quast, J.F., J.W. Henck, B.J. Postma, D.J. Schuetz, and M.J. McKenna. 1979a. Epichlorohydrin - Subchronic Studies. I. A 90-Day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats, and B6C3F_1 Mice. Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No. 878210756. Microfiche No. OTS0206139.

Quast, J.F., T.S. Lederer, B.J. Postma, D.J. Schuetz, and M.J. McKenna. 1979b. Epichlorohydrin B Subchronic Studies. II. A 12-Day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats and B6C3F_1 Mice). Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No.878210753. Microfiche No. OTS0206139.

Robinson, B.L., D.E. Guinnup, J.E. Andrews, J.W. Allis, A. McDonald, J.C. Seely, T.J. Mohin, and J.E. Simmons. 1995. Hepatic and renal assessment of acute exposure to inhaled epichlorohydrin: Toxicological evaluation and exposure modeling. Inhal. Toxicol. 7(2):289-301.

Ruijten, M.W.M.M., R. von Doorn, and A.P. van Harreveld. 2009. Assessment of Odour Annoyance in Chemical Emergency Management. RIVM Report 609200001. National Institute for Public Health and the Environment, Bilthoven, The Netherlands [online]. Available: http://www.rivm.nl/bibliotheek/rapporten/609200001.pdf [accessed August 2, 2010]

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Santodonato, J., S.S. Lande, P.H. Howard, D. Orzel, and D. Bogyo, 1980. Investigation of Selected Potential Environmental Contaminants: Epichlorohydrin and Epibromohydrin. EPA-560/11-80-006. Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

Schaper, M. 1993. Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am. Ind. Hyg. Assoc. J. 54(9):488-544.

Schultz, V.C. 1964. Fatty liver and chronic asthma-like bronchitis after inhalation of a paint solvent (epichlorohydrin) [in German]. Dtsch. Med. Wochenschr. 89(28):1342-4344.

Shell Oil Co. 1977. Epichlorohydrin Toxicity and Safety Bulletin 6-76. Submitted to EPA, Washington, DC, by Rhone-Poulenc Inc., Cranbury, NJ with Cover Letter Dated October 27, 1992. EPA Document No. 88-920009884. Microfiche No. OTS0571537.

Shell Oil Co. 1994. Initial Submission: Letter from Shell Co. to EPA Regarding Genotoxicity Studies of Ethylene Oxide, Epichlorohydrin and 1,3-Butadiene with Attachments Dated 05/06/94. EPA Document No. 88-940000277. Microfiche No. OTS0556235.

Shumskaya, N.I., N.M. Karamzina, and M.Y. Savina. 1971. Evaluation of the sensitivity of integral and specific indices during acute epichlorohydrin poisoning [in Russian]. Tokiskol. No. Prom. Khim. Vesh. 12:33–44.

Sienel, G., R. Rieth, and K.T. Rowbottom. 2000. Epoxides. Ullmann's Encyclopedia of Industrial Chemistry [online]. Available: http://onlinelibrary.wiley.com/doi/10.1002/14356007.a09_531/abstract [accessed May 9, 2013].

Slott, V.L., J.D. Suarez, J.E. Simmons, and S.D. Perreault. 1990. Acute inhalation exposure to epichlorohydrin transiently decreases rat sperm velocity. Fundam. Appl. Toxicol. 15(3):597-606.

Smith, F.A., P.W. Langvardt, and J.D. Young. 1979. Pharmacokinetics of Epichlorohydrin Administered to Rats by Gavage or Inhalation, January 15, 1979. Submitted to EPA, Washington, DC by Dow Chemical Company, Midland, MI with Cover Letter Dated December 20, 1983. EPA Document No. 878210754. Microfiche No. OTS 0206139.

Solvay. 2011. Epichlorohydrin. Solvay Chemicals. Tavaux, France [online]. Available: http://www.solvaychemicals.com/EN/products/chlorinated/Allylicproducts/Epichlorohydrin.aspx [accessed July 2013].

Sram, R.J., Z. Zudova, and N.P. Kuleshov. 1980. Cytogenetic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mutat. Res. 70(1):115-120.

Sram, R.J., M. Cerna, J. Fernandez, J. Kocisova, I. Kodytkova, J. Novakaova, P. Rossner, A. Siskova, and E. Topinkova. 1981. Mutagenic activity of inhaled epichlorohydrin in mice and rats. Mutat. Res. 85(4):287-288.

Sram, R.J., L. Landa, and I. Samkova. 1983. Effect of occupational exposure to epichlorohydrin on the frequency of chromosome aberrations in peripheral lymphocytes. Mutat. Res. 122(1):59-64.

Stott, W.T., and M.J. McKenna. 1984. The comparative absorption and excretion of chemical vapors by the upper, lower, and intact respiratory tract of rats. Fundam. Appl. Toxicol. 4(4):594-602.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Tsai, S.P., S.R. Cowles, D.L. Tackett, M.T. Barclay, and C.E. Ross. 1990. Morbidity prevalence study of workers with potential exposure to epichlorohydrin. Br. J. Ind. Med. 47(6):393-399.

Tsai, S.P., E.L. Gilstrap, and C.E. Ross. 1996. Mortality study of employees with potential exposure to epichlorohydrin: A 10 year update. Occup. Environ. Med. 53(5):299-304.

Venable, J.R., C.D. McClimans, R.E. Flake, and D.B. Dimick. 1980. A fertility study of male employees engaged in the manufacture of glycerine. J. Occup. Med. 22(2):87-91.

Weil, C.S., N. Condra, C. Haun, and J.A. Striegel. 1963. Experimental carcinogenicity and acute toxicity of representative epoxides. Am. Ind. Hyg. Assoc. J. 24:305-325.

Wexler, B. 1971. Determination of epichlorohydrin contamination in an industrial facility for the manufacturing of epoxy resins [in Romanian]. Mater. Plast. (Bucharest) 8:322-323.

WHO (World Health Organization). 1984. Epichlorohydrin. Environmental Health Criteria 33. Geneva: World Health Organization, Geneva. [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc33.htm [accessed Apr. 3, 2014].

ZSITC (Zhongshun Scientific Industrial and Trading Co., Ltd). 2013. Epichlorohydrin [online]. Available http://www.mpresinscn.com/ [accessed June 2013].

APPENDIX A

DERIVATION OF AEGL VALUES FOR EPICHLOROHYDRIN

Derivation of AEGL-1 Values

Key study:	Kobernick J.H., Nair, III., U.C. Pozzani, L.D. Roger, Jr., and J.S. West1983. Epichlorohydrin Repeated Inhalation, Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983.EPA Document No. 878212138. Microfiche No. OTS0206066.
Toxicity end point:	Irritation in humans; no-effect level was 17 ppm for 2 min; exposure at 68 ppm for 2 min was associated with irritation of the pharynx, and exposure at 136 ppm for 2 min was associated with irritation to the eyes and pharynx.
Time scaling:	Not applicable
Uncertainty factors:	10 for intraspecies variability
Calculations:	
For all AEGL-1 durations:	17 ppm ÷ 10 = 1.7 ppm

Derivation of AEGL-2 Values

Data on epichlorohydrin were inadequate for deriving AEGL-2 values. Because epichlorohydrin has been shown to have a steep concentration-response curve, AEGL-2 values were estimated by dividing the AEGL-3 values by 3.

Calculations:	1/3 AEGL-3 values (30-min, 1-, 4-, and 8-h)
10-min AEGL-2:	53 ppm; set equal to the 30-min value, because reducing the 10-min AEGL-3 value by a factor of 3 yields an AEGL value of 188 ppm for a 10-min exposure. Anecdotal information provided by Lefaux (1968) suggested that concentrations greater than 100 ppm for short intervals might result in pulmonary edema and renal damage.

	Support for those effects comes from a study of rats exposed to epichlorohydrin at 150 ppm for 1 h that exhibited evidence of severe renal damage (Ito et al. 1995). Thus, the 10-min value was set equal to the 30-min value to protect against pulmonary and renal effects.
30-min AEGL-2:	160 ppm ÷ 3 = 53 ppm
60-min AEGL-2:	72 ppm ÷ 3 = 24 ppm
4-h AEGL-2:	44 ppm ÷ 3 = 14 ppm
8-h AEGL-2:	20 ppm ÷ 3 = 6.7 ppm

Derivation of AEGL-3 Values

10-min, 30-min, 1-h AEGL-3:

Key study:	Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC50 Determination in Fischer-344 Rats. Lake Jackson Research Center, Health & Environmental Sciences - Texas, Dow Chemical, Freeport, TX. .
Toxicity end point:	1-h rat LC_{01} of 721 ppm
Time scaling:	$C^n \times k = t$; n = 0.87, based on regression analysis of rat lethality data (1-, 4-, 6-, and 8-h LC_{50} values); C = 721 ppm ÷ 10 = 72.1 ppm; t = 60 min, n = 0.87 $k = 72.1^{0.87}$ ppm × 60 min = 2,480.6 ppm-min
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10- min AEGL-3:	$C = (k/t)^{1/0.87} = (2{,}480.6 \text{ ppm-min} \div 10)^{1/0.87}$ C = 570
30-min AEGL-3:	$C = (k/t)^{1/0.87} = (2{,}480.6 \text{ ppm-min} \div 30)^{1/0.87}$ C = 160
1-h AEGL-3:	721 ppm ÷ 10 = 72.1 ppm (rounded to 72 ppm)

4- and 8-h AEGL-3:

Key study:	Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.
Toxicity end point:	6-h rat LC_{01} of 274 ppm
Time scaling:	$C^n \times k = t$; n = 0.87; C = 274 ppm ÷ 10 = 27.4 ppm; t = 360 min $k = 27.4^{0.87}$ ppm × 360 min = 6,414.2 ppm-min
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
4-h AEGL-3:	$C = (k/t)^{1/0.87} = (6{,}414.2 \text{ ppm-min} \div 240 \text{ min})^{1/0.87}$ C = 44 ppm
8-h AEGL-3:	$C = (k/t)^{1/0.87} = (6{,}414.2 \text{ ppm-min} \div 480 \text{ min})^{1/0.87}$ C = 20 ppm

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR EPICHLOROHYDRIN

The unit risk or q_1* for inhalation exposure to epichlorohydrin is 1.2×10^{-6} $(\mu g/m^3)^{-1}$ (EPA 1994). That value was derived from a carcinogenicity study in which rats developed nasal tumors after exposure to epichlorohydrin at 0, 10, or 30 ppm for 6 h/day, 5 days/week for a lifetime (Laskin et al. 1980). This study was summarized in Section 3.4.

Data summary: Groups of 100 male Sprague-Dawley rats were exposed to epichlorohydrin at 10 or 30 ppm for 6 h/day, 5 days/week for a lifetime. A total of 150 sham-exposed or untreated animals served as controls. One of 100 rats in the 30-ppm group developed squamous cell carcinomas of the nasal cavity; none of the 10-ppm or control animals developed nasal tumors.

The unit risk (q_1*) derived from the linearized multistage model is $(1.2 \times 10^{-6}$ $\mu g/m^3)^{-1}$.

The calculations for AEGL values following the method presented by NRC (1986) are presented below.

To calculate a virtually safe dose (VSD of d) at a cancer risk of 10^{-6}:

$$d = 10^{-6} \div (1.2 \times 10^{-6}\ \mu g/m^3)^{-1} = 8.3 \times 10^{1}\ g/m^3$$

To calculate the total cumulative dose for a total lifetime exposure of 70 years, which is equivalent to 25,600 days:

$$\text{total } d = d \times 25{,}600 = (8.33 \times 10^{1}\ \mu g/m^3) \times 25{,}600 = 2.13 \times 10^{6}\ \mu g/m^3.$$

Adjustment to allow for uncertainties in assessing potential cancer risks due to short-term exposure under the multistage model (Crump and Howe 1984), the total dose is divided by a factor of 6:

$$2.13 \times 10^{6}\ \mu g/m^3 \div 6 = 3.56 \times 10^{5}\ \mu g/m^3 = 3.56 \times 10^{2}\ mg/m^3 = 94\ ppm$$

Therefore, a 24-h exposure concentration associated with a 10^{-4} risk is 94 ppm. The 10^{-4} cancer risk associated with exposures for 10, 30, 60, 240, and 480 min can be calculated from the following equation:

$$PC \times t = k, \text{ where c = concentration, t = time, and k is a constant.}$$

The AEGL values are compared with cancer risk-based values associated with risks of 10^{-4}, 10^{-5}, and 10^{-6} below:

Risk	10 min	30 min	1 h	4 h	8 h
AEGL values (ppm)					
AEGL-1	1.7	1.7	1.7	1.7	1.7
AEGL-2	53	53	24	14	6.7
AEGL-3	570	160	72	44	20
Cancer risk-based values (ppm)					
10^{-6}	140	45	23	5.6	2.8
10^{-5}	1,400	450	230	56	28
10^{-4}	14,000	4,500	2,300	560	280

APPENDIX C

DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS FOR EPICHLOROHYDRIN

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than one-half of the exposed population will experience at least a distinct odor intensity and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by Ruijten et al. (2009).

The odor detection threshold (OT_{50}) for epichlorohydrin is calculated from the odor threshold of 10 ppm (50% of unconditioned personnel) reported by Shell Oil Co. (1977) and adjusted by Ruijten et al. (2009):

$$10 \text{ ppm} \times 40 \text{ ppm} \div 100 \text{ ppm} = 4.0 \text{ ppm}$$

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = k_w \text{ x } \log(C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default $k_w = 2.33$ will be used because of the lack of chemical specific data.

$$3 = 2.33 \times \log (C \div 4.0) + 0.5, \text{ which can be rearranged to}$$
$$\log (C/4.0) = (3 - 0.5) \div 2.33 = 1.07, \text{ and results in}$$
$$C = (10^{1.07}) \times 4.0 = 34.4 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life factors, such as sex, age, sleep, smoking, upper airway infections, and allergy, as well as distractions, may increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustments for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

$$LOA = C \times 1.33 = 34.4 \text{ ppm} \times 1.33 = 46 \text{ ppm (Ruijten et al. [2009])}$$

Therefore, the LOA for epichlorohydrin is 46 ppm.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR EPICHLOROHYDRIN

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)

Key reference: Kobernick, J.L., J.H. Nair, III., U.C. Pozzani, L.D. Roger, Jr., and J.S. West. 1983. 1983. Epichlorohydrin Repeated Inhalation, Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983 EPA Document No. 878212138, Microfiche No. OTS0206066.

Test species/Strain/Number: Humans

Exposure route/Concentration/Durations: Inhalation; 17, 68, or 136 ppm for 2 min.

Effects:
17 ppm: 2/4 detected odor, 0/4 experienced irritation
68 ppm: 2/4 had pharyngeal irritation; 4/4 detected odor
136 ppm: 2/4 had pharyngeal irritation and ocular irritation

End point/Concentration/Rationale: Irritation (no-effect level); none of the four subjects experienced irritation.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1, human study
Intraspecies: 10, although irritation would likely be confined to the eyes and nasal passage (portal of entry), and variability in this response is expected to be limited to variability in pharmacodynamics, a factor of 10 was applied to provide sufficient protection for asthmatic persons.

Modifying factor: 1

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applicable

Data adequacy: The subjects were exposed for only 2 min; however, the irritating properties of epichlorohydrin are not expected to vary considerably in an exposed human population.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)

Data adequacy: The animal and human data on epichlorohydrin pertaining to nonlethal end points were not adequate.
for deriving AEGL-2 values. Therefore, AEGL-3 values were divided by a factor of 3 to estimate the AEGL-2 values. Because of the steepness of the dose-response curve, this method should provide a reasonable estimate of the values and provide an adequate margin of safety relative to lethality and adequate protection against pulmonary edema. Further, long-term studies showed that high concentrations for shorter durations are more effective than lower concentrations for longer durations; therefore, the 3-fold reduction should provide adequate protection against disabling or serious effects. The 10-min value was set equal to the 30-min AEGL-2 value because human and animal data suggested that pulmonary edema and renal damage could occur at concentrations greater than 100 ppm for short intervals.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

Key reference: Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC_{50} Determination in Fischer-344 Rats. Lake Jackson Research Center, Health & Environmental Sciences - Texas, Dow Chemical, Freeport, TX.	Key reference: Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4): 751-757.
Test species/Strain/Sex/Number: Rats; Fischer-344; males and females; 6/group.	Test species/Strain/Sex/Number: Rats; Sprague-Dawley; male; 20/group.
Exposure route/Concentration/Duration: Inhalation; 552, 1,008, 1,970, or 3,995 ppm (male and female) and 2,865 and 3,275 ppm (male only) for 1 h.	Exposure route/Concentration/Duration: Inhalation; 283, 303, 339, 369, 421, or 445 ppm for 6 h.
Effects: Weight loss (all concentrations); ocular and nasal irritation, respiratory difficulty, and secretion of porphyrin-like material, corneal cloudiness (~1,970 ppm); central nervous system effects and cyanosis (~3,275 ppm); mortality: 0/12, 0/12, 2/12, 0/6, 0/6, 12/12, respectively.	Effects: Acute respiratory irritation; pulmonary hemorrhage and edema; elevated lung:body weight at ~339 ppm; mortality: 0/20, 1/20, 1/20, 15/20, 16/20, and 17/20, respectively.
Point of departure: 1-h rat LC_{01} of 721 ppm.	Point of departure: 6-h rat LC_{01} of 274 ppm.

(Continued)

AEGL-3 VALUES Continued

Uncertainty factors:
Total uncertainty factor: 10
Interspecies: 3, LC_{50} values for rats, mice, guinea pigs, and rabbits were 573-820 ppm for a 4-h exposure. Humans appear to be more sensitive than rats but are within a factor of about 2.5. A concentration of 50 ppm for 66-262 min caused squinting, hypoactivity, and salivation in animals; 20 ppm for 1 h caused burning of eyes and nose in humans. Epichlorohydrin is an epoxide and direct alkylating agent and effects are not expected to differ by more than a factor of 3.
Intraspecies: 3, the irritation and systemic toxicity caused by epichlorohydrin are likely to involve its alkylating activity. Therefore, the concentrations causing severe pulmonary irritation are not expected to vary considerably in the population. The systemic toxicity may be modulated by the detoxification enzymes, most likely epoxide hydrolase or glutathione-S-transferase. The structural similarity of epichlorohydrin to ETO suggests that metabolism involves glutathione-S-transferase, which is genetically polymorphic in human. This similarity in structure provides additional support for a factor of 3. The use of an intraspecies uncertainty factor of 3 is also supported by data on human exposures to epichlorohydrin. Use of higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value of 6.6 ppm; however, occupational exposures as high as 15-54 ppm have occurred (Pet'ko et al. 1966 [cited in NIOSH 1976]; de Jong et al. 1988) and were apparently not life-threatening.

Time scaling: $C^n \times t = k$, where n = 0.87 (derived from LC_{50} data for the rat exposed for 1, 4, 6, or 8 h).

APPENDIX E

CATEGORY PLOT FOR EPICHLOROHYDRIN

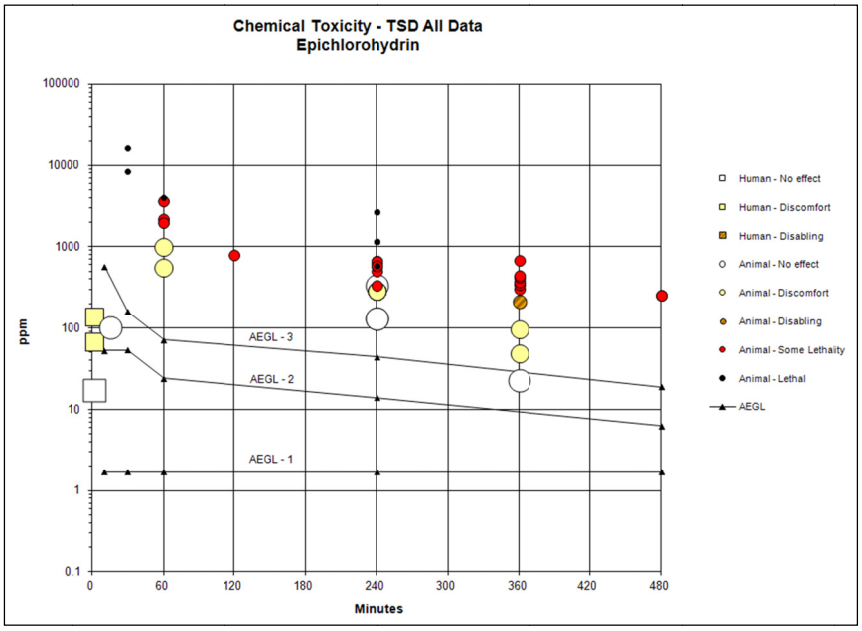


FIGURE E-1 Category plot of toxicity data and AEGL values for epichlorohydrin.

TABLE E-1 Data Used in Category Plot for Epichlorohydrin

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				1.7	10	AEGL	
AEGL-1				1.7	30	AEGL	
AEGL-1				1.7	60	AEGL	
AEGL-1				1.7	240	AEGL	
AEGL-1				1.7	480	AEGL	
AEGL-2				53	10	AEGL	
AEGL-2				53	30	AEGL	
AEGL-2				24	60	AEGL	
AEGL-2				14	240	AEGL	
AEGL-2				6.7	480	AEGL	
AEGL-3				570	10	AEGL	
AEGL-3				160	30	AEGL	
AEGL-3				72	60	AEGL	
AEGL-3				44	240	AEGL	
AEGL-3				20	480	AEGL	
Kobernick et al. 1983	Human		1	17	2	0	
	Human		1	68	2	1	Throat irritation.
	Human		1	136	2	1	Ocular, throat and nasal irritation.
Berdasco and Waechter 2012	Rat	Males	1	2,165	60	SL	LC_{50}
	Rat	Females	1	3,617	60	SL	LC_{50}
	Rat		1	500	240	SL	LC_{50}
	Rat		1	250	480	SL	LC_{50}

Dietz et al. 1985	Rat	Both	1	552	60	1	
	Rat	Both	1	1,008	60	1	
	Rat	Both	1	1,970	60	SL	Mortality (2/12)
	Rat	Both	1	3,995	60	3	Mortality (12/12)
Grigorowa et al. 1974	Rat	Males	1	635	240	SL	LC_{50}
	Rat	Males	1	582	240	SL	LC_{50}
Kimmerle 1967	Rat		1	132	240	0	
	Rat		1	331	240	0	
	Rat		1	661	240	SL	Mortality (5/10), moderate irritation to mucus membranes.
	Rat		1	2,646	240	3	Mortality (10/10)
Kobernick et al. 1983	Rat	Both	1	580	240	3	Mortality (12/12)
	Rat	Both	1	580	240	SL	Mortality (15/30)
Slott et al. 1990	Rat	Both	1	1,160	240	3	Mortality (6/6)
Laskin et al. 1980	Rat	Males	1	100	240	0	
	Rat	Males	1	303	360	SL	Mortality (1/20)
	Rat	Males	1	339	360	SL	Mortality (1/20), acute respiratory irritation with hemorrhage and severe edema.
	Rat	Males	1	369	360	SL	Mortality (15/20), acute respiratory irritation with hemorrhage and severe edema.
	Rat	Males	1	421	360	SL	Mortality (16/20), acute respiratory irritation with hemorrhage and severe edema.

(Continued)

TABLE E-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Rat	Males	1	445	360	SL	Mortality (17/20), acute respiratory irritation with hemorrhage and severe edema.
Weil et al. 1963	Rat		1	250	480	SL	Mortality (4/6)
Freuder and Leake 1941	Mouse		1	8,300	30	3	100% mortality
	Mouse		1	16,600	30	3	100% mortality
Grigorowa et al. 1974	Mouse	Males	1	794	120	SL	LC_{50}
Kobernick et al. 1983	Mouse	Males	1	1,160	240	3	Irritation of mucous membranes, increased respiration, lethargy, and labored breathing.
Kimmerle 1967	Mouse	Males	1	132	240	0	
	Mouse	Males	1	331	240	0	
	Mouse	Males	1	661	240	SL	Mortality (1/20)
	Mouse	Males	1	2,646	240	3	Mortality (20/20)
Buckley et al. 1984	Mouse		1	687	360	SL	
Kobernick et al. 1983	Guinea pig	Males	1	290	240	1	Irritation of mucous membranes.
	Guinea pig	Males	1	580	240	SL	Mortality (2/6), irritation of mucous membranes.
	Guinea pig	Males	1	1,160	240	3	Mortality (4/4)
Kimmerle 1967	Guinea pig	Males	1	132	240	0	
	Guinea pig	Males	1	331	240	SL	Mortality (4/5)
	Guinea pig	Males	1	661	240	SL	Mortality (4/5)

	Guinea pig	Males	1	2,646	240	3	Mortality (5/5)
Kobernick et al. 1983	Rabbit	Males	1	290	240	1	Irritation of mucous membranes.
	Rabbit	Males	1	580	240	SL	Mortality (2/3), irritation of mucous membranes.
	Rabbit	Males	1	1,160	240	3	Mortality (3/3)
Kobernick et al. 1983	Dog		1	290	240	1	Irritation of mucous membranes.
	Dog		1	580	240	3	Mortality (1/1)
	Dog		1	1,160	240	3	Mortality (1/1)
	Monkey		1	290	240	1	Irritation of mucous membranes.
Industrial Bio-Test Laboratories 1977a	Rat	Both	1	9.7	360	0	
	Rat	Both	1	23	360	0	
	Rat	Both	1	48.8	360	1	
	Rat	Both	1	97.3	360	1	
	Rat	Both	1	209.8	360	2	
Gardner et al. 1985	Rat		1	101	15	0	

For category 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

5

Ethylene Chlorohydrin[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager George Rusch (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Ethylene chlorohydrin is used in the manufacture of pesticides, plasticizers, plant-protection agents, and dye intermediates. It is generally manufactured with a purity of greater than 99% with some being produced as an anhydrous grade. It is also used as a precursor in the production of ethylene oxide. An odor threshold of 0.4 ppm has been reported for ethylene chlorohydrin but data are not available from which to determine an acute level of odor awareness.

Data on ethylene chlorohydrin were insufficient for deriving AEGL-1 values. There were neither human nor animal data on AEGL-1 severity effects following exposure to ethylene chlorohydrin vapor.

Data on AEGL-2 severity effects in humans were not available. Because animal data involved either no lethality or 100% lethality, the concentration-response relationship for ethylene chlorohydrin vapor exposure is unknown. No data pertaining to AEGL-2 effects were available. Data in mice (Goldblatt 1944) showed there to be less than a four-fold difference between the concentration associated with a nonlethal response (280 ppm for 120 min) and the concentration producing 100% lethality (1,090 ppm for 120 min), which suggests a steep exposure-response relationship. In accordance with NRC (2001) guidance, the AEGL-2 values were estimated as a three-fold reduction of the AEGL-3 values.

The point-of-departure for deriving AEGL-3 values was 280 ppm for 120 min, which was the concentration that did not produce lethality in mice (Goldblatt 1944). Values were scaled across time using the equation $C^n \times t = k$. Default values for n of 3 for extrapolating to shorter durations and 1 when extrapolating to longer durations were used to derive values protective of human health (NRC 2001). Two uncertainty factors of 10 were applied; one to account for interspecies differences and one to account for intraspecies variability. Ethylene chlorohydrin does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged epithelial tissue of the respiratory tract; however, the available data are not sufficient to conclusively describe the mechanism of toxicity.

The AEGL values for ethylene chlorohydrin are presented in Table 5-1.

1. INTRODUCTION

Ethylene chlorohydrin may be used in the manufacture of pesticides, plasticizers, plant-protection agents, and dye intermediates (HSDB 2005). It is generally manufactured with a purity greater than 99% with some being produced as an anhydrous grade. It is a precursor in the production of ethylene oxide. Production volumes of $1.6\text{-}2.0 \times 10^7$ kg have been reported (HSDB 2005).

The chemical and physical properties of ethylene chlorohydrin are presented in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Goldblatt and Chiesman (1944) described two cases originally reported by Koelsch (1927) involving acute exposure to ethylene chlorohydrin. In one case, a worker was exposed to ethylene chlorohydrin while cleaning a machine with a rag soaked in the chemical (dermal and inhalation exposure) for 2.5 h. Exposure concentrations were not measured and there was no report of the use of protective equipment. He became nauseous and vomited and experienced a violent headache and giddiness. He died the next day, and autopsy showed inflammatory detachment of mucous membranes in the respiratory passages and pulmonitis of the right lung. The other case concerned one of four men involved in staining oil-cloth with dye mixed with ethylene chlorohydrin. Exposure concentrations were not measured and there was no report of the use of protective equipment. The man experienced nausea and narcosis and stopped working. The duration of exposure was not specified. He died in the evening after suffering from dyspnea, and autopsy showed cerebral and pulmonary edema, acute gastrointestinal catarrh, renal degeneration, disease of the cardiac valves and aorta, and arterial calcification.

TABLE 5-1 AEGL Values for Ethylene Chlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)	One-third of the AEGL-3 values (NRC 2001).
AEGL-3 (lethal)	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)	Nonlethal exposure of mice at 280 ppm for 120 min (Goldblatt 1944).

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposures at concentrations below the AEGL-2 value are without effect.

TABLE 5-2 Chemical and Physical Data for Ethylene Chlorohydrin

Parameter	Value	Reference
Synonyms	2-chloroethanol; 2-chloro ethyl alcohol	HSDB 2005
CAS registry no.	107-07-3	HSDB 2005
Chemical formula	C_2H_5ClO	HSDB 2005
Molecular weight	80.52	HSDB 2005
Physical state	Liquid	HSDB 2005
Melting point	-67°C	HSDB 2005
Boiling point	128-130°C	HSDB 2005
Density/specific gravity	1.197 at 20°C	HSDB 2005
Solubility in water	1×10^6 mg/L	HSDB 2005
Relative vapor density	2.78	HSDB 2005
Vapor pressure	4.9 mm Hg at 20°C	HSDB 2005
Saturated vapor concentration	645 ppm	Calculated according to Perez and Solderholm (1991)
Conversion factors in air	1 ppm = 3.29 mg/m^3 1 mg/m^3 = 0.30 ppm	NIOSH 2011

Goldblatt and Chiesman (1944) also reported a fatality following exposure to ethylene chlorohydrin vapor. In one case, a worker became ill after exposure for about 1.5 h to vapors of ethylene chlorohydrin and ethylene dichloride while performing maintenance in an ethylene chlorohydrin tower. Exposure concentrations were not measured and there was no report of the use of protective equipment. He experienced repeated vomiting 1 h after the exposure, unsteadiness at 2 h, weak pulse and restlessness at 4 h, and low blood pressure and rales between 4 and 11.5 h after exposure. He deteriorated rapidly and died 14 h after exposure. Autopsy showed congestion of the tracheal mucous membranes, marked and extensive collapse of the lungs, pulmonary edema, and cerebral congestion.

Dierker and Brown (1944) reported a fatal case in which a man was exposed for 2 h to ethylene chlorohydrin and petroleum solvents during a cleaning operation. The worker wore rubber gloves to prevent dermal contact, but was exposed to solvent vapors by inhalation. He experienced nausea and vertigo and was later sent to a hospital for treatment. He was cyanotic with labored breathing and a slightly irregular pulse and died from respiratory failure that night. Autopsy showed congested lungs and kidneys, edema of the liver, and cloudy swelling of the renal tubules. Post-exposure estimates of the concentration of petroleum solvents and ethylene chlorohydrin were determined by resuming the cleaning operation and measuring the exposure concentration at the breathing level. The petroleum solvent concentration was 150-400 ppm and the average ethylene chlorohydrin concentration was estimated to be 305 ppm.

Agricultural exposure to ethylene chlorohydrin during treatment of seed potatoes to enhance germination resulted in one death (Bush et al. 1949). The inhalation exposure concentration estimated by field and laboratory tests was 300-500 ppm. Dermal contact also occurred during the treatment process. The use of protective equipment was not reported. The worker experienced nausea, vomiting, dizziness, abdominal pain, weakness, and diminished vision after working several hours. He eventually returned to work, but collapsed several hours later and was transported to a hospital in a comatose condition where he died that night. Autopsy findings revealed fatty infiltration of the liver, edema of the brain and lungs, dilation of the heart chambers, degeneration of the myocardium, congestion of the spleen, cloudy swelling and hyperemia of the kidneys, petechial hemorrhages of the skin and conjunctiva, ascites, and hydrothorax.

2.2. Nonlethal Toxicity

An odor threshold for ethylene chlorohydrin of 0.4 ppm has been reported (ACGIH 2001).

Several nonfatal case reports of exposure to ethylene chlorohydrin vapor were summarized by Goldblatt and Chiesman (1944). These cases occurred during a time period where the average exposure concentration was 18 ppm. There was also likely concurrent exposure to ethylene dichloride. The exposure duration was not specified and the use of protective equipment was not reported. A qualitative summary of signs and symptoms by organ system was provided: digestive system (nausea, epigastric pain, and vomiting); cardiovascular system (shock and depressed circulation); nervous system (headache, giddiness, incoordination, confusion, and mild narcotic effects); respiratory system (cough and rhonchi); and skin (erythema on arms and trunk in severe cases).

In addition to the fatality described in Section 2.1, Bush et al. (1949) also reported nonlethal toxicity in five agricultural workers exposed intermittently to ethylene chlorohydrin at 300-500 ppm (estimated by field and laboratory tests). The exposure duration was not specified and the use of protective equipment was not reported. The workers experienced nausea, vomiting, irritation of the

eyes, nose, and lungs, dizziness, diminished vision, and numbness of the hands and fingers. Four workers required hospitalization for treatment of symptoms.

2.3. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of ethylene chlorohydrin in humans were not available.

2.4. Genotoxicity

No information regarding the genotoxicity of ethylene chlorohydrin in humans was available.

2.5. Carcinogenicity

Greenberg et al. (1990) reported an increased risk of mortality from pancreatic cancer and leukemia in workers at a Union Carbide plant in which ethylene chlorohydrin was manufactured. In a 10-year follow-up of 278 male workers at the plant, Benson and Teta (1993) reported excess deaths from pancreatic cancer (8 observed vs. 1.6 expected, SMR = 492 with 95% confidence interval of 158-1,140) and lymphopoietic and hematopoietic cancers (8 observed vs. 2.7 expected; SMR = 294 with 95% confidence interval of 127-580). Olsen et al. (1997) found no increased risk for these cancers in workers at Dow Chemical facilities.

2.6. Summary

Human data with which to develop AEGL values are not available. Only qualitative information is available regarding the inhalation toxicity of ethylene chlorohydrin in humans. The available reports lack details about exposure and involved concurrent exposure to other chemicals. Case reports failed to provide definitive information regarding target organs or cause of death.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Ambrose (1950) describe experiments in which groups of five adult male rats (strain not specified) were exposed using various exposure regimens and various dilutions of the test material. Various dilutions of ethylene chlorohydrin were placed in a bubbling tower immersed in a 40°C water bath. Air was passed through the tower and into the exposure chamber (neither air temperature nor air

flow were specified, but air flow was noted as never exceeding 570 mL/min). No indication (other than the air flow value) was given that the possibility of aerosolization of the test material was considered. The inhalation exposure concentrations associated with specific dilutions of ethylene chlorohydrin in water were not measured or estimated (whether vapor phase, aerosol, or mixed) in the study report. On the basis of the experimental results, the investigators noted that ethylene chlorohydrin was extremely toxic but deaths were delayed from 1-24 h, depending on the concentration of the chemical in aqueous solution. The inhalation exposure concentrations associated with specific dilutions of ethylene chlorohydrin in water were not measured or estimated. Ambrose (1950) concluded that a 1-h exposure to ethylene chlorohydrin at 7.5 ppm and repeated exposure at 2 ppm was lethal to rats; however, the study did not describe the source of these air concentration values. In addition, the report did not specify the incidence of lethality at each concentration. Qualitatively, rats exhibited no signs of toxicity prior to ethylene chlorohydrin-induced lethality. Necropsy findings included cyanosis, dark blood, and "darker than normal" liver and kidneys. The reporting limitations associated with this study (lack of measured or estimated exposure concentrations, lack of lethality data) preclude the use of these data in deriving AEGL values.

Goldblatt (1944) reported results of single exposure experiments in young adult rats (three animal per, strain and sex not specified) exposed to ethylene chlorohydrin vapor. The exposure apparatus consisted of a gas meter, flow meter, constant dropping apparatus, a suction system, and chambers for vaporization, mixing, and exposure. Air flow was maintained at 8-10 L/min and dropping of the test article was precisely controlled. Although no analytic data were provided, the investigator noted that the vapor concentration could be calculated within reasonable limits for any air flow or test article drop rate. It was stated that the ethylene chlorohydrin was pure but no data were provided. A 15-min exposure at 0.003 g/L (840 ppm, based on the conversion factor of 0.001 g/L = 280 ppm, v/v, reported by Goldblatt [1944]) and a 120-min exposure at 0.001 g/L (280 ppm) were not lethal whereas a 30-min exposure at 0.004 g/L (1,120 ppm) and 60-min exposure at 0.003 g/L (840 ppm) killed all three rats within 1 day (see Table 5-3). Narcosis was not produced and most exposure-related deaths occurred following the exposure rather than during the exposure. Histologic examinations revealed renal damage (medullary hemorrhage, hemolysis, and swollen and detached convoluted tubules) and areas of collapse in the lungs, but no pulmonary hemorrhage or edema.

Goldblatt (1944) also described a repeated-exposure experiment in which three rats (strain and sex not specified) were exposed for 15 min/day to ethylene chlorohydrin at 0.002-0.005 g/L (about 560-1,400 ppm/day) for 11 days. One rat died on day 3, another on day 6, and a third on day 11. Observed signs included weight loss and lethargy. Urinalysis revealed no signs of renal toxicity although histologic examination of dead rats showed renal "congestion" and hemorrhage and hepatic congestion.

A 4-h LC_{50} (lethal concentration, 50% lethality) value of 32 ppm for rats was reported in a review by Browning (1965).

3.1.2. Mice

Dierker and Brown (1944) exposed six mice (sex not reported) to ethylene chlorohydrin at 365 ppm for 120 min. The atmosphere was maintained by evaporating anhydrous ethylene chlorohydrin in an air stream through the exposure chamber. The animals became ill in less than 1 h. One mouse died 4 h after exposure from a respiratory-related cause. Examination showed pulmonary edema, capillary engorgement, and interstitial hemorrhages in the liver, kidney, and lungs.

Goldblatt (1944) also reported lethality data for groups of three adult mice (strain and sex not specified) following single 15- to 120-min exposures to ethylene chlorohydrin (see Table 5-4). Experimental protocols were the same as those as described for rats in Section 3.1.1.

TABLE 5-3 Lethality in Rats Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Duration (min)	Effect
0.003 g/L (840 ppm)	15	Nonlethal
0.004 g/L (1,120 ppm)	30	3/3 dead next day
0.003 g/L (840 ppm)	60	Lethal next day
0.001 g/L (280 ppm)	120	Nonlethal

[a]Three rats/group. Conversion of g/L to ppm based on 0.001 g/L = 280 ppm.
Source: Adapted from Goldblatt 1944.

TABLE 5-4 Lethality in Mice Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Duration (min)	Effect
0.001 g/L (280 ppm)	120	Nonlethal
0.003 g/L (840 ppm)	60	3/3 dead next day
0.0032 g/L (896 ppm)	60	3/3 dead next day
0.0039 g/L (1,090 ppm)	15	2/3 dead after 2 days
0.0039 g/L (1,090 ppm)	120	3/3 dead in 140-170 min
0.0045 g/L (1,260 ppm)	30	3/3 dead next day
0.0052 g/L (1,460 ppm)	60	3/3 dead in 100 min to next day
0.007 g/L (1,960 ppm)	120	3/3 dead in 110-129 min

[a]Three mice/group. Conversion of g/L to ppm based on 0.001 g/L = 280 ppm.
Source: Adapted from Goldblatt 1944.

In a toxicity study by Lawrence et al. (1971), duplicate groups of five male Swiss-Webster mice were exposed at various non-specified concentrations of ethylene chlorohydrin (99% pure) for 10-15 min. An LT_{50} (duration resulting in 50% lethality) of 13.3 min reported, but the data were insufficient for calculating an LC_{50}. Although the vapor concentration was not stated, the actual concentration in the chamber was not constant and that equilibrium was likely occurring after 14 min. The data, which appeared to be from five exposure concentrations over the previously noted 10-15 min durations, were insufficient as a basis for any exposure-response estimate.

3.1.3. Guinea Pigs

Lethality data for guinea pigs were reported by Goldblatt (1944) and are summarized in Table 5-5. Although the investigator suggested guinea pigs were less sensitive to the lethal effects of ethylene chlorohydrin, the data are for only one animal per exposure group.

3.1.4. Summary of Animal Lethality Data

In studies of laboratory animals exposed to ethylene chlorohydrin, lethality generally did not occur during exposure but was delayed from approximately 2 h to 1 day postexposure. Both interspecies and intraspecies variability in lethal response is evident, but the guinea pig data are based on a study that used only one animal per concentration.

3.2. Nonlethal Toxicity

3.2.1. Rats

A 1-h exposure to ethylene chlorohydrin at 4 ppm was not lethal to rats (Ambrose 1950). Goldblatt (1944) reported that a single 15-min exposure of rats (sex and strain not specified) to ethylene chlorohydrin at 0.003 g/L (about 840 ppm) was not lethal. Exposed rats exhibited discomfort, closure of the eyes, and nasal irritation, but it was unclear whether the effects were observed in all of the rats or just those more severely affected.

TABLE 5-5 Lethality in Guinea Pigs Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Exposure Duration (min)	Effect
0.003 g/L (840 ppm)	30	Nonlethal
0.003 g/L (840 ppm)	120	Dead next day
0.0039 g/L (1,090 ppm)	108	Dead next day
0.005 g/L (1,400 ppm)	55	Nonlethal

[a]One guinea pig/group. Conversion pf g/L to ppm based on 0.001 g/L = 280 ppm.
Source: Adapted from Goldblatt 1944.

3.2.2. Mice

A 120-min exposure of mice (sex and strain not specified) to ethylene chlorohydrin at 0.001 g/L (about 280 ppm) was not lethal (Goldblatt, 1944).

In the experiment by Dierker and Brown (1944), five of six mice survived a 120-min exposure to ethylene chlorohydrin at 365 ppm. The animals became ill less than an hour into the exposure, and displayed increased respiratory rates and minimal activity. Labored respiration was observed 4 h postexposure, and improvement was observed 6-h postexposure. The mice were reported to be normal 24 h after exposure and did not develop any untoward symptoms during a 1-week postexposure observation period.

3.2.3. Guinea Pigs

A single 30-min exposure to ethylene chlorohydrin at 0.003 g/L (about 840 ppm) or a 55-min exposure at 0.005 g/L (about 1,400 ppm) was not lethal to guinea pigs (one animal/exposure) (Goldblatt 1944).

3.2.4. Cats

Goldblatt (1944) reported that cats (number, sex, and breed were not specified) exposed to ethylene chlorohydrin at concentrations of 10-15 mg/L (2,800-4,200 ppm) for several hours showed no effects on blood pressure and no signs of respiratory disturbances regardless of whether the exposure was via a tracheal cannula or through the nasal passages.

3.2.5. Rabbits

Goldblatt (1944) reported that rabbits (number, sex, and breed not specified) exposed to ethylene chlorohydrin at concentrations of 10-15 mg/L (2,800-4,200 ppm) for several hours showed no effects on blood pressure and no signs of respiratory disturbances regardless of whether the exposure was via a tracheal cannula or through the nasal passages.

3.2.6. Summary of Nonlethal Toxicity in Animals

Available data do not precisely characterize the concentration-response relationship for nonlethal effects of exposure to ethylene chlorohydrin vapor. Most studies were lethality assays and, although identifying some exposures as nonlethal, do not provide detailed information on the nature or severity of the effects (if any) that occurred. Generally, the exposure-response relationship is poorly defined.

3.3. Developmental and Reproductive Effects

No information is available regarding the developmental and reproductive toxicity of ethylene chlorohydrin in animals following inhalation exposure. Results of intravenous studies in CD-1 mice showed that ethylene chlorohydrin increased the incidence of malformed fetuses only at a dose that was associated with an increased maternal mortality (NTP 1983a). Studies in New Zealand white rabbits also intravenously exposed to ethylene chlorohydrin failed to demonstrate fetotoxic or teratogenic effects (NTP 1983b).

3.4. Genotoxicity

NTP (1985) reported that ethylene chlorohydrin was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 with and without Aroclor-induced hamster or rat liver S9. Ethylene chlorohydrin was not mutagenic in strains TA1537 or TA98 and did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. Overall, the compound is considered a weak base-pair substitution mutagen in bacteria. It is essentially negative in other test systems such as fungi, *D. melanogaster*, mammalian cell cultures, and rodents.

3.5. Carcinogenicity

Information regarding the carcinogenicity of ethylene chlorohydrin following inhalation exposure is not available. In dermal studies with rats and mice, NTP (1985) concluded that increases in incidences of lymphomas or leukemias, as well as increased incidences in alveolar/bronchiolar adenomas and carcinomas, were not treatment related.

3.6 Summary

Lethality generally did not occur during inhalation exposure to ethylene chlorohydrin but rather was delayed from approximately 2 h to 1 day after exposure. Nonlethal effects were not well characterized and information was generally not available to describe the nature or severity of the effects. No information is available regarding the developmental and reproductive toxicity or carcinogenicity of ethylene chlorohydrin in animals following inhalation exposure. The chemical is considered a weak base-pair substitution mutagen in bacteria, but is essentially negative in other test systems such as fungi, *D. melanogaster*, mammalian cell cultures, and rodents.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There is no information on the metabolism and disposition of ethylene chlorohydrin following inhalation exposure. In Wistar rats, up to 80% of an oral-

ly administered radiolabeled dose was excreted in the urine although none of the radioactivity represented the parent compound (Grunow and Altmann 1982). Radioactivity in the blood declined by 50% after 4 h. The major urinary metabolites were thiodiacetic acid and thionyldiacetic acid. Radio-labeled carbon dioxide was also detected in expired air, indicating that carbon dioxide is a metabolite of ethylene chlorohydrin. Johnson (1965) hypothesized that ethylene chlorohydrin toxicity may, in part, be a function of increased chloroacetaldehyde resulting from saturation of glutathione conjugation. Results of in vitro and in vivo metabolism studies showed formation of S-carboxymethyl-GSH in livers of rats given ethylene chlorohydrin (Johnson 1967).

4.2. Mechanism of Toxicity

The precise mode of action of ethylene chlorohydrin is not known. Goldblatt and Chiesman (1944) noted the delay between exposure and onset of symptoms in humans, suggesting the absence of warning properties of exposure. Bush et al. (1949) reported autopsy findings of severe liver and brain damage as well as involvement of other organs in an occupational accident. Signs and symptoms in nonfatal exposures suggested multi-organ involvement including gastrointestinal disorders, nervous system effects, and respiratory tract irritation. In animals, Goldblatt (1944) stated that although inhalation exposure to ethylene chlorohydrin appeared to have a depressant effect on the central nervous system and would induce immobility, a typical narcosis was not observed. Additionally, necropsy results from the Goldblatt (1944) experiments did not reveal significant evidence of respiratory-tract tissue damage but did suggest renal involvement. Goldblatt (1944) reported that inhalation exposure of rats (chamber exposure or via a tracheal cannula) produced neither respiratory disturbances nor effects on blood pressure.

4.3. Structure-Activity Relationships

There are no structure activity data from which to develop AEGL values for ethylene chlorohydrin. It has been hypothesized that chloroacetaldehyde is a metabolite of ethylene chlorohydrin (Johnson 1965). AEGL values for ethylene chlorohydrin and chloroacetaldehyde vary by less than two-fold; 10- and 30-min values for ethylene chlorohydrin are somewhat lower than those for chloroacetaldehyde while the 1-, 4-, and 8-h values for ethylene chlorohydrin values are slightly higher.

4.4. Species Variability

Data are insufficient to accurately assess species variability in the toxic response to inhalation exposure to ethylene chlorohydrin. Goldblatt and Chiesman (1944) suggested that women may be somewhat more liable to develop symptoms than men on the basis of case reports.

4.5. Concurrent Exposure Issues

There are no concurrent exposure issues unique to ethylene chlorohydrin that would be instrumental in developing the AEGL values.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Studies in humans show that nonlethal exposure to ethylene chlorohydrin causes several effects which exceed the definition of both AEGL- 1 and AEGL-2 effects, including vomiting, dizziness, diminished vision, shock, depressed circulation, incoordination, confusion, and mild narcotic effects (Goldblatt and Chiesman 1944; Bush et al. 1949). These studies also either include concomitant exposure to other chemicals or do not provide adequate exposure information. Therefore, data in humans are not suitable for derivation of AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Studies in animals either identify effects which exceed the AEGL-1 definition or do not identify any effects. Goldblatt (1944) reported signs of discomfort, eye closure, and nasal irritation in rats exposed to ethylene chlorohydrin at 840 ppm for 2 h; however, since eye closure is an AEGL-2 effect, the data are not suitable for derivation of AEGL-1 values. Minimal activity, an AEGL-2 level effect, was reported in mice exposed to ethylene chlorohydrin at 365 ppm for 2 h (Dierker and Brown 1944). Exposure of mice (280 ppm for 2 h), guinea pigs (840 for 30 min or 1,400 ppm for 55 min), cats (2,800-4,200 ppm for “several hours”), and rabbits (2,800-4,200 ppm for “several hours”) did not produce adverse effects. Thus, no data are available to define the concentration-response relationship for AEGL-1 effects.

5.3. Derivation of AEGL-1 Values

There are no exposure-response data consistent with AEGL-1 severity effects and estimation of exposures consistent with such minor responses is not possible. Thus, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are no quantitative human data with which to develop AEGL-2 values for ethylene chlorohydrin. Although nonlethal exposures reportedly resulted in a wide range of effects (Goldblatt and Chiesman 1944; Bush et al. 1949), reliable exposure concentration and duration estimates are lacking.

6.2. Animal Data Relevant to AEGL-2

Animal data appropriate for AEGL-2 derivation are deficient in characterization of the nonlethal effects and do not characterize an exposure-response relationship.

6.3. Derivation of AEGL-2 Values

Exposure-response data for toxic effects consistent with AEGL-2 severity are lacking for ethylene chlorohydrin. Case reports in humans lack adequate exposure descriptions and animal toxicity data focus on lethal response, with most experimental results showing near 100% lethality. In experiments with less than 100% lethality, no information is provided about nonlethal effects.

Following the guidelines in NRC (2001), AEGL-2 values for ethylene chlorohydrin were estimated as one-third of the AEGL-3 values. Data in mice (Goldblatt 1944) showed there to be a less than four-fold difference between a nonlethal response (280 ppm for 120 min) and 100% lethality (1,090 ppm for 120 min), which implies a steep exposure-response relationship. The AEGL-2 values for ethylene chlorohydrin are presented in Table 5-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Reports of human deaths following occupational exposure accidents lack adequate description of the exposures. Estimated exposures of 300 ppm for approximately 2 h and at 500 ppm (unknown duration) were reportedly lethal.

7.2. Animal Data Relevant to AEGL-3

Exposures to ethylene chlorohydrin as low as 1,120 ppm for 30 min (rats) and 1,260 ppm for 30 min (mice) caused 100% lethality (Goldblatt 1944). Results from this study also showed that exposing rats at 840 ppm for 15 min or mice at 280 ppm for 120 min was not lethal. The study was compromised by the small number of animals used (three per group). Although the animal data do not precisely describe the exposure-response relationship for inhalation exposure to ethylene chlorohydrin vapor, the data do differentiate between nonlethal and lethal exposures. Although Ambrose (1950) reported lethality and nonlethal observations, analytic concentrations were not provided and the details of the experiments were insufficient to justify use of the data in deriving AEGL-3 values.

TABLE 5-6 AEGL-2 Values for Ethylene Chlorohydrin

10 min	30 min	1 h	4 h	8 h
2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)

7.3. Derivation of AEGL-3 Values

No data are available with which to definitively assess the exposure-response relationship for lethality resulting from inhalation exposure to ethylene chlorohydrin. Experiments in animals are compromised by the small numbers of animals tested and by response data showing near 100% lethality or no lethality. Such data do not allow for a valid estimation of a lethality threshold using benchmark dose methods. Therefore, exposure data from the Goldblatt (1944) study showing no lethality were considered were used to estimate a lethality threshold for AEGL-3 development. Data from studies of mice provided both a nonlethal (280 ppm) and 100% lethal (1,090 ppm) estimate for the same exposure duration (120 min) and, therefore, were considered most appropriate for determining a point-of-departure for AEGL-3 derivation.

The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on ethylene chlorohydrin were inadequate to calculate an empirical value of n, so default values of n =3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used.

Two uncertainty factors of 10 were applied; one to account for interspecies differences and one to account for intraspecies variability. Ethylene chlorohydrin does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged respiratory tract epithelial tissue; however, the available data are not sufficient to conclusively describe a mechanism of toxicity. The resulting AEGL-3 values are presented in Table 5-7 and their derivation summarized in Appendix A. A comparison of the AEGL-3 values with the human lethality estimate (300 ppm for 2 h) reported by Dierker and Brown (1944) shows that the AEGL-3 values are sufficiently protective (protection of sensitive populations would necessitate an order of magnitude reduction of the 300 ppm exposure to 30 ppm) and serves to justify the interspecies uncertainty factor.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Data were not available for developing AEGL-1 values for ethylene chlorohydrin. In lieu of AEGL-2 specific data, the AEGL-2 values were estimated as one-third of the AEGL-3 values (NRC 2001). For lethal exposures, deaths occurred both during and up to a day following exposure. Animals exhibited a wide range of effects during exposure, including eye closure, nasal irritation, labored respiration, and decreased activity. Signs and toxicity and limited necropsy findings suggested multiple organ and system involvement (cyanosis, dark blood, renal medullary hemorrhage, hemolysis, detached convoluted tubules, areas of collapse in the lungs, pulmonary congestion, and pulmonary edema)

with no definitive mode of action being described. Derivation of the AEGL-3 values was based on a nonlethal exposure of rats as an estimate of a lethal threshold; there was very little margin between exposures causing no lethality and those causing 100% lethality. AEGL values for ethylene chlorohydrin are presented in Table 5-8.

8.2. Other Standards and Guidelines

A summary of available standards and guidelines for ethylene chlorohydrin is presented in Table 5-9. The National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit have ceiling notations indicating that 1 ppm should not be exceeded at any time. The German maximum concentration and the Dutch maximum allowable concentration are also set at 1ppm, but there is no ceiling notation. The Occupational Safety and Health Administration (OSHA) has a permissible exposure limit of 5 ppm for ethylene chlorohydrin. All of the standards for the chemical have a skin notation recognizing the potential for toxicity from dermal absorption. The NIOSH immediately dangerous to life or health (IDLH) value was set at 7 ppm on the basis of acute inhalation toxicity data in animals (Patty 1963; Browning 1965). The AEGL values are consistent with current standards and guidelines and protective of human health. The AEGL-2 value for 30 min is comparable but less than the IDLH value, as would be expected from the differences in the target populations. At exposures higher than the AEGL-2, individuals could experience impaired ability to escape or long-lasting health effects.

TABLE 5-7 AEGL-3 Values for Ethylene Chlorohydrin

10 min	30 min	1 h	4 h	8 h
6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

TABLE 5-8 AEGL Values for Ethylene Chlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)
AEGL-3 (lethal)	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

TABLE 5-9 Standards and Guidelines for Ethylene Chlorohydrin

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)
AEGL-3	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)
IDLH (NIOSH)[a]	–	7 ppm (23 mg/m^3)	–	–	–
PEL-TWA (OSHA)[b]	–	–	–	–	5 ppm (16 mg/m^3)
TLV-C (ACGIH)[c]	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)
REL-C (NIOSH)[d]	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)
MAK (Germany)[e]	–	–	–	–	1 ppm (3.3 mg/m^3)
MAC (the Netherlands)[f]	–	–	–	–	1.0 ppm (3 mg/m^3)

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[b]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2013]) is defined as an employee's exposure to any substance that shall not exceed the 8-h TWA given for that substance in any 8-h work shift of a 40-h work week. The PEL for ethylene chlorohydrin includes a skin notation.

[c]TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2012) is the concentration that should not be exceeded at any time. The TLV-ceiling for ethylene chlorohydrin includes a skin notation.

[d]REL-C (recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined as the value that should not be exceeded at any time. The REL ceiling for ethylene chlorohydrin includes a skin notation.

[e]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 2002) is defined analogous to the OSHA PEL-TWA. The MAK for ethylene chlorohydrin includes a skin notation.

[f]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]), Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2004) is defined analogous to the OSHA PEL-TWA. The MAC for ethylene chlorohydrin includes a skin notation.

8.3. Data Adequacy and Research Needs

Data reported for human exposure to ethylene chlorohydrin demonstrate systemic effects of ethylene chlorohydrin and add support to the toxicologic end points of the animal data. Quantitative animal data are available from a few inhalation studies of rats, mice, guinea pigs, cats, and rabbits. The data demonstrate toxicity outcomes in animals that are similar to those observed in humans. Although the animal data provide information on lethal and nonlethal exposures, data used to derive AEGL-3 values are from a single dose-ranging study that used a small number of animals. Additional data providing information at exposures that are irritating or nonincapacitating would be useful for deriving AEGL-1 values and refining AEGL-2 values. Additional data are needed with respect to the exposure-response relationship and mode of action of ethylene chlorohydrin vapor exposure.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Ethylene chlorohydrin (CAS Reg. No. 107-07-3). Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. Ethylene chlorohydrin (CAS Reg. No. 107-07-3). 2012 TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substance and Physical Agents. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Ambrose, A.M. 1950. Toxicological studies of compounds investigated for use as inhibitors of biological processes. II. Toxicity of ethylene chlorohydrin. AMA Arch. Ind. Hyg. Occup. Med. 2(5):591-597.

Benson, L.O., and M.J. Teta. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br. J. Ind. Med. 50(8):710-716.

Browning, E. 1965. Ethylene chlorohydrin. Pp. 397-401 in Toxicity and Metabolism of Industrial Solvents. New York: Elsevier.

Bush, A.F., H.K. Abrams, and H.V. Brown. 1949. Fatality and illness caused by ethylene chlorohydrin in an agricultural occupation. J. Ind. Hyg. Toxicol. 31(6):352-358.

DFG (Deutsche Forschungsgemeinschaft). 2002. 2-Chlorethanol. The MAK Collection for Occupational Health and Safety. Wiley-Online Library [online]. Available: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10707d0034/full [accessed Apr. 8, 2014].

Dierker, H., and P.G. Brown. 1944. Study of a fatal case of ethylene chlorohydrin poisoning. J. Ind. Hyg. Toxicol. 26: 277-279.

Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1(4):213-223.

Goldblatt, M.W., and W.E. Chiesman. 1944. Toxic effects of ethylene chlorohydrin. Part I. Clinical. Br. J. Ind. Med. 1(4):207-213.

Greenberg, H.L., M.G. Ott, and R.E. Shore. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. Br. J. Ind. Med. 47(4):21-30.

Grunow, W., and H.J. Altmann. 1982. Toxicokinetics of chloroethanol in the rat after single oral administration. Arch. Toxicol. 49(3-4): 275-284.

Haber, F. 1924. The history of the gas war. Pp. 76-92 in Five Lectures from the Years 1920-1923, F. Haber, ed. [in German]. Berlin: Springer.

HSDB (Hazardous Substances Data Bank). 2005. 2-Chloroethanol (CAS Reg. No. 107-07-3). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Apr. 8, 2014].

Johnson, M.K. 1965. The influence of some aliphatic compounds on rat liver glutathione levels. Biochem. Pharmacol. 14(9):1383-1385.

Johnson, M.K. 1967. Metabolism of chloroethanol in the rat. Biochem. Pharmacol. 16(1):185-199.

Koelsch, F. 1927. The toxicity of the ethylene chlorohydrins. Zentralbl. Gewerbehyg. 4:312-316 (as cited in Goldblatt and Chiesman 1944).

Lawrence, W.H., J.E. Turner, and J. Autian. 1971. Toxicity of ethylene chlorohydrin. I. Acute toxicity studies. J. Pharm. Sci. 60(4):568-571.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: 2-Chloorethanol. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Apr. 8, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs): Ethylene chlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/107073.html [accessed July 2013].

NIOSH (National Institute of Occupational Safety and Health). 2011. Pocket Guide to Chemical Hazards: Ethylene chlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0268.html [accessed July 2013].

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NTP (National Toxicology Program). 1983a. Teratologic Evaluation of Ethylene Chlorohydrin (CAS Reg. No. 107-07-3) in CD-1 Mice. NTP studies TER84070A, TER84070B, TER84070C, and TER84070D. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program). 1983b. Teratologic Evaluation of Ethylene Chlorohydrin (CAS Reg. No. 107-07-3) in New Zealand White Rabbits. NTP study TER84071. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program). 1985. Toxicology and Carcinogenesis Studies of 2-Chloroethanol (Ethylene Chlorohydrin) (CAS Reg. No. 107-07-3) in F344/N Rats and Swiss CD-1 Mice (Dermal Studies). NTP TR 275. NIH 86-2531. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC. November 1985 [online]. Available: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr275.pdf [accessed Apr. 8, 2014].

Olsen, G.W., S.E. Lacy, K.M. Bodner, M. Chau, T.G. Arceneaux, J.B. Cartmill, J.M. Ramlow, and J.M. Boswell. 1997. Mortality from pancreatic and lymphoietic cancer among workers in ethylene and propylene chlorohydrin production. Occup. Environ. Med. 54:592-598.

Patty, F.A., ed. 1963. β-Chloroethyl alcohol. Pp. 1492-1496 in Industrial Hygiene and Toxicology, Vol. Toxicology, 2nd Rev. Ed. New York: John Wiley and Sons.

Perez, C., and S.C. Soderholm. 1991. Some chemicals requiring special consideration when deciding whether to sample the particle, vapor, or both phases of an atmosphere. Appl. Occup. Environ. Hyg. 6(10):859-864.

Rinehart, W. E., and T. Hatch. 1964. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. Ind. Hyg. J. 25(6):545-553.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

APPENDIX A

DERIVATION OF AEGL VALUES FOR ETHYLENE CHLOROHYDRIN

Derivation of AEGL-1 Values

Because of insufficient data regarding AEGL-1 severity effects and the overall exposure-response relationship for ethylene chlorohydrin vapor exposure, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

Because of insufficient data on AEGL-2 severity effects, the AEGL-2 values were estimated as one-third of the AEGL-3 values as per guidance in NRC (2001). The lethality data in rats, mice, and guinea pigs indicate a steep exposure-response relationship.

10-min AEGL-2:	6.4 ppm ÷ 3 = 2.1 ppm
30-min AEGL-2:	4.4 ppm ÷ 3 = 1.5 ppm
1-h AEGL-2:	3.5 ppm ÷ 3 = 1.2 ppm
4-h AEGL-2:	1.4 ppm ÷ 3 = 0.47 ppm
8-h AEGL-2:	0.70 ppm ÷ 3 = 0.23 ppm

Derivation of AEGL-3 Values

Key study:	Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1(4):213-223.
Critical effect:	A 120-min nonlethal exposure at 280 ppm in mice was used as an estimated lethality threshold. A 120-min exposure at 1,090 ppm resulted in 100% lethality.
Time scaling:	$C^n \times t = k$, where n = 1 or 3 (NRC 2001)
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability; ethylene chlorohydrin does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged respiratory tract epithelial tissue. In the absence of data

	regarding the mode of action of ethylene chlorohydrin toxicity and because of the small numbers of animals used in the reported studies, an intraspecies uncertainty of 10 is retained. Sensitive populations could not be identified.
Modifying factor:	None applied
Calculation:	$(280 \text{ ppm})^1 \times 120 \text{ min} = 560 \text{ ppm-h}$ $(280 \text{ ppm})^3 \times 120 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$
10-min AEGL-3:	$C^3 \times 10 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 637 \text{ ppm}$ $C = 637 \text{ ppm} \div 100 = 6.4 \text{ ppm}$
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 444 \text{ ppm}$ $C = 444 \text{ ppm} \div 100 = 4.4 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 60 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 353 \text{ ppm}$ $C = 353 \text{ ppm} \div 100 = 3.5 \text{ ppm}$
4-h AEGL-3:	$C \times 240 \text{ min} = 560 \text{ ppm-h}$ $C = 140 \text{ ppm}$ $C = 140 \text{ ppm} \div 100 = 1.4 \text{ ppm}$
8-h AEGL-3:	$C \times 480 \text{ min} = 560 \text{ ppm-h}$ $C = 70.0 \text{ ppm}$ $C = 70.0 \text{ ppm} \div 100 = 0.70 \text{ ppm}$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYLENE CHLOROHYDRIN

Derivation Summary

AEGL-1 VALUES

Because of insufficient data regarding AEGL-1 severity effects and the overall exposure-response relationship for ethylene chlorohydrin vapor exposure, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)

Data adequacy: Data on ethylene chlorohydrin were insufficient for deriving AEGL-2 values. In accordance with NRC (2001) guidance, AEGL-2 values were estimated by dividing the AEGL-3 values by 3. Animal lethality data indicate a steep exposure-response relationship for ethylene chlorohydrin.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

Reference: Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1(4):213-223.

Test Species/Strain/Sex/Number: Mouse; strain and gender not specified; 3/group

Exposure route/Concentrations/Durations: Inhalation

Concentration (ppm)	Duration (min)	Effect
280[a]	120	No lethality
1,090	120	3/3 dead at 140-170 min
1,960	120	3/3 dead at 110-129 min

[a]Concentration used as the point-of-departure for AEGL-3 derivation.

Effects: Signs of discomfort and irritation, and incoordination at higher concentrations (group-specific observations were not provided) and death.

End point/Concentration/Rationale: Lowest concentration with no mortality (280 ppm for 120 min)

Uncertainty factors/Rationale:
Interspecies: 10, absence of information available to describe species differences in toxicity.
Intraspecies: 10, ethylene chlorohydrin does not appear to be a direct-contact irritant and

death in animals does not appear to be a function of damaged respiratory tract epithelial tissue. In the absence of data regarding the mode of action of ethylene chlorohydrin toxicity and because of the small numbers of animals used in the studies, a factor of 10 is retained.
Modifying factor: None applied
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: $C^n \times t = k$, where n = 1 for extrapolation to longer durations or n = 3 for extrapolation to shorter durations (NRC 2001)
Data adequacy: Marginal; the exposure-response relationship is not fully defined by the available data; animal data are based on exposures with only three animals per group.

APPENDIX C

CATEGORY PLOT FOR ETHYLENE CHLOROHYDRIN

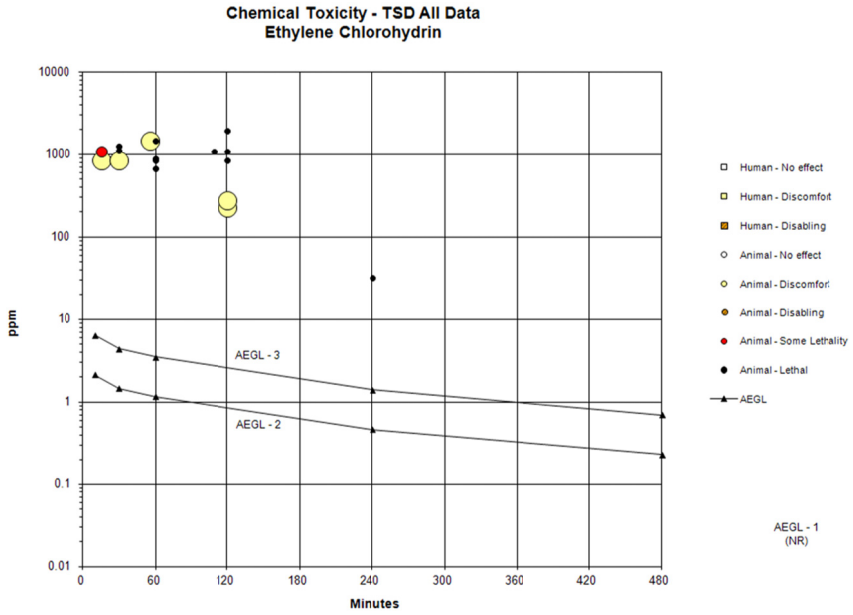


FIGURE C-1 Category plot of toxicity data and AEGL values for ethylene chlorohydrin.

TABLE C-1 Data Used in Category Plot of Ethylene Chlorohydrin

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				2.1	10	AEGL	
AEGL-2				1.5	30	AEGL	
AEGL-2				1.2	60	AEGL	
AEGL-2				0.47	240	AEGL	
AEGL-2				0.23	480	AEGL	
AEGL-3				6.4	10	AEGL	
AEGL-3				4.4	30	AEGL	
AEGL-3				3.5	60	AEGL	
AEGL-3				1.4	240	AEGL	
AEGL-3				0.7	480	AEGL	
Goldblatt 1944	Rat		1	840	15	1	Nonlethal; no details but minor effects possible.
	Rat		1	1,120	30	3	100% lethality.
	Rat		1	678	60	3	Lethal
	Rat		1	226	120	1	Nonlethal; no details but minor effects possible.

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Mouse		1	280	120	1	Nonlethal; no details but minor effects possible.
	Mouse		1	840	60	3	100% lethality
	Mouse		1	896	60	3	100% lethality
	Mouse		1	1,090	15	SL	Lethal
	Mouse		1	1,090	120	3	Lethal
	Mouse		1	1,260	30	3	Lethal
	Mouse		1	1,460	60	3	Lethal
	Mouse		1	1,960	120	3	Lethal
	Guinea pig		1	840	30	1	Nonlethal; no details but minor effects possible.
	Guinea pig		1	840	120	3	Lethal
	Guinea pig		1	1,090	108	3	Lethal
	Guinea pig		1	1,460	55	1	Nonlethal; no details but minor effects possible.
Patty 1963	Rat		1	32	240	3	LC_{50} no details.
Dierker and Brown 1944	Human		1	300	120	3	Human lethality (estimated exposure concentration).

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

6

Toluene[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory), Chemical Manager George Woodall (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Toluene is a widely used raw material in the chemical manufacturing industry. It is a component of automotive and aviation gasoline and a solvent in lacquers, paint thinners, glue, and other household products. A major concern with the uncontrolled release of toluene is explosion and fire.

The odor threshold for toluene ranges from 0.16 to 100 ppm for detection and 1.9 to 69 ppm for recognition; the odor is not unpleasant. Toluene is readily absorbed by the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. Liquid toluene can be absorbed through intact skin and the alimentary tract. Toluene is a central nervous system (CNS) depressant and is irritating to the eyes at high concentrations. Other effects observed in humans after accidental or intentional inhalation of high concentrations of toluene include renal toxicity, cardiac arrhythmias, hepatomegaly, and developmental abnormalities. Considerable human and animal toxicity data were available for deriving AEGL values.

Clinical, metabolism, and occupational-monitoring studies were available for deriving AEGL-1 values. Many of the studies evaluated sensory irritation and CNS depression. Numerous studies of neurotoxicity have also been conducted in rodents. Lethality data on toluene were available for the mouse and rat.

AEGL-1 values were based on the preponderance of data from clinical and occupational studies and from metabolism studies of human subjects that indicated that an 8-h exposure to toluene at 200 ppm is near a threshold for AEGL-1 effects (headache), and also near a level for detectable neurologic effects (moderate lightheadedness and increased simple reaction time). More than 300 indi-

viduals have been evaluated in 20 clinical studies that involved exposures to toluene at 40-700 ppm, and several thousand workers were surveyed in occupational-monitoring studies that involved exposures at up to 1,500 ppm. Those populations are presumed to be composed of healthy individuals, but they represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions) and individual differences in metabolism rates (Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Brugnone et al. 1986; Hjelm et al. 1988). Although many clinical studies tested toluene at 100 ppm, the addition of exercise to the protocol in the studies of Astrand et al. (1972), Baelum et al. (1990), and Rahill et al. (1996) more than doubled the toluene blood concentration; concentrations were greater than that from a 200-ppm exposure with the subject at rest (Astrand et al. 1972; Veulemans and Masschelein 1978).

The weight of evidence from these studies indicates that an 8-h exposure to toluene at 200 ppm was without adverse health effects in the tested populations, and was an appropriate basis for the AEGL-1 values. At concentrations of 80-200 ppm, toluene approaches a steady-state in the blood within 15-30 min (Astrand et al. 1972; Carlsson 1982). Storage takes place in lipid-rich tissues (including the brain), but elimination is rapid. Toluene reaches a steady-state in the blood and brain fairly rapidly, and no cumulative effects were observed after repeated exposure at 100 ppm for 5 days (Stewart et al. 1975); therefore, 200 ppm was used as the basis for all AEGL-1 durations. Although there was no notable discomfort and only mild irritation (effects expected to be concentration dependent and not subject to changes in activity level), headaches (potentially related to CNS effects), dizziness, and measurable neurologic effects were reported after exposure to toluene at 100-200 ppm. Neurologic effects would be expected to be affected by an increase in activity level, leading to higher concentrations in the brain (target tissue for CNS effects). As noted earlier, physical activity may double the blood concentration of toluene. On the basis of the range of alveolar concentrations among humans exposed to anesthetic gases, an uncertainty factor of 3 for human variability was applied to calculate an AEGL-1 value of 67 ppm for all durations. That concentration is deemed protective for all observed effects, including those at 100-200 ppm.

The AEGL-2 values for toluene are based on impaired neurologic function that affects the ability to escape. The point of departure was a no-observed-adverse-effect level (NOAEL) of 1,600 ppm for a doubling of the choice reaction time in Long-Evans rats exposed for 34 min (Bushnell et al. 2007a). The CNS effects observed during exposure were assumed to be directly related to parent material reaching the brain. Therefore, the toluene concentration in brain (BrTC) after 34 min provides an internal dose measurement correlating with the NOAEL. The physiologically-based pharmacokinetic (PBPK) model of Kenyon et al. (2008) was used to calculate the internal dose or BrTC in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a value of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncer-

tainty factor of 3 was applied because the minimum alveolar concentration for volatile anesthetics should not vary by more than 2- to 3-fold among humans. A human model for toluene (Benignus et al. 2006) was then used to determine the exposure concentrations at each of the AEGL exposure durations that would yield the same brain concentration in humans.

Further support for the AEGL-2 values is provided by comparisons with the results obtained from the published model of Benignus et al. (2009, 2011), which calculates the BrTC leading to an effect level comparable to an individual with a blood ethanol level of 0.10% (the legal level of incapacitation in the United States). Although the routes of exposure are different between the two chemicals (inhalation for toluene inhalation and oral for ethanol), the relative effect levels are relevant for comparison purposes.

The AEGL-3 values for toluene were based on a NOAEL for lethality in rats. A 2-h exposure to toluene at 6,250 ppm was not lethal but produced prostration in rats (Mullin and Krivanek 1982). A 2-h exposure of rats at 10,000 ppm resulted in 20% mortality (Kojima and Kobayashi 1973). The same PBPK models and uncertainty factors that were used to derive the AEGL-2 values were used to calculate the AEGL-3 values.

The AEGL values for toluene are presented in Table 6-1.

TABLE 6-1 AEGL Values for Toluene

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	No-effect level for notable discomfort and neurologic effects in 20 clinical studies.[a]
AEGL-2 (disabling)	1,400 ppm[b] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)	No-effect level for impaired ability to escape, decrement in neurological function.[c]
AEGL-3 (lethal)	_[d]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6,800 mg/m^3)	1,400 ppm[b] (5,300 mg/m^3)	No-effect level for lethality in rats (Mullin and Krivanek 1982)

[a]Clinical studies include Astrand et al. (1972), Gamberale and Hultengren (1972), Stewart et al. (1975), and Baelum et al. (1990).

[b]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

[c]No-effect level for a doubling in choice reaction time in rats (Bushnell et al. 2007a). Effect level supported by comparison of toluene inhalation with ethanol consumption in humans (Benignus et al. 2011).

[d]The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

1. INTRODUCTION

Toluene is a colorless, flammable liquid with a pungent floral or aromatic odor similar to that of benzene (Henderson 2001). The odor has also been described as sour or burnt (Hellman and Small 1974), rubbery, or similar to that of moth balls (Billings and Jonas 1981; Ruth 1986). The chemical and physical properties of toluene are presented in Table 6-2.

A major concern with the uncontrolled release of toluene is explosion and fire. The flash point of toluene is 4.4°C and the ignition temperature is 536°C. The saturated vapor is only slightly heavier (about 10% more) than air and may travel a considerable distance in still air to a source of ignition and flash back. Toluene may be rapidly dispersed by normal eddy currents. The vapor may explode if ignited in an enclosed area (Weiss 1980). For example, a fatal explosion occurred when workers were sawing an opening in the side of an empty 10,000-gallon toluene storage tank (NIOSH 1985).

TABLE 6-2 Chemical and Physical Properties of Toluene

Parameter	Value	Reference
Synonyms	Methyl benzene; phenyl methane; methyl benzol; monomethyl benzene; toluol; methacide; tolu-sol; antisal 1a	ATSDR 2000
CAS registry no.	108-88-3	O'Neil et al. 2006
Chemical formula	C_7H_8	O'Neil et al. 2006
Molecular weight	92.140	O'Neil et al. 2006
Physical state	Clear liquid	O'Neil et al. 2006
Boiling point	110.6°C	O'Neil et al. 2006
Density/specific gravity	0.866 g/cm^3	O'Neil et al. 2006
Solubility in water	Slightly soluble, 0.067%	O'Neil et al. 2006
Vapor density (air = 1)	3.1	Henderson 2001
Vapor pressure	36.7 mmHg	Henderson 2001
Log K_{ow}	2.72	ATSDR 2000
Flash point	4.4°C (closed cup) 12.8°C (open cup)	O'Neil et al. 2006 Weiss 1980
Flammability limits		Henderson 2001
Lower explosive limit	1.4%	
Upper explosive limit	7.9%	
Conversion factors in air	1 ppm = 3.77 mg/m^3 1 mg/m^3 = 0.265 ppm	NIOSH 2011

In 1999, world production of toluene was nearly 13,000,000 tons. Approximately 79% of total production is from catalytic reforming of refinery streams, an additional 16% is separated from pyrolysis gasoline, and 4% is produced via separation from coal tars. Most of the toluene produced (85-90%) is not isolated but remains as a benzene-toluene-ethylbenzene-xylene (BTEX) mixture for use in gasoline as an octane booster. Of the remaining capacity, the primary use is for chemicals and solvents such as benzene (via dealkylation). In the chemical industry, toluene is used as raw material in the production of benzyl chloride, benzoic acid, phenol, cresols, vinyl toluene, trinitrotoluene (TNT), and toluene diisocyanate. Approximately 14% of toluene is also used as a solvent for paints and coatings and in adhesives, inks, and pharmaceuticals (US Air Force, 1989; EPA, 1990; Ozokwelu 1997; Chemical Week 2000).

In the past, commercial toluene contained benzene and xylenes at up to 2-15% and 10%, respectively (NIOSH 1973; Low et al. 1988). Highly purified toluene (benzene at less than 0.01%) began to be produced commercially in 1973. Therefore, greater consideration was given to more recent toxicity studies, in which the toluene is more chemically pure.

For both the general population and for occupationally-exposed individuals, inhalation is the primary route of exposure to toluene. Evaporation of gasoline and automobile exhaust is the largest source of toluene in the environment, and industries that use toluene as a solvent are the second largest source (EPA 1990). Toluene is also a common indoor-air contaminant due to releases from common household products and from cigarette smoke (ATSDR 2000).

2. HUMAN TOXICITY DATA

The typical sequence of events that result from exposure to toluene at concentrations high enough to produce unconsciousness include euphoria, delusions, and sedation (Benignus 1981; Bruckner and Warren 2001). Mood elevation, nausea, and subtle changes in performing intricate tasks have been reported at 200 ppm and higher (ACGIH 2005), although some of the studies are poorly documented (see Table 6-3). Exposure to toluene may be occupational or recreational; in the latter case it is reported to produce a pleasant euphoria with few side effects (Massengale et al. 1963). Its abuse potential may be enhanced by its apparent low irritancy in humans (von Oettingen et al. 1942; Carpenter et al. 1944; Nielsen and Alarie 1982).

The major effect of toluene is its narcotic effects, manifested in muscular weakness, incoordination, and mental confusion (NIOSH 1973). Adverse effects on the liver, kidneys, lungs, and heart are limited to acute and chronic exposures at high vapor concentrations. Early reports suggesting deleterious effects on the bone marrow involved the use of toluene contaminated with benzene (NIOSH 1973). The health effects of toluene have been reviewed by Cohr and Stockholm (1979), NRC (1981, 2008), WHO (1985), CIR (1987), Low et al. (1988), EPA (1990), ATSDR (2000), Bruckner and Warren (2001), and Henderson (2001).

TABLE 6-3 Sensory and Neurobehavioral Effects of Toluene in Controlled Human Studies

Concentration (ppm)	Duration	Subjects/Effects	Reference
10, 40, 100	6 h	16 males (21-32 y): slight irritation of eyes and nose at 100 ppm; no effect on mood, fatigue, or sleepiness; increased frequency of headache, dizziness, and feeling of slight to moderate intoxication; no effect on pulmonary function or nasal mucous flow; no significant effect on performance in eight psychomotor tests.	Andersen et al. 1983
40	4 h	12 males (20-50 y): no effects on measures of motor performance, attention, perceptual coding and memory, or mood.	Lammers et al. 2005a
110	Three 30-min peaks over 4 h		
50[a]	3 h	10 males, 20 females (19-45 y): no subjective symptoms.	Luderer et al. 1999
50	4.5 h	20 males: no increase in sleepiness; increase in scores of unpleasant smell and irritation to the throat.	Muttray et al. 2005
80	4 h	8 males (22-50 y): no impairment on neurobehavioral tasks.	Cherry et al. 1983
80	4 h	16 males (23-38 y): no differences in subjective symptoms compared with controls; no impairment in tests of simple reaction time, short-term memory, or choice reaction time; no effect on heart rate.	Olson et al. 1985
80	4.5 h	12 males (22-44 y): increase in subjective symptoms (nausea, headache, irritation), but rated negligible; no impairment in tests of simple and choice reaction time, color-word vigilance, or memory; no effect on heart rate, electroencephalograph results, or sleep latency.	Iregren et al. 1986
100	3.5 h	18 subjects: no behavioral deficits in psychomotor tests.	Winneke 1982

(Continued)

TABLE 6-3 Continued

Concentration (ppm)	Duration	Subjects/Effects	Reference
100	4 h	30 males and females: no serious impairment in neurobehavioral tests (small impairment in one measure of a visual-vigilance test).	Dick et al. 1984
100	6 h	6 males and females (27-38 y): No significant effect on pulmonary function (subjects exercised for 30 min); slight effect on some multitask and neuropsychologic tests (increased latency but not accuracy on neurobehavioral tasks); no symptoms reported in a double-blind questionnaire.	Rahill et al. 1996
100	6.5 h (printers were previously exposed for 9 to 25 y)	43 male printers and 43 referents (29-50 y). Four groups tested (two exposed and two controls): sensory irritation (no annoyance or nausea); sleepiness; fatigue; slightly decreased performance on four of 10 tests (manual dexterity, color discrimination, visual perception) in one or both exposed groups; no changes in renal function.	Baelum et al. 1985; Nielsen et al. 1985
100	1, 3, or 7.5 h/d for 5 d	10 males and 9 females (19-47 y): no decrement in psychomotor-test results on first day of exposure; slight decrement in performance in tests involving visual vigilance and tone detection on days 2 and 5 in females exposed for 7.5 h; similar subjective symptoms between exposed and control groups.	Stewart et al. 1975
100 (constant) or 100 (TWA; exposure varied with peaks of 300 ppm every 30 min)	7 h (three 15-min exercise periods; both exposures)	32 males and 39 females (31-50 y): sensory irritation of nose and lower airways; increase in dizziness and feeling of intoxication; slight decrement in one of four psychomotor-performance tests; no differences in symptoms or performance found between constant and varying exposures.	Baelum et al. 1990
75, 150	7 h/d for 3 d	42 male and female students (18-35 y): 7% (mean) decrement in several neurobehavioral tests at 150 ppm; slight increases in headache, ocular irritation; sleepiness on first day; CNS effect demonstrated by dose-response in number of times subjects slept. No clear pattern of neurobehavioral effects. Variation in the control data across 3 d was greater than with toluene.	Echeverria et al. 1989; 1991

100, 200[a]	30, 60 min	11 males and 4 females (18-46 y): no difference in heart rate, pulmonary ventilation, oxygen consumption, or blood lactate, either at rest or during a work load of 50 W.	Astrand et al. 1972; Astrand 1975
100, 200	3 h or 7 h with 1-h break	23 males (23 y, average age): decrease in pulse rate at 200 ppm for 3 h; tendency to have prolonged reaction time at 200 ppm; no clear concentration-response relationship.	Ogata et al. 1970
100, 300, 500, 700[a]	Successive 20-min exposure at increasing concentrations (one 5-min break); total 85 min.	12 males (20-35 y): no effect on reaction time or perceptual speed at 100 ppm; increase in simple reaction time at 300 ppm; increase in complex reaction time at 500 ppm; decrease in perceptual speed at end of exposure at 700 ppm; no effect on heart rate during total exposure; one of 12 subjects able to distinguish between control and toluene exposures.	Gamberale and Hultengren 1972
220[b] 427[b]	15 min 15 min	6/6 subjects willing to work for 8 h; negligible sensory symptoms. 3/6 subjects willing to work for 8 h; 2 subjects reported slight "lightheadness"; 1 reported a "stuffy, drowsy feeling."	Carpenter et al. 1976
200	6 h	5 males, resting: no change in respiration; increased heart rate.	Suzuki 1973
240	Three 30-min sessions	11 males (20-21 y): impaired vigilance in third session; decreased fatigue during second session.	Horvath et al. 1981

[a]Subjects exposed via a mouthpiece.
[b]Measured as toluene in "toluene concentrate."

2.1. Acute Lethality

Inhalation of "high concentrations" can result in paresthesia, vision disturbances, dizziness, nausea, CNS depression, and collapse (Henderson 2001). Most deaths involve solvent abuse or "glue sniffing", which involves sniffing a mixture of solvents from a plastic bag to concentrate the vapors. Solvents, such as paint thinners, may contain as much as 99% toluene (Donald et al. 1991). Prior to 1975, an estimated 125 deaths involving solvent abuse occurred per year in the United States (Winek and Collom 1975). Few deaths have been attributed solely to the inhalation of pure toluene, but are associated with paint thinners, spray paints, glues, and other products containing toluene. Few data are available on the concentrations of toluene that caused deaths in these studies. The concentration of toluene achieved when inhaling directly from a paper bag containing gauze soaked with toluene from a tube of polystyrene cement is estimated to be 10,000 ppm (Press and Done 1967). According to the authors, this concentration causes unconsciousness within a few minutes, which results in cessation of exposure.

Bass (1970) reviewed reports of "sudden sniffing death syndrome." Eyewitness accounts of the events prior to death were similar and included: inhalation of volatile hydrocarbons from a bag, panic, physical exertion (usually involving running), and sudden collapse and death. This pattern was characterized by the author as being the result of severe cardiac arrhythmia associated with fulminate pulmonary edema, the excitement of a light plane anesthesia, hyperadrenergic crisis, or some combination of these and possibly unknown factors. The author suggests a mechanism of action involving sensitization of the myocardium by volatile hydrocarbons and subsequent physical exertion coalescing to produce sudden and severe arrhythmia. No cardiac-sensitization tests of toluene in dogs was found, but dogs exposed to toluene at 30,000 ppm for 9-10 min died of ventricular fibrillation and severe hypoxia (Ikeda et al. 1990; see Section 3.1.1).

2.2. Nonlethal Toxicity

The odor threshold of toluene in air ranges between 2 and 40 ppm (Amoore and Hautala 1983; Ruth 1986). According to Hellman and Small (1974), the odor can be detected at 0.17 ppm and recognized at 1.74 ppm. The American Industrial Hygiene Association (AIHA1989) reports the detectable range as 0.16-100 ppm and the odor recognition range as 1.9-69 ppm. According to a literature survey (Ruth 1986), the threshold for "irritation" is 200 ppm. In a more recent series of studies, the odor threshold and thresholds for ocular and nasal irritation were measured using squeeze bottles and a two-alternative, forced-choice procedure with an ascending method of limits (Cometto-Muniz and Cain 1995; Abraham et al. 1996). Thresholds for ocular irritation and nasal pungency were approximately >20,000 and 29,850 ppm, respectively. The nasal

pungency threshold was developed with anosmics (subjects who were clinically diagnosed as lacking a sense of smell and were, thus, unbiased by odor sensations).

Solvent abusers repeatedly inhale anesthetizing concentrations on a daily basis. Toluene abuse, an extreme form of exposure, has resulted in myocardial infarction and cardiac effects (Cunningham et al. 1987; Wiseman and Banim 1987; Carder and Fuerst 1997), renal toxicity that includes renal tubular acidosis (Taher et al. 1974; Reisin et al. 1975; Patel and Benjamin 1986; Gupta et al. 1991; Kamijima et al. 1994), metabolic acidosis often with "anion gap" (the sum of the cations in the blood minus the sum of the anions in the blood) (Fischman and Oster 1979; Jone and Wu 1988), acute encephalopathy in children (8-14 years old) (King et al. 1981), and cerebellar ataxia (Boor and Hurtig 1977). Streicher et al. (1981) described syndromes of toluene sniffing in adults, which included a pattern of three dominant symptoms: muscle weakness, gastrointestinal disorders, and neuropsychiatric disorders. Neuropsychiatric symptoms included headache, dizziness, syncope, paresthesias or peripheral neuropathy, hallucinations, lethargy, and cerebellar ataxia. Some exposures were to mixtures of solvents and ethanol. Exposure concentrations could not be ascertained. In a review of neurologic and psychiatric consequences of toluene abuse, Ron (1986) concluded that evidence for such sequelae remains inconclusive.

Distal renal tubular acidosis is an established consequence of toluene abuse and has been reported in numerous studies. This consequence is notable with the extremely high vapor concentrations associated with chronic abuse situations (O'Brien et al. 1971; Taher et al. 1974; Fischman and Oster 1979; Kroeger et al. 1980; Moss et al. 1980; Russ et al. 1981; Streicher et al. 1981; Patel and Benjamin 1986; Marjot and McLeod 1989). In life-threatening cases, patients present with severe generalized muscle weakness, nausea and vomiting, and neuropsychiatric derangements (Streicher et al. 1981; Marjot and McLeod 1989). The mechanism of action for this disorder is discussed in Section 4.2. In spite of reports of hepatic, adrenal, and renal damage, there appears to be a low incidence of these injuries among glue sniffers. Only modest elevations of serum glutamic-oxaloacetic transaminase and alkaline phosphatase and transient abnormalities in urinalyses were observed among groups of glue sniffers (Press and Done 1967; Litt et al. 1972; Weisenberger 1977).

2.2.1. Occupational Exposures

Studies of workers exposed to toluene in occupational settings have focused on functional impairment. These exposures are usually not of a magnitude required to produce serious sustained effects. Even though exact exposure parameters of concentration and duration are usually not determined in these studies, the investigations provide information about the more common effects and at what approximate concentrations these effects are observed. Interpretation of most occupational exposure studies of toluene is confounded by co-exposure to

other solvents. Only the study by Wilson (1943) addressed acute effects immediately following the work day. Additional occupational monitoring studies are briefly discussed below.

Wilson (1943) surveyed the effects of various concentrations of toluene in workers at a large industrial plant. Approximately 1,000 workers were exposed to toluene at concentrations of 50-1,500 ppm for periods of 1-3 weeks. Approximately 10% of the employees had symptoms severe enough to require examination at a hospital. The employees were grouped according to the concentration of toluene fumes measured at their job sites; measurements were made with a combustible gas indicator. (Combustible gas indicators measure all combustibles and are generally incapable of measuring concentrations of less than 5%.) In workers exposed to toluene at 200 ppm or lower, the most common complaints were headache, lassitude, and loss of appetite. At 200-500 ppm, complaints included headache, lassitude, and anorexia that were more pronounced. These subjects also complained of nausea, a bad taste in the mouth, loss of coordination, decreased reaction time, and momentary loss of memory. At concentrations greater than 500 ppm, the major complaints were nausea, headache, dizziness, anorexia, palpitation, and extreme weakness. Physical and laboratory examinations of the approximately 60 workers exposed to toluene at 200 ppm or lower were negative. Also, no significant physical or laboratory findings were noted for the 30 workers exposed at 200-500 ppm. Physical examination of the remaining 10%, exposed at 500 ppm or higher, found loss of coordination, decreased reaction time, and petechiae under the skin. Laboratory results from these patients revealed low erythrocyte counts and leukopenia, and bone marrow biopsy demonstrated aplastic anemia in two subjects. The hospitalized workers were treated symptomatically. No deaths occurred. The analytic methodology in this study and the confounding issue of benzene exposure precludes the use of this study for developing AEGL values.

Monitoring studies show that workers have been routinely exposed to toluene at 32 ppm (0.1-457 ppm) (Neubert et al. 2001b); a lifetime weighted average of 45 ppm (Seeber et al. 2005); a time-weighted average (TWA) of 63-118 ppm (5-353 ppm) (Ovrum et al. 1978); a TWA of 88 ppm (49-130 ppm) (Foo et al. 1990); 50-100 ppm (Neubert et al. 2001a); 50-150 ppm (Iregren 1982); ≥100 ppm (Ukai et al. 1993); an estimated average of 117 ppm (Juntunen et al. 1985); 132 ppm (66-250 ppm) (Zavalic et al. 1998); 1->100 ppm (Lee et al. 1988); 100-440 ppm with peak values of 200-500 ppm (Eller et al. 1999); 9-467 ppm (Deschamps et al. 2001); ≥200 ppm (Forni et al. 1971); 200-800 ppm (Parmeggiani and Sassi 1954); and ≤ 500 ppm (Greenberg et al. 1942). In most cases when psychomotor tests were performed, the tests were administered before the workday; therefore, acute effects were not measured. In most of these studies, only subtle differences in neurologic parameters, such as alterations in the visual evoked response or small decreases in reaction time, were found compared with control groups (Yin et al. 1987; Foo et al. 1990; Abbate et al. 1993; Murata et al. 1993; Vrca et al. 1995; Boey et al. 1997; Zavalic et al. 1998; Eller et al. 1999). Seeber et al. (2005) found no evidence of neurobehavioral effects following

long-term exposure to toluene below 50 ppm. Irritation of the conjunctiva and upper respiratory tract was found in only one of 11 workers exposed at 200-800 ppm (Parmeggiani and Sassi 1954). In some studies, incidences of subjective symptoms, such as sore throat, were greater than in matched control groups (Tanaka et al. 2003). Symptoms correlated with duration and extent of exposure in some studies (Lee et al. 1988) but not in others (Gericke et al. 2001). Chronic exposures of workers to toluene at low concentrations have not resulted in alterations in liver-enzyme activity or hormone concentrations (Gericke et al. 2001) or in serious renal damage (ATSDR 2000). An acute exposure of flexoprint workers to toluene at approximately 100 ppm for 6.5 h failed to show significant changes in β-microglobulin or albumin excretion compared with air-exposed controls (Nielsen et al. 1985).

Studies of occupationally-exposed workers indicate that chronic exposure to toluene at low concentrations results in hearing loss (Morata et al. 1997; ATSDR 2000). However, in a study of 333 rotogravure printing workers, exposure at less than 50 ppm could not be related to ototoxicity (Schaper et al. 2003). In animal models, toluene was shown to damage outer hair cells in rats exposed to toluene at 1,400 ppm for 14 h/day for 8 days (Johnson and Canlon 1994; see also Section 3.2.2). A question of whether toluene impaired color vision in workers was raised by Zavalic et al. (1998). Color vision was impaired in these workers, but alcohol and age were confounding factors.

2.2.2. Accidental Exposures

Two men working with toluene to remove excess glue from tiles in a swimming pool were exposed to toluene at concentrations greater than 1,842 ppm for 2 or 3 h (Meulenbelt et al. 1990). The concentration of toluene was measured at the edge of the pool by Drager tube 3 h after the men were rescued. Concentrations were presumed to be higher at the bottom of the pool where the men were found because toluene is heavier than air and would have accumulated at the bottom of the pool. Both men were disoriented when found; one was unable to walk or sit, and the other was barely able to walk. Physical examinations carried out 1 h after they were found revealed mucosal irritation of the eyes, slurred speech, headache, paresis, and amnesia. The patient exposed for 3 h had an excessive anion gap and a sinus bradycardia. The second patient, who was exposed for 2 h, complained of headache, and clinical examination revealed a sinus tachycardia and a slightly excessive anion gap. Neither patient showed abnormalities in hepatic function or hematologic parameters. Blood toluene concentrations taken 2 h after exposure were 4.1 and 2.2 mg/L in the patients exposed for 3 and 2 h, respectively. The most striking effect of this acute exposure was the increased anion gap in both patients, which the authors attributed to either the high plasma concentration of toluene metabolites (benzoic acid and/or hippuric acid) or distal tubular acidosis. Recovery for both patients appeared complete at the 1-week postexposure medical examination.

Two cases of accidental occupational exposure to toluene at very high concentrations were reported by Longley et al. (1967). One of the case reports involved several men who were exposed to toluene in an enclosed space aboard a commercial ship. Initially, two men were assigned to spray ballast tanks with an "anti-rust" paint containing toluene. One man climbed out of the tank because he felt dizzy, and shortly afterwards noticed that the other man had collapsed. Seventeen more men suffered symptoms of exposure during rescue operations, which lasted for about 2 h. Symptoms of exposure included unconsciousness, severe mental confusion, amnesia, and illogical behavior. All affected workers recovered fully within 30 min after breathing oxygen. No estimate of the toluene concentrations was possible.

The second incident also took place on a merchant ship (Longley et al. 1967). An accidental exposure to a concentrated insecticide containing malathion (20%), piperonyl butoxide (8%), pyrethrum (1.5%), and toluene (to 100%) occurred. Thirty gallons of this mixture, which contained 21 gallons of toluene, was mistakenly sprayed undiluted into a hold with a volume of about 102,000 cu. ft. within about 75 min. Seven men, including the workers and rescuers, were overcome, and three lost consciousness. The men were taken off the ship and given medical examinations. Because the cholinesterase activity of the men remained at 100%, the authors judged that the malathion was not absorbed appreciably. Using a Department of Scientific and Industrial Research (DSIR) pump which was designed by the British Department of Scientific and Industrial Research to make spot determinations of hazardous atmospheres, the toluene concentrations were estimated to be 5,000-10,000 ppm. However, calculations of the distribution of the 21 gallons of toluene in the hold results in approximate concentrations of 10,000-12,000 ppm. Because the vapor rapidly anesthetized the kneeling worker but not for a standing one, the concentrations were probably higher near the floor than at head level. Therefore, some sources estimate or report that the concentrations of toluene were 10,000 ppm at waist level and 30,000 ppm at floor level (NIOSH 1973; NRC 1981). In addition to unconsciousness, the men also suffered nausea, incoordination, amnesia, and feelings of intoxication, but they did not complain of ocular or throat irritation. The exposed men recovered without persistent effects.

2.2.3. Clinical Studies

Numerous clinical studies have been conducted with healthy human subjects exposed in controlled settings to monitored concentrations of toluene for varying durations. Studies performed in the 1940s are now considered compromised because toluene was less pure at that time and contained other solvents, including benzene, and limited analytic characterization of exposure concentrations were available. However, there are recent, well-conducted clinical studies of toluene that are suitable for estimating AEGL values (Table 6-3).

More than 300 individuals have been evaluated in clinical studies involving toluene exposures of 40-700 ppm. The subjects are presumed to be healthy individuals, but represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions). Although many clinical studies used a toluene concentration of 100 ppm, the addition of exercise to the protocol in the studies of Astrand et al. (1972), Baelum et al. (1990), and Rahill et al. (1996) more than doubled the blood concentration of toluene to a level greater than that from a 200-ppm exposure with the subjects at rest (Astrand et al. (1972; Veulemans and Masschelein 1978). Baelum et al. (1990) investigated peak exposures of 300 ppm (14 times during a 7-h exposure; mean concentration of 100 ppm) with exercise (50-100 W) undertaken for 15 min during three of the peak exposures. Astrand et al. (1972) also incorporated exercise into the 200-ppm exposures.

These studies generally addressed the threshold for subjective and CNS effects to set guidelines for chronic exposures. Some of these studies provide information on the threshold for subtle psychomotor dysfunction (impairment of mental traits, abilities, and processes) in humans. Several studies also addressed air quality and odor adaptation or olfactory fatigue. Although slight irritation involving the eyes and nose in humans was reported in several studies of toluene at 80-100 ppm, toluene is not a primary respiratory irritant as evidenced by the high RD_{50} (concentration the reduces respiratory rate by 50%) of 5,300 ppm (see Section 3.2.3). In general, complaints increased among control subjects, especially in studies with long exposure durations. Other studies reported exposures at 80-100 ppm to be nonirritating (Stewart et al. 1975; Cherry et al. 1983; Olson et al. 1985; Rahill et al. 1996). No CNS effects were reported at 80-100 ppm in studies of Winneke (1982), Cherry et al. (1983), and Stewart et al. (1975); effects were minor in other studies at 100-700 ppm (Gamberale and Hultengren 1972; Dick et al. 1984; Baelum et al. 1990). There were no biologically significant pulmonary or cardiovascular effects at 100 and 200 ppm for exposures up to 6 h (Astrand et al. 1972; Suzuki 1973) and no indications of renal damage (Nielsen et al. 1985). Exposure to toluene at 100 ppm in the study by Stewart et al. (1975) was repeated for 5 days, with no greater effects over time.

Two studies that addressed only sensory effects are summarized here (Astrand et al. 1972; Suzuki 1973). Experimental studies in controlled settings that evaluated neurotoxicity and subjective symptoms are summarized in Section 2.3 (Neurotoxicity), and a reproductive study that evaluated subjective symptoms (Luderer et al. 1999) is summarized in Section 2.4 (Developmental and Reproductive Toxicity). All of these studies are summarized in Table 6-3, and are arranged in order of increasing concentration. Additional studies of controlled human exposures that evaluated the metabolism and disposition of toluene, but that did not address subjective symptoms, are summarized in Section 4.1 (Uptake, Metabolism, and Disposition).

Astrand et al. (1972) exposed 15 healthy male and female subjects, ages 18-46 year, to toluene at concentrations of 100 or 200 ppm for 30-min periods at rest and during exercise on a bicycle ergometer at work loads of 50 and 150 W. Some exposure periods were extended to 60 min at 100 ppm and 90 min at 200

ppm, the latter with exercise at 75 and 50 W for 30 min each. Toluene concentrations were measured by gas chromatography. No differences in measurements taken before or during exposure of heart rate, pulmonary ventilation, oxygen consumption, or blood lactate content for the corresponding workloads were found. Differences between males and females were minor. Although individual differences in uptake were noted, childhood asthma and obesity did not appear to affect uptake, and the presence of heart arrhythmias in two individuals, noted preexposure, was unaffected by the exposures. Exercise at 50 W in subjects exposed to toluene at 100 ppm more than doubled the subjects'arterial concentration of toluene (Astrand et al. 1972; Astrand 1975).

Suzuki (1973) exposed groups of five male students to toluene at 0 or 200 ppm for 6 h and measured several physiologic functions. The students reclined on a bed during the exposure. No significant changes were observed in galvanic skin reflex, vasoconstriction, respiration rate, or activity on electroencephalogram (EEG). Only heart rate was significantly increased (by 0.1 second) in the exposed group.

2.3. Neurotoxicity

The effects of toluene on nasal mucus flow, pulmonary function (nasal flow resistance, forced vital capacity, and forced expiratory volume), subjective response (headache and dizziness), and psychometric performance (both manual and mental tests) were evaluated several times during 6-h exposures to toluene at 10, 40, or 100 ppm (Andersen et al. 1983). The tests were carried out in an atmosphere-controlled chamber, and toluene concentrations were continuously monitored using gas chromatography and photo-ionization detection. Sixteen healthy male Danish students (average age 24), who were "nose breathers" volunteered for the study. Adaptation to the odor occurred, but odor was still noticeable at the higher concentrations at the end of the exposures. Three subjects reported that the odor/air quality at 100 ppm was unacceptable (not further explained). There was an increase in slight irritation of the eyes and nose, described as slight, and a reported decrease in air quality at 100 ppm as well as an increase in the perceived odor levels as test concentrations increased. The average irritation score was 13 on a scale of 100, with one subject reporting a score of 64; six subjects reported no irritation during exposure at 100 ppm. No irritation of the throat or lower airways was reported at any concentration, and there was no effect on mood, fatigue, or sleepiness and no cough or nausea. However, an increase in the occurrence of headache, dizziness, and feeling of intoxication was found during the 100-ppm exposure; effects were described as slight to moderate and involved about half of the subjects (data were not presented). Pulmonary function and nasal mucus flow were unaffected by toluene inhalation. Furthermore, toluene had no significant effects on the performance of eight psychometric tasks measuring 20 different parameters, but there was a borderline significant decrease in three tests (multiplication errors, Landolt's rings, and the screw plate test) at 100 ppm.

Twelve healthy, adult men (ages 20-50) inhaled toluene at a constant concentration of 40 ppm for 4 h or were exposed to three 30-min peaks at 110 ppm over a 4-h period (Lammers et al. 2005a). Neurobehavioral tests were performed repeatedly during and after exposure. No effect on motor performance, attention, perceptual coding and memory, or mood was found with either exposure regimen. There were no further details in the available abstract.

In a study that evaluated acute symptoms and neurotoxicity manifest as sleepiness, Muttray et al. (2005) exposed 20 healthy male subjects to toluene at 0 or 50 ppm for 4.5 h. Toluene was monitored by infrared spectroscopy. Acute symptoms were assessed with a questionnaire, and sleepiness was assessed with the pupillographic sleepiness test, which measures changes in the diameter of the pupil of the eye. The subjects reported a bad smell and irritation of the throat during exposure at 50 ppm, but symptoms of headache, dizziness, nausea, tiredness, pain or pressure on the chest, coughing spells, shortness of breath, irritation of the eyes, watering eyes, blurred vision, irritation to the nose, running nose, an unpleasant taste, irritation to the skin, and feeling of fainting or vertigo were not significantly increased over control symptoms. Sleepiness was not increased.

Cherry et al. (1983) assessed the effects of a 4-h exposure to toluene at 80 ppm on four measures of performance and on mood. The subjects were eight male postgraduate students (ages 22-50), who were tested in groups of four in an atmosphere-controlled chamber. Test results of simple reaction time, four-choice reaction time, tracking task, and visual search were compared with those from a control group. Test results were also compared with those following exposure to alcohol (0.4 mL/kg) and following exposure to toluene and alcohol (0.4 mL/kg). In the control exposures, the chamber was primed with toluene to mask the control chamber. In both the control and exposure sessions, peppermint oil was used to mask the odor of toluene. The exposures were controlled by the investigators, but they took no part in the testing which was carried out blind. For the single exposures, the mean alcohol blood level was 49.9 mg%, and the mean blood toluene concentration was 12.7 mmol/L (both taken at the end of 4 h). Toluene alone had no significant effect on any of the behavioral measures, whereas alcohol caused a significant deterioration on pursuit tracking, visual search tasks, and mood. Although the combination of toluene and alcohol had no significantly greater effect on any of the test results than alcohol alone, there was a nonsignificant tendency for performance and mood to deteriorate more than when alcohol was administered alone.

In a similar study, 16 healthy adult male volunteers, ages 23 to 38, were exposed to toluene at 0 or 80 ppm for 4 h in a controlled atmosphere chamber (Olson et al. 1985). Three different performance tests were administered: simple reaction time, choice reaction time, and memory. There were no differences in performance of tests involving simple reaction time, short-term memory, or choice reaction time immediately after entering the exposure chamber or after 2 or 4 h of exposure. On a rating scale of no, negligible, slight, and considerable,

the subjects rated the discomfort (nausea, headache, or irritation in the eyes, nose, or esophagus) during the exposure as negligible.

The same investigators (Iregren et al. 1986) conducted another study in which they compared effects of toluene exposure to alcohol ingestion. Twelve men, ages 22-44 years, were exposed to toluene at 80 ppm toluene for 4.5 h. Results were compared with control exposures, exposure to toluene at 80 ppm accompanied by ingestion of alcohol (15 mmol/kg), and ingestion of alcohol alone. Neurobehavioral tests addressed choice reaction time, simple reaction time, color-word vigilance, and memory. The tests were administered prior to exposure and after 2 and 3.5 h of exposure. Symptoms and mood, including wakefulness, were also surveyed. Exposure to toluene at 80 ppm failed to affect performance on any of the tests, whereas the moderate ethanol intake resulted in gross performance changes in simple reaction time and color-word vigilance. There were no interactive effects of toluene and ethanol. Heart rate, EEG recordings, and sleep latencies were not affected by toluene treatment, although subjective symptoms of nausea, headache, and irritation were increased during the toluene and combined toluene and ethanol exposures. However, mood symptoms (feeling bored, sleepy, or irritated) were not different between the exposed and control groups. The subjective symptoms were the same as those reported in the earlier study of Olson et al. (1985), which were rated in that study as negligible in the control and exposed groups.

Winneke (1982) exposed 18 subjects to either air or toluene at 100 ppm in a controlled chamber for a 3.5 h period. Critical flicker frequency (the illusion of motion due to persistent sensory neuron excitation after a stimulus has ended) was measured as a perceptual measure of CNS activation. Sustained attention was measured with a bisensory vigilance task. At the end of the exposure, a comprehensive battery of psychomotor tests (not defined) was administered. None of the measures showed a significant effect from toluene exposure.

Dick et al. (1984) exposed 30 male and female subjects to toluene at 100 ppm for 4 h. Subjects were exposed to either a placebo (a 2-min exposure to toluene at 25 ppm followed by air) or toluene at a concentration of 100 ppm in an atmosphere-controlled chamber. Solvent concentration was monitored using an infrared analyzer and analysis was carried out by gas chromatography every 3 min. Compared with the control values, toluene exposure did not adversely affect the outcomes on 27 psychomotor tests. A slight, but statistically significant, decrement was observed on the visual-vigilance test; the percentage of correct hits was lower. The authors considered the overall results to demonstrate a failure to induce cognitive effects.

A double-blind study by Rahill et al. (1996) tested toluene at 100 ppm or air only for 6 h. Six healthy male and female subjects, ages 27-38, performed complex psychometric and response-time tasks during rest and following exercise sessions sufficient to quadruple the resting ventilation rate. Pulmonary function tests, consisting of forced vital capacity and forced expiratory volume in 1 second (sec), were also carried out prior to and after the exposure. The subjects filled out a 56-item questionnaire concerning symptoms and mood before and

after the exposure. Each subject served as his or her own control. The exposures were carried out in a large atmosphere-controlled chamber, and the toluene concentration was monitored by an infrared analyzer. Latency but not accuracy during neuropsychologic tests proved sensitive to toluene. The latency was greatest following the exercise period. The composite score obtained over time during toluene exposure was lower than that during the air exposure. However, the differences between the air- and toluene-exposed groups, while in some cases statistically significant, were characterized by the study authors as subtle. For example, the composite score for an hour-long multitasking test was reduced by 11% following the toluene exposure compared with control score. Pulmonary function was not affected by toluene exposure in this study. No subjective symptoms were reported, and mood was only slightly changed. The mood change was characterized as a "reduced positive mood." This experiment demonstrated that physical activity can exacerbate the response to toluene as greater, but subtle, differences in performance were observed after exercise.

Baelum et al. (1985) reported that the acute effects of toluene exposure are slightly more pronounced for previously exposed workers (rotogravure printers) compared with previously unexposed controls. The printers had been exposed to solvents for 9-25 years. Male subjects (43 printers and 43 controls), ages 29-50 years, were divided into four matched groups (20 control printers, 19 toluene-exposed printers, 21 unexposed controls, and 15 toluene-exposed controls) and exposed to either air (20 control printers and 21 controls) or toluene at 100 ppm (19 printers and 15 controls) for 6.5 h, preceded by a 1-h acclimatization period. Subjective evaluations concerning the quality of the environment were taken before exposure and at 0.5 and 6.5 h. Nine visuomotor-coordination and perceptual-speed tests were administered at several hours into the exposure. A color-discrimination test was administered before and during exposure. The effects observed at 100 ppm for both exposed groups compared with control groups included discomfort with complaints of low air quality, strong odor, fatigue, sleepiness, a feeling of intoxication, and irritation of the eyes, nose, and throat. However, complaints increased for all subjects during the test periods (including the controls) and neither annoyance nor nausea was experienced. Toluene-exposed printers were slightly slower than nonexposed printers on one of six manual dexterity tests ($p < 0.05$), but toluene-exposed controls and nonexposed controls had similar results on this test. The same relationship was found for one visuomotor test (Landolt's rings); more errors were made by exposed printers compared with unexposed printers and no differences were found between exposed and unexposed control groups. Both groups of printers made fewer errors on a color-discrimination test administered before exposure compared with both groups of controls, but the error rate decreased later in the exposure for both groups of controls, whereas there was almost no improvement for either of the toluene-exposed groups. Although no significant differences were observed between the occupationally-exposed group and the naive subjects, the authors stated that there was a tendency toward greater sensitivity among occupationally-exposed subjects.

As part of the same study, Nielsen et al. (1985) evaluated the renal function of the printers and control groups. Urinary samples were taken before the exposure, at 3 h after the start of exposure, and again at 6 h after the start of exposure. No significant changes in β-microglobulin- or albumin-excretion rates were observed for the exposed subjects compared with the air controls. The authors concluded that there is no causal relationship between moderate exposure to organic solvents and renal injury.

Stewart et al. (1975) exposed 10 male subjects to toluene at 0, 20, 50, or 100 ppm and nine female subjects at 100 ppm for 1, 3, or 7.5 h over several days. The exposures at 100 ppm were for five consecutive days. Males were also exposed to a fluctuating concentration of 50-150 ppm (mean concentration 100 ppm) for 1, 3, or 7.5 h for 2 days. Ages ranged from 19-47 years old. Subjects were exposed at each concentration in groups of two to four, with never more than eight subjects in the chamber at one time (subjects exposed for 1 h exited the chamber after 1 h and the subjects exposed for the longer durations remained). Male subjects exercised for 5-6 min once during the shorter exposures and twice during the 7.5-h exposure. Chamber atmospheres were monitored with gas chromatography and infrared spectroscopy. Each subject was given a complete medical examination before and after exposure; additional evaluations included hematology and clinical chemistry parameters, EEG recordings (with an amplified visual evoked response), pulmonary-function tests, heart rate, equilibrium tests (modified Romberg), and cognitive tests. Subjective symptoms were also evaluated. Not all evaluations took place every day or with all subjects. There was no decrement in several psychomotor performance tests, except for females exposed at 100 ppm for 7.5 h on the second day. They had fewer correct responses on a dual task involving visual vigilance and tone detection on the second and fifth days of exposure. This decrement was not observed in male subjects or in females during the 3-h exposure. Performance on time estimation, addition, and coordination tests did not change. On the fifth day of exposure at 100 ppm for 7.5 h and during the fluctuating exposure at 100 ppm, one of two male subjects had a slight increase and decrease, respectively, in the visual evoked potential. This change was not observed in female subjects. When toluene was present in the chamber, all subjects noticed a mild to strong odor when entering the chamber; adaptation occurred for most subjects. There was no increase in drowsiness, fatigue, sleepiness, or headache or change in appetite or sleep habits. Subjective complaints of irritation were greater during the 3-h exposure at 100 ppm than during the 1- or 7.5-h exposure at 100 ppm. Types and incidences of subjective complaints were similar between controls and the exposed subjects during the 7.5-h exposure at 100 ppm.

An evaluation of human responses to varying concentrations of toluene with a TWA of 100 ppm (with peaks at 300 ppm every 30 min) was conducted by Baelum et al. (1990). The authors compared the symptoms during the varying concentrations to those during exposure to a constant concentration of toluene at 100 ppm and to those reported in a clean air control. Thirty-two males and 39 females comprised a random sample of the population between the ages of 31

and 50. The subjects were healthy males and females who did not abuse alcohol or drugs and were able to exercise for 15-min periods with a load of 50, 75, or 100 W during the peak exposures. The clean air, constant exposure, and varying exposure groups comprised 23-24 subjects each. Exposures were carried out for 7 h, and concentrations were measured using a flame ionization detector. Both toluene-exposed groups complained significantly more about the poor air quality, altered temperature perception, feeling of intoxication, and increased irritation in the nose and lower airways (but not of the eyes); there was a tendency toward an increase in dizziness and feeling of intoxication in the exposed groups (controls reported scores similar to those of the constant exposure-group for fatigue, sleepiness, and headache). There was a tendency toward lower scores on vigilance tests for the toluene-exposed groups compared with the control, indicating only a minimal effect on psychomotor performance, as scores on other assessment tests were normal. There was not, however, a significant difference between symptoms or performance between the two toluene-exposed groups.

Echeverria et al. (1989, 1991) reported on the acute neurobehavioral effects of toluene in tests with 42 healthy male and female college students. The toluene concentrations tested were 0, 75, and 150 ppm over a 3-day period (7 h each day) and were administered in random order. The odor of toluene was masked with menthol (0.078 ppm). Chamber atmospheres were measured with an infrared analyzer and confirmed by gas chromatography. A battery of 12 performance tests (verbal, visual, and psychomotor) was administered to each participant before the exposures and again at 4 and 7 h during the exposures. Test results were averaged over the 3 days. The initial test results served as control values. A mood and fatigue checklist was also incorporated into the protocol. A 5-12% decrement in performance was considered significant if consistent with a linear trend. The results of this study included a significant decrement in performance on several tasks when subjects were exposed to toluene at 150 ppm; they included losses of 6.0% for digit span, 12.1 % for pattern recognition (increase in latency of 0.3 sec), 5.0% for pattern memory (number correct), 6.5% for one hole, and 3% for critical tracking. These differences, although statistically significant, were small. Although the pattern of moods scale and fatigue symptoms were not affected by toluene, the frequency of headaches and ocular irritation increased slightly in a concentration-dependent manner, as did the number of observations of sleep during exposure. For example, headache was reported by 8, 11, and 14% of individuals exposed at 0, 75, and 150 ppm, respectively. Sleep did not confound the behavioral scores. The reports of ocular irritation and headache were greatest on the first day of exposure.

Ogata et al. (1970) measured the effects of exposure to toluene at 100 or 200 ppm on blood pressure, pulse rate, flicker value (not defined), and eye-to-hand reaction time in 23 male students. Subjects were exposed for 3 h in the morning and 4 h in the afternoon, the latter following a 1-h break. After a 3-h exposure at 200 ppm, the mean pulse rate was decreased significantly compared with a control group. However, there was no dose-response relationship and all pulse rates were lowered as exposures continued. The authors stated that there

was a tendency for reaction time to be prolonged during the 200-ppm exposure, but there was no clear concentration-response relationship.

Twelve healthy male subjects, ages 20 to 35, were exposed to successively increasing concentrations of toluene at 100, 300, 500, and 700 ppm, for four successive 20-min periods (Gamberale and Hultengren 1972). There was a 5-min break between the exposure at 300 ppm and at 500 ppm. The air-toluene mixture was administered via a breathing valve and a mouthpiece to the sedentary subjects. The odor of toluene was masked with menthol-crystals, and only one of the 12 subjects was able to correctly distinguish between conditions with and without toluene. Four performance tests were administered during the last 15 min of each exposure: two perceptual speed tests, simple reaction time, and choice reaction time. Test results were compared with results during air exposures. An increase in simple reaction time (to a stimulus) was observed at 300 ppm (controls, 222 msec; 300 ppm, 236 msec), complex reaction time was affected at 500 ppm, and a decrease in perceptual speed occurred at 700 ppm. The decrease in perceptual speed was relative to the control values, which decreased with each successive exposure (learning effect); speed also decreased for the exposed group but not as rapidly as for the control group. The authors stated that short-term exposures to toluene below 300 ppm are not associated with psychomotor dysfunction. Heart rate declined during the 85-min test period in accordance with increasing familiarity with the test situation and individual test and was little affected by toluene exposure.

Carpenter et al. (1976) reported several human and animal responses to "Toluene Concentrate," a hydrocarbon mixture produced by a large solvent manufacturer in the United States. This mixture contained toluene (45.89 %), butanes, pentanes, hexanes, heptanes, octanes, cyclopentanes, cyclohexanes, and benzene. Gas-chromatographic analysis was used to monitor exposure concentrations. Six of six subjects indicated they would be willing to work an 8-h day while being exposed to toluene concentrate at 480 ppm (220 ppm of toluene), a concentration at which some ocular irritation was reported after a 15-min exposure. Three of these six people reported that they would be willing to work an 8-h shift while being exposed to toluene concentrate at 930 ppm (427 ppm of toluene).

Horvath et al. (1981) exposed a group of 11 male volunteers, ages 20-21, to three 70-min sessions of toluene at 240 ppm, during which the subjects performed a vigilance task. The task consisted of spatial discrimination of low frequency acoustical clicks, which contributed to the monotony of the task, and a concurrent visual feedback task. The toluene concentration was increased gradually over the test period, reaching and maintaining a maximum concentration of 240 ppm over the last 30 min of each session. There was a 70-min period between exposures. For comparison purposes, additional subjects ingested 5 or 10 mg of diazepam, a known psychotropic drug, or were exposed to a combination of toluene and diazepam (5 mg). There were no effects from exposure to either toluene or diazepam on vigilance during the first session, and there was no effect of toluene on vigilance during the second session, although vigilance errors were increased in the groups that had ingested diazepam (both doses) and in the group

exposed to both toluene and diazepam. During the third session, vigilance errors were increased for all groups except the control group. Errors were highest in the groups exposed to 10 mg of diazepam and both diazepam and toluene. The authors considered the effect an impaired alertness. The subjective symptom survey found decreased fatigue and sleepiness, especially during the second session.

Two older studies are reported here for completeness of the data base (von Oettingen et al. 1942; Carpenter et al. 1944). These studies used outdated analytic techniques and a small number of subjects compared, and are not included in Table 6-3. von Oettingen et al. (1942) conducted a study with three healthy human volunteers, ages 35 to 53; toluene concentrations were controlled and measured by interferometric determinations. Subjects were exposed at 0, 50, 100, 200, 300, 400, or 600 ppm for 8-h sessions (with a 30-min break) over the course of an 8-week period (each exposure was separated by several days). Two of the subjects were also exposed at 800 ppm for 3 h, then for another 2 h following a 2-h break. Many of the exposures were repeated, with a break of several days between exposures. Blood pressure, pulse rate, respiratory rate and volume, differential blood cell count, and clinical chemistry parameters were monitored. Subjective symptoms were also evaluated. There were no effects of exposure on cardiac or respiratory parameters or hematology or clinical chemistry parameters at concentrations up to 500 ppm. Decreased erythrocyte count was observed at 800 ppm. At 50 ppm, one of two subjects had no subjective complaints and the other complained of very mild headache and drowsiness (subjects also complained of moderate tiredness toward the end of the control exposure). At 100 ppm, moderate fatigue and sleepiness were the only complaints. Acute exposure to toluene at a concentration of 200 ppm for 8 h produced headache, nausea, muscular weakness, confusion, impaired coordination, and dilated pupils, as well as after-effects including fatigue, general confusion, and moderate insomnia in one, two, or all of the subjects. Higher concentrations produced effects similar to the 200-ppm exposure; however, the effects were more pronounced and the after-effects were prolonged. Olfactory adaptation to the odor was rapid, and other than a slight smarting of the eyes and nose, none of the exposures produced irritation of the mucous membranes.

Carpenter et al. (1944) exposed two subjects to toluene at 200, 400, 600, or 800 ppm for 7-8 h. Subjective symptoms ranged from transitory mild throat and ocular irritation and slight exhilaration at 200 ppm to metallic taste, transitory headache, extreme lassitude, scotomata, verbosity, inebriation, and slight nausea at 800 ppm. After the initial exposure, some adaptation to the subjective symptoms occurred. The threshold for inability to perform a steadiness task (holding a wire in a 0.25-in hole without touching the sides) was 800 ppm. Toluene was evaporated from a heated dish; vapor concentrations were measured with an interferometer.

In order to simulate an abuse situation, a researcher inhaled toluene from a paper bag containing gauze soaked with toluene (Press and Done 1967). The exposure consisted of “rapid, deep inhalations and exhalations directly into a

brown paper bag containing the contents of two tubes of 3/4 oz each of Testor's cement...". The estimated concentration of toluene in the paper bag was 10,000 ppm (3.6 mg of toluene/100 mL of air). During the 5-min exposure, the subject had sensations of dizziness, blurred vision, roaring and buzzing in the ears, and slurred speech. An electroencephalogram taken during the exposure was normal. "Blood levels exceeding 1.75 mg/100 mL were reached." Because the concentration was estimated, this study is not included in Table 6-3.

2.4. Developmental and Reproductive Toxicity

Reproductive and developmental toxicity of toluene have been reviewed by Donald et al. (1991) and ATSDR (2000). Data regarding human developmental and reproductive toxicity are restricted to chronic exposures and include only continuous occupational or abuse situations. Intrauterine growth retardation, spontaneous abortion, premature delivery, congenital malformations, and postnatal developmental delays are clearly associated with gross toluene exposure; maternal toxicity at very high abuse concentrations includes overt CNS depression, renal tubular acidosis, and fatty liver. Further confounding these report are social and health status variables, as well as the possibility of exposure to other fetotoxic agents (either as impurities or admixtures in toluene-containing products) or deliberate or accidental exposures to other chemicals or drugs (especially ethanol), which are not accounted for in these reports. These studies provide little quantitative information regarding dose response and are not considered in the development of AEGL values.

Luderer et al. (1999) examined the reproductive endocrine effects of acute exposure on males and females. Women were divided into two groups comprised of those in the follicular phase and those in the luteal phase of the menstrual cycle. Groups consisted of four or five individuals with a similar number of matched controls. A 3-h exposure at 50 ppm via a mouthpiece did not result in alterations of the serum gonadotrophins comprising luteinizing hormone and follicle-stimulating hormone; however, subtle effects on luteinizing-hormone secretion in men and women, the latter in the luteal phase, were found. There was no effect on blood testosterone concentrations in men. The authors stated that the clinical relevance of the subtle effects on luteinizing-hormone secretion is unclear.

Gericke et al. (2001) found no effect of chronic toluene exposure on follicle-stimulating hormone, luteinizing hormone, or testosterone of 1,077 male subjects compared with a referent group. There is some indication that lower concentrations of hormones, follicle-stimulating hormone, luteinizing hormone, and serum testosterone (Svensson et al. 1992) and dysmenorrhea (Ng et al. 1992) may be associated with occupational exposure to toluene. However, Ng et al. (1992) state that it is uncertain whether other behavioral and work-related factors may also have contributed to the incidence of dysmenorrhea.

2.5. Genotoxicity

Several investigators examined the effect of occupational exposures to toluene on peripheral lymphocytes. Chromosome analyses of 24 workers (Forni et al. 1971) and 32 workers (Maki-Paakkanen et al. 1980) at rotogravure plants revealed no significant differences in the frequencies of sister chromatid exchanges (SCEs) or chromosomal aberrations between the workers and matched controls. Bauchinger et al. (1982) examined peripheral lymphocytes in a group of male rotogravure workers who were occupationally exposed only to toluene for more than 16 years. The ages ranged from 32 to 60; 11 workers were heavy smokers (more than 10 cigarettes per day). A similar number of smokers (eight of 24) comprised the control group. Subjective complaints were similar among both groups and there was no evidence of neurologic damage in either group. The rotogravure workers had significantly more chromatid breaks, chromatid exchanges, and gaps than the control group. The continuously measured toluene concentration in the work room was between 200 and 300 ppm (benzene was <0.3%). Hammer (2002) found a three-fold increase in SCEs in 42 rotogravure printing plant workers exposed to toluene at 38-88 ppm compared with a control group. Ambient air and blood toluene concentrations did not show a relationship to SCEs, but there was a significant relationship with cresol metabolites in the urine.

Five adult male volunteers were exposed to toluene at a concentration of 50 ppm for 7 h/day for 3 days; this exposure regimen was repeated three times over 2 weeks (Richer et al. 1993). Peripheral blood lymphocytes were evaluated for SCEs, cell-cycle delay, and cell mortality. Although cell mortality was temporarily increased, disappearing after 15 h, there were no changes in cytogenetic parameters.

An in vitro experiment conducted by Gerner-Smidt and Friedrich (1978) showed that toluene concentrations up to of 1.52 mg/mL failed to alter the number of SCEs or the number of chromosomal aberrations in human lymphocytes compared with controls. In this study, toluene at 1,520 ppm did, however, produce significant cell-growth inhibition compared with controls.

2.6. Carcinogenicity

An epidemiologic study by Carpenter et al. (1988) compared deaths from cancers of the CNS in workers at the Y-12 nuclear facility or Oak Ridge National Laboratory (Oak Ridge, TN) with a group of controls. The workers had been exposed for a mean period of 5 years to solvents (toluene, xylene, and methyl ethyl ketone). No increased incidence in death from cancers of the CNS was found compared with controls. No estimation of exposure concentrations was made in this study.

Another study of occupational exposure to toluene was conducted involving 1,020 rotogravure printers exposed to toluene who were employed for a minimum of 3 months between 1925 and 1985 (Svensson et al. 1990). Estimated

concentrations of toluene ranged from 450 ppm in the 1940s to as low as 30 ppm by the mid-1980s; workers were also exposed to various concentrations of benzene and other hydrocarbons for various durations. When the data were analyzed for workers who had been exposed for at least 5 years and a latency of 10 years, no significant increase in deaths from cancers was observed.

The International Agency for Research on Cancer (IARC 1999) has assessed the carcinogenicity of toluene. Its evaluation states that there is *inadequate evidence* in humans and *evidence suggesting lack of carcinogenicity* of toluene in experimental animals. IARC (1999) concluded that "toluene is *not classifiable as to its carcinogenicity to humans (Group 3)*." EPA (2007) has not classified toluene as to its carcinogenicity because there are no human data and animal data are inadequate.

2.7. Summary

Toluene is relatively nontoxic (NRC 1981). Effects of acute exposures are limited to CNS depression, cardiac arrhythmias, and renal toxicity (NRC 1981). Even concentrations that produced unconsciousness failed to produce residual organ damage. Deaths have been reported following exposure at "high concentrations" of toluene and are usually associated with intentional solvent abuse. The "high concentrations" in these abuse situations can seriously inhibit CNS function and predispose subjects to cardiac arrhythmias. Severe renal tubular acidosis has been described in several abuse situations and in some accidental exposures. Effects on the blood and bone marrow were observed during some early studies, when industrial toluene was contaminated with benzene or used in conjunction with benzene (von Oettingen et al. 1942; Massengale et al. 1963), a known bone marrow suppressant. The highest non-fatal vapor exposures occurred during accidental exposures and the concentrations were either calculated or measured after the exposure. Concentrations of greater than 5,000 ppm for an undefined time (Longley et al. 1967) and greater than 1,842 ppm for several hours (Meulenbelt et al. 1990) resulted in unconsciousness and disorientation, respectively. Recovery was complete in both cases.

Toluene is not a primary irritant. Slight irritation of the eyes and nose has been reported in several controlled clinical studies during 6- to 8-h exposures to at 100 ppm or higher (Carpenter et al. 1944; Andersen et al. 1983; Baelum et al. 1985, 1990; Echeverria et al. 1989), but there was no annoyance or discomfort associated with the exposures (Baelum et al. 1985). Furthermore, irritation was not among the reported symptoms during exposures of up to 800 ppm (von Oettingen et al. 1942) or in many occupational monitoring studies where concentrations were 100 ppm or higher (Greenberg et al. 1942; Wilson 1943; Foo et al. 1990; Ukai et al. 1993; Neubert et al. 2001a). No dermal, ocular, or throat irritation was reported in painters exposed to toluene at 1,100 ppm (Greenberg et al. 1942) or in accident situations where concentrations may have been greater than 5,000 ppm (Longley et al. 1967). Adaptation occurs to the odor (Stewart et

al. 1975; Andersen et al. 1983; Mergler and Beauvais 1992) and potential drying effects on the mucous membranes (Carpenter et al. 1944; Andersen et al. 1983).

The primary effect associated with inhalation exposure to toluene is CNS depression. Fifteen of the approximately 20 studies in Table 6-3 addressed neurobehavioral effects. The neurobehavioral end points in these studies measure very subtle changes in reaction time and cognitive ability. The concentration of 100 ppm was a no-effect level for most neurobehavioral end points, including vigilance and reaction time (Ogata et al. 1970; Gamberale and Hultengren 1972; Stewart et al. 1975; Winneke 1982; Andersen et al. 1983; Dick et al. 1984; Baelum et al. 1990; Rahill et al. 1996). The effect of exercise, which results in increased uptake of toluene, was evaluated in the studies by Baelum et al. (1990) and Rahill et al. (1996). No gross neurobehavioral deficits were observed at 150 ppm (Echeverria et al. 1989), 200 ppm (Ogata et al. 1970), or 100 ppm with peaks to 300 ppm with an exercise protocol (Baelum et al. 1990). No greater effects were observed when exposures were repeated over several days (Stewart et al. 1975; Echeverria et al. 1989), and no significant gender differences were observed (Stewart et al. 1975). No impairment in alertness occurred during two successive 70-min exposures to toluene at 240 ppm (Horvath et al. 1981), although the results of the study were difficult to interpret. A significant increase in time to complete a complicated task involving perceptual speed (45.5 vs 36.9 sec) was observed at 700 ppm, following 20-min exposures at lower concentrations (Gamberale and Hultengren 1972). The studies by von Oettingen et al. (1942) and Carpenter et al. (1944) were reported for completeness of the data base, but were not considered in development of AEGL values because of the impurity of the toluene, the less accurate analytic measurement methods (inferometrics is no longer an acceptable analytic method and the reliability of the combustible gas indicator is lower than the range measured), and the small number of subjects compared with later studies.

Developmental toxicity data from animal studies show that the developing embryo is no more sensitive to the toxic effects of toluene exposure than is the mother (ACGIH 2005). Developmental delay and congenital malformations resembling those of fetal alcohol syndrome have been observed in pregnant women after intentional inhalation of concentrated toluene vapor. These conditions were the result of chronic toluene abuse during pregnancy. There is no evidence that this syndrome occurs in women who are exposed occupationally to toluene.

The relationship of toluene exposure to mutagenicity and genotoxicity is unclear as conflicting results were observed in several studies. Examination of peripheral lymphocytes of clinically-exposed volunteers and occupationally-exposed workers were generally negative for chromosome aberrations and SCEs, but were positive or questionable in other studies (Bauchinger et al. 1982; Hammer 2002). The human data are insufficient for cancer classification of toluene exposure in humans at this time, but examinations have found no association between cumulative toluene dose (as ppm-years) and standardized mortality ratios for either all sites or for respiratory tract cancers (Svensson et al. 1990).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data were available for the rat and mouse, and lethal concentration data from these studies are summarized in Table 6-4. Additional data from studies with the dog, cat, and rabbit were available but provide little information on the threshold for lethality.

3.1.1. Dogs

Ikeda et al. (1990) examined the cardiovascular response in 25 dogs during acute inhalation of toluene at 30,000 ppm for 9-10 min. Electrocardiograms revealed no changes for the first 3-4 min of exposure; tachycardia ensued for several minutes and was followed by a period of bradycardia. In some dogs, ventricular fibrillation ensued shortly thereafter, followed by death. Kobayashi et al. (1989) reported that the threshold concentration of toluene for decreasing left-ventricle contractility in dogs was 3,800 ppm.

3.1.2. Rats

Pryor et al. (1978) exposed groups of male Fischer rats to various undefined concentrations of toluene. All rats died during a 1-h exposure at 40,000 ppm. The 1-h LC_{50} (lethal concentration, 50% lethality) was 26,700 ppm.

Cameron et al. (1938) in a summary of their earlier work reported that the 6.5-h LC_{50} for Wistar rats was approximately 12,200 ppm. Mortality was 60% during a 1.5 h exposure at 24,400 ppm and all 10 rats died when this exposure was extended to 6 h. No rats died during a 24-h exposure to toluene at 6,100 ppm. Nine-day old rats were more resistant to toluene than adult rats. Rats survived fourteen 8-h exposures at 1,525 ppm. No details of the exposures were provided. Smyth et al. (1969) reported that one of six rats exposed at 4,000 ppm for 4 h died. No further details were provided in this range-finding study, and the study is not reported in Table 6-4.

In a study by Shell Oil Company (1982), groups of three male and three female Wistar rats inhaled measured concentrations of toluene at 18,100-18,800 ppm for up to 7 h. All rats survived the 3-min exposure. After exposures at 18,100 ppm for 1 min, 18,500 ppm for 30 min, and 18,900 ppm for 7 h, mortality was 17, 83, and 100%, respectively. At all concentrations, signs during exposure included agitation, salivation, and ocular and nasal discharge. Except for the 3-min exposure, rats became comatose, usually with whole-body tremors. Animals gained consciousness 1h after exposure. DuPont Chemical Company (1966) reported a 4-h LC_{50} of 18,300 ppm for male CD rats.

TABLE 6-4 Summary of Acute Lethal and Sublethal Toxicity of Toluene in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
Dog	30,000	10 min	Successive tachycardia, bradycardia, and ventricular fibrillation, followed by death.	Ikeda et al. 1990
Rat	26,700	1 h	LC_{50}	Pryor et al. 1978
	40,000	1 h	100% mortality	
Rat	24,400	6 h	100% mortality	Cameron et al. 1938
	24,400	1.5 h	60% mortality	
	12,200	6.5 h	50% mortality	
	6100	24 h	No deaths	
Rat	20,000	50 min	100% mortality	Kojima and Kobayashi 1973
	15,000	2.5 h	80% mortality	
	12,200	2-2.5 h	LC_{50}	
	10,000	2 h	20% mortality	
	5,000	2 h	No deaths	
Rat	18,900	7 h	100% mortality	Shell Oil Company 1982
	18,500	30 min	83% mortality	
	18,100	10 min	17% mortality	
	18,500	3 min	No deaths	
Rat	18,300	4 h	LC_{50}	DuPont Company 1966
Rat	15,000	1 h	No deaths	Hinman 1987
Rat	6,000	4 h	No deaths	Wada et al. 1989
	7,670	4 h	25% mortality	
Rat	6,250	2 h	No deaths	Mullin and Krivanek 1982
	3,100	4 h	No deaths	
Rat	2,667	7.5 h	No deaths	Lammers et al. 2005b

(Continued)

TABLE 6-4 Continued

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
Mouse	38,465	10 min	LC_{50}	Moser and Balster 1981; 1985
	21,872	30 min	LC_{50}	
	19,018	60 min	LC_{50}	
	6,000[a]	30 min	No deaths	
Mouse	24,400	6 h	100% mortality	Cameron et al. 1938
	24,400	1.5 h	10% mortality	
	12,200	6.5 h	100% mortality	
	6,100	24 h	No deaths	
Mouse	12,000	20 min	No deaths	Bruckner and Peterson 1981a,b
	8,600	3 h	LC_{50}	
	4,000	3 h	No deaths	
Mouse	10,000	1 h	No deaths	Bushnell et al. 1985
Mouse	6,940	6 h	LC_{50}	Bonnet et al. 1979
Mouse	5,320	7 h	LC_{50}	Svirbely et al. 1943

[a]Exposures were repeated for 7 weeks.

Kojima and Kobayashi (1973) exposed groups of five male albino rats to concentrations of toluene ranging from 5,000 to 25,000 ppm for 2 to 2.5 h. No rats died following exposure at 5,000 ppm for 2 h. One of five rats died during a 2-h exposure at 10,000 ppm. Four of five rats died during a 2.5-h exposure at 15,000 ppm. All rats exposed at 20,000 ppm died within 50 min. Death was attributed to CNS depression.

As part of a neurotoxicity study (see Section 3.3.2), Mullin and Krivanek (1982) exposed groups of six male CD rats to measured concentrations of toluene at 810, 1,660, and 3,100 ppm for 4 h and at 6,250 ppm for 2 h. No deaths were reported following exposures to toluene, whereas deaths were reported in similar tests with other chemicals. In other neurotoxicity tests described in Section 3.3, no deaths occurred in adult male Long-Evans rats exposed to toluene at 15,000 ppm for 1 h (Hinman 1987) or in male WAG/RijCrlBR rats exposed at 2,667 ppm for 7.5 h (Lammers et al. 2005b). No deaths occurred in adult male Wistar rats exposed at 6,000 ppm for 4 h, but two of eight rats exposed at 7,670 ppm for 4 h died (Wada et al. 1989). The fact that some of these animals were performing learned tasks increased the rate of uptake of toluene.

3.1.3. Mice

Moser and Balster (1985) exposed groups of 12 male CD-1-mice to several undefined toluene concentrations for 10, 30, or 60 min. Animals were examined for lethality and behavioral toxicity (inverted screen test). The LC_{50} values for the 10-, 30-, and 60-min durations were 38,465 ppm (confidence limit: 36,067-41,023 ppm), 21,872 ppm (confidence limit: 20,731-23,076 ppm), and 19,018 ppm (confidence limit: 17,350-20,846 ppm), respectively. The authors noted that as solvent concentrations were increased for the lethality studies, mice displayed a progression of clinical signs from excitability and hyperactivity to lethargy and hypoactivity. Shallow, rapid respiration ensued and was followed by death within 1 h after the exposure. All mice survived repeated exposure at 6,000 ppm for 30 min/day, 5 days/week for 7 weeks and appeared in good health (Moser and Balster 1981).

Cameron et al. (1938) exposed groups of 10 mice (strain not specified) to concentrations of toluene at 6,100-24,400 ppm for various durations. Mortalities were 10% and 100% following 1.5- and 6-h exposures, respectively, at 24,400 ppm. Mortality was also 100% after a 6.5-h exposure at 12,200 ppm. All mice survived a 24-h exposure at 6,100 ppm. No further details of the exposures were given.

As part of a study on the pharmacology and pharmacodynamics of toluene, Bruckner and Peterson (1981a) exposed groups of up to 14 male ICR mice to toluene at concentrations ranging from 2,600 to 12,000 ppm. The 3-h LC_{50} was 8,600 ppm (95% confidence interval: 8,000-9,200 ppm). No further details were provided. In a companion paper, no deaths were reported in mice exposed at 4,000 ppm for 3 h/day, 5 times weekly for 8 weeks (Bruckner and Peterson et al. 1981b). Similarly, no deaths were reported in adult C57BL/6J male mice

exposed at 10,000 ppm for approximately 1 h or in mice exposed at 3,000 ppm for 5 h/day for 90 days (Bushnell et al. 1985). In a study by Bonnet et al. (1979), the 6-h LC_{50} was 6,940 in mice. No further details were available.

Acute toxicity studies in Swiss mice conducted by Svirbely et al. (1943) revealed progressive symptoms prior to death, including restlessness, muscular twitching, an S-shaped curve in the tail, dyspnea, incoordination, and evidence of a narcotic effect. Toluene concentrations ranged from 3,660-8,520 ppm, as measured by a refractometer. The 7-h LC_{50} was 5,320 ppm (confidence limits: 4,960 and 5,710 ppm). Microscopic examination of the major organs failed to identify lesions with the exception of casts and debris in the renal tubules of some mice.

3.2. Nonlethal Toxicity

3.2.1. Dogs

von Oettingen et al. (1942) exposed six dogs to toluene at 850 ppm for 1 h. This exposure resulted in an increase in respiratory rate and a decrease in respiratory volume. No further details were provided.

3.2.2. Rats

Most studies of acute exposures of rats to sublethal concentrations of toluene evaluated neurotoxicity and are summarized in Section 3.3.2. Subacute exposures to toluene have produced hearing loss in rats. Hearing loss was found in young rats after exposure to toluene at 2,000 ppm for 8 h/day for 3 days or at 1,500 ppm for 14 h (Pryor et al. 1984). Permanent loss of hearing in the high frequency range was found when young rats were exposed at 1,200 ppm for 14 h/day, 7 days/week for 5 weeks. Morphologic examinations revealed loss of, or damage to, hair cells in the basal turn of the cochlea.

Toluene was also tested for its influence on ventricular arrhythmias in the rat. Previous inhalation of toluene by Wistar rats, at up to 7,387 ppm for 15 min, reduced the ectopic ventricular activity caused by coronary ligation or administration of aconitine (Magos et al. 1990). These results contrast with those with benzene, in which arrhythmias were increased in the 30 min following induction of arrhythmia. Following a near-lethal exposure to toluene at 66,000 ppm for 30 min, injection of epinephrine did not induce arrhythmia or ectopic beats in anesthetized rats (Vidrio et al. 1986).

3.2.3. Mice

Exposure of eight male ICR mice to toluene at 4,000 ppm for 3 h resulted in elevated blood SGOT 24 h after (Bruckner and Peterson 1981b). Repeated exposures for 3 and 5 days also resulted in elevated SGOT, with the increase significant after the 1- and 3-day exposures. When the exposures were extended to five times

weekly for 8 weeks, transient body weight depression and increased hepatic weights were observed. Histopathologic findings in the heart, lungs, kidneys, brain, and liver were generally unremarkable.

The sensory irritation response in groups of four male Swiss-Webster mice during a 30-min exposure at several concentrations of toluene (900, 1,700, 2,600, 3,500, 4,100, 5,050, 6,400, or 7,800 ppm) was evaluated by Nielsen and Alarie (1982). From these data, the RD_{50}, the concentration that depresses the respiratory rate by 50%, was calculated. At 900 ppm, there was no effect on the respiratory rate. Toluene concentrations of 2,600 ppm and higher produced a rapid, brief (approximately 1 min) decrease in the respiratory rate, followed by an increase above the control level within the next 6 min (stimulatory effect). At 7,800 ppm, the initial depressive effect on the respiratory rate was modified by the stimulatory effect at this concentration; after the brief depression, the increased respiratory rate, up to 140% of the control value, was sustained over the 30-min exposure. The RD_{50}, calculated on the basis of the initial depression, was 5,300 ppm. In cannulated mice, only a small decrease in respiratory rate occurred at the beginning of exposures, even at the higher concentrations. The authors discuss the fading of the sensory-irritation response or desensitization that occurs with some chemicals including some alkylbenzenes, making measurement of an RD_{50} difficult. The stimulatory effect was attributed to systemic absorption of toluene from the lung. In a similar study and using OF_1 mice, De Ceaurriz et al. (1981) reported a RD_{50} of 3,373 ppm.

3.3. Neurotoxicity

3.3.1. Non-human Primates

Weiss et al. (1979) evaluated the capacity of squirrel monkeys to self-administer toluene as a model of abuse. Monkeys (number not specified) previously trained to self-administer drugs on a single response were tested with toluene at concentrations of 0, 560, 1,000, 3,000, or 10,000 ppm during 1-h sessions. Pushing a button delivered a 15-sec exposure to toluene vapor. The highest rate of response (141 responses/h) was at 1,000 ppm. This rate decreased thereafter with increasing concentrations.

Taylor and Evans (1985) subjected adult female cynomolgus macaques to 50-min head-only exposures to toluene at 0, 100, 200, 500, 1,000, 2,000, 3,000, or 4,500 ppm and simultaneously tested for delayed matching-to-sample behavior as a measure of cognitive function. Monkeys were exposed singly to each concentration, with each monkey tested twice at each concentration. This procedure took 6 weeks. Previously, two of the monkeys had been exposed at 100 ppm and one monkey had been exposed at 1,000 ppm toluene for 6 h/day, 5 days/week for 90 days. Toluene concentration was monitored continuously with an infrared gas analyzer. Responses at 100 and 200 ppm were similar to those during the control sessions. The responses at 500 and 1,000 ppm were lower than, but not significantly different from the control responses. Cognitive func-

tion was impaired at 2,000 ppm or higher, as indicated by an increase in response time and a decrease in accuracy of matching. Response time at 4,500 ppm increased by 0.26 sec over the control response time, and monkeys failed to respond during the second half of the session. Most monkeys remained awake at 4,500 ppm, but failed to respond. The effect was characterized as an attention deficit with no specific memory effect. Expired carbon dioxide, measured during the exposures, displayed an inverted U-shaped concentration-effect curve.

3.3.2. Rats

Many of the nonlethal studies in rats evaluated the acute CNS effects of toluene exposure (Table 6-5). Most of these studies demonstrated the biphasic nature of reaction to toluene: an initial stimulatory effect followed by CNS depression. The effects of 0.5-, 1-, 2-, and 4-h exposures at 150 ppm in male Sprague-Dawley rats were evaluated using a multiple fixed ratio-fixed interval (FR-FI) schedule of reinforcement (Geller et al. 1979). Both schedules of reinforcement were increased during the shorter exposures (0.5 and 1 h), showing a stimulatory effect, and decreased during the longer exposures (2 and 4 h) compared with controls. Values for individual rats were presented graphically; aside from the general pattern of an increase followed by a decrease in rate of responding over time, there were considerable individual differences among toluene-exposed rats. Furthermore, the pattern of the control session over time was not provided.

The acute effects of toluene inhalation on the detection of auditory signals (sensitivity index and response index) were evaluated by Bushnell et al. (1994). Male Long-Evans rats were exposed to toluene at 0, 1,000, 1,500, or 2,000 ppm for 1 h. Toluene eliminated the normal increase in sensitivity index that occurred over a session. The responsitivity index was decreased by toluene at the beginning of each session but returned to control levels during exposure at 1,000 or 1,500 ppm, and within 40 min of exposure at 2,000 ppm was increased above control levels. Increases in latency were concentration- and time-dependent.

Groups of four adult male Long-Evans rats weighing 350 g were exposed to toluene at 0, 1,200, 1,600, 2,000, or 2,400 ppm for up to 70 min (Bushnell et al. 2007a), and responses were measured at five 12-min intervals from 22-70 min (22, 34, 46, 58 and 70 min). Each rat inhaled one concentration/day and each rat was exposed at each concentration over the course of 5 days; concentrations were administered in counter-balanced order. Rats were previously trained in a signal-detection task consisting of a food reward in response to a visual signal. There was a concentration-related change in a signal-detection task, with accuracy (attention to the signal) decreased and response time increased, but the number of false hits was not affected. Mean response times in the control group (exposure to air) and the group exposed to toluene at 2,400 ppm were approximately 0.4 sec and 1.9 sec, respectively. A doubling in the response time (from

TABLE 6-5 Neurbehavioral Effects of Acute Inhalation Exposure to Toluene in Rats

Concentration (ppm)	Duration	Effects	Reference
150	0.5, 1 h	Stimulatory effect, multiple schedule performance.	Geller et al. 1979
	2, 4 h	Reduced performance.	
0, 1,200, 1,600, 2,000, 2,400	22, 34, 46, 58, 70 min	Signal detection task: concentration- and duration-related reduction in attention and increase in response time; no effect on false hits; NOAEL for doubling of reaction time was 1,600 ppm for 34 min and 2,000 ppm for 46 min.	Bushnell et al. 2007a
178, 300, 560	2 h	Increased activity (for reward).	Wood and Cox 1995
1,000, 1,780	2 h	Increased activity, then return to control rate.	
3,000	2 h	Increased activity, then decrease below control rate.	
810	4 h	Threshold, decreased unconditioned reflex.	Mullin and Krivanek 1982
1,660	4 h	Increased number of failures.	
3,100	2 h	Decreased conditioned avoidance response.	
6,500	1 h	Rats failed numerous test; prostrate after 2 h.	
1,340	1-4 h	EC_{50}: most sensitive unconditioned reflex (calculated).	
125, 250, 500	4 h	Decreased conditioned avoidance responses.	Kishi et al. 1988
1,000, 2,000	4, 2 h	Increased incorrect responses and reaction time.	
4,000	4 h	Excitation, increased response rate, ataxia.	
1,000, 1,500, 2,000	1 h	Initial decrease in detection of auditory signals at all concentrations followed by return to control levels.	Bushnell et al. 1994
1,000	4 h	Little effect on avoidance responses.	Shigeta et al. 1978
3,000	4 h	Changes in response pattern.	

(Continued)

TABLE 6-5 Continued

Concentration (ppm)	Duration	Effects	Reference
1,000, 1,780, 3,000	2 h	1,780 and 3,000 ppm: concentration-dependent increase in response rates to food reward despite electric shock punishment.	Wood et al. 1984
3,000	4 h	Ataxia.	
1,000	4 h	No change in behavior (number of rearings).	Takeuchi and Hisanaga 1977
2,000	4 h	Increased rearings and seizures.	
4,000	4 h	Excitation followed by narcosis.	
2,000	4 h	Increased number of lever presses to avoid shock; no change in avoidance behavior.	Harabuchi et al. 1993
4,000	4 h	Increased number of lever presses to avoid shock; decrease in avoidance response.	
1,700	4 h	No decrease in activity following exposure.	Miyagawa et al. 1986
3,400	4 h	Activity decreased by 31% followed by recovery.	
5,100	4 h	Inactivity followed by partial recovery.	
2,000	4 h	Increased locomotor activity.	Wada et al. 1989
4,000	4 h	Decreased conditioned avoidance responses.	
6,000, 8,000	4 h	Decreased conditioned avoidance responses, ataxia, narcosis.	
1,333, 2,667 or 8,000 (five 15-30 min peaks)	7.5 h	Effects on visual discrimination; increased motor activity; return to baseline on following day.	van Asperen et al. 2003
2,500	1 h	No effect on motor activity during exposure.	Hinman 1987
5,000	1 h	Increased locomotor activity.	
10,000	1 h	Increased activity followed by slight decrease.	
15,000	1 h	Increased activity followed by cessation of activity.	

0.4 sec to 0.8 sec) compared with controls was evident at exposures of 2,000 and 2,400 ppm for 34 min and at 1,600 ppm for 46 min. The NOAEL for this effect was noted at 1,600 ppm for 34 min and at 2,000 ppm for 46 min. A doubling in reaction time was identified by Dr. Bushnell as a relatively unambiguous demarcation of a clear effect on CNS function and comparable to the effect level observed in ethanol intoxication (P.J. Bushnell, personal communication, 2013; Appendix D). A physiologically-based toxicokinetic (PBPK) model quantitatively predicted behavioral effects based on concentrations in the brain (Bushnell et al. 2007a), but not predictions based on the area under the curve (AUC) of exposure or on the AUC of brain toluene concentration. Rats developed a tolerance to toluene after repeated exposure at high concentrations during performance testing (Oshiro et al. 2007), and performance was also affected by motivation as reward or punishment (Bushnell et al. 2009).

Wood and Cox (1995) exposed 12 male Long-Evans rats to toluene at 178, 300, 560, 1,000, 1,780, or 3,000 ppm for 2 h and performed behavioral evaluations of nose-poking on a probabilistic schedule of food delivery. Animals served as their own controls, and exposures were repeated. Exposure sessions were 3-4 days apart. The general pattern of responses over the 2-h session for all exposures including the control was an initial high response rate during the first 20 min of the exposure followed by a tapering-off effect; the number of responses also generally increased with increasing concentration. This pattern of concentration-dependent increased numbers of responses over the control value was observed except at the higher doses. During the 3,000-ppm session, the initial high rates of responding fell below the control rates after 50 min of exposure. During the session at 1,780 ppm, the rates returned to control values by the end of the exposure. Between 178 and 560 ppm, responses over the number of control responses increased in both concentration-dependent and time-dependent manners. The authors described these results as biphasic concentration-effect, time-effect, and concentration-response functions at the higher concentrations. A weighted regression analysis determined that a response increase of 10% in all animals would be achieved at a concentration of 182 ppm, with a lower 95% confidence limit of 157 ppm. In an earlier study with a similar protocol (Wood et al. 1984), rats trained to press a lever for a food reward increased their rate of response following 2-h exposures to toluene at 1,780 and 3,000 ppm in spite of electric shock punishment.

Mullin and Krivanek (1982) tested unconditioned reflexes and conditioned reflex tasks in groups of six 5-week-old male Charles River CD rats exposed to toluene at 0, 800, 1,600, 3,200, or 6,400 ppm for 4 h. Measured concentrations were 810, 1,660, 3,100, and 6,250 ppm. Unconditioned reflex tests consisted of locomotor activity, coordination, corneal reflex, and righting reflex. The conditioned reflex involved shock avoidance. A few rats began to fail unconditioned reflex tests at 800 ppm (one of 16 tests); the 1-, 2-, and 4-h EC_{50} for the most sensitive test were all 1,340 ppm. Rats showed excitement during the first half-hour of exposure at 3,100 ppm, decrements in conditioned avoidance were observed after exposure for 1 h, and rats began to show prostration by 2 h. At

6,250 ppm, rats failed numerous tests at 1 h and were prostrate at 2 h, at which time the test was terminated. There were no mortalities.

A group of eight male Wistar rats were exposed to toluene at 0, 125, 250, 500, 1,000, 2,000, and 4,000 ppm for 4 h on separate days (Kishi et al. 1988). Exposures were in ascending order of concentration. Chamber concentrations were measured with a gas chromatograph. This experiment incorporated shock-avoidance behavioral observations during toluene exposure. Rats were exposed to toluene or air for 4 h a day, and the interval between exposures was 10-20 days to avoid lingering effects. Rats were tested continuously for 2 h after each exposure. When rats were exposed at 125, 250, or 500 ppm, a decline in conditioned avoidance responses 20 min into the exposure were found compared with baseline. However, results were variable, and there was no concentration-response relationship. Rats almost completely recovered during the postexposure period. After exposure at 1,000 ppm for 4 h or 2,000 ppm for 2 h, there were concentration-related increases in lever presses and incorrect responses (implying excitation), acceleration of the reaction time, and decreases in the effective avoidance response rate. At the beginning of the 4,000 ppm exposure, the response rate increased and then gradually decreased until slight ataxia was observed in six of eight rats.

A similar study by Wada et al. (1989) also used shock-avoidance training as a measure of CNS impairment when male Wistar rats (in groups of eight) were exposed to measured concentrations of toluene at 2,000, 4,000, 6,000, or 8,000 ppm for 4 h. Shock avoidance, motor activity, and latency of response were measured immediately after the exposure and at 3 and 6 h and 1, 2, and 3 days postexposure. As in the previous experiment, shock-avoidance responses were decreased in pretrained rats at 4,000 ppm and higher, but recovery was achieved within 3-6 h postexposure. Also, at 2,000 and at 4,000 ppm, locomotor activity was transiently increased. Paradoxically, at 4,000 ppm, response latencies were increased. The authors also reported a failure in rats exposed at 6,000 or 8,000 ppm to avoid electrical shock, and the percentage of escape responses was decreased as well. Locomotor activity was dramatically decreased at those concentrations; therefore, ataxia and narcosis could have contributed to impaired avoidance performance.

Takeuchi and Hisanaga (1977) exposed groups of male Wistar rats to toluene at 1,000, 2,000, or 4,000 ppm for 4 h. They observed general activity and measured EEG activity. No change in general activity was found at 1,000 ppm, as evidenced by the number of rearings, and there were few changes in the EEG results. At 2,000 ppm, there were increased rearings and occasional myoclonic seizures; these changes were accompanied by increases of high-frequency EEG activity and a disturbance of the sleep pattern. At 4000 ppm there was increased activity followed by narcosis. These rats also experienced myoclonic seizures. All sleep pattern activity was disturbed. Shigeta et al. (1978) also found that a 4-h exposure at 1,000 ppm had little effect on avoidance responses (to an electrical shock) of adult male Wistar rats. At 3,000 ppm, the responses increased, but the inter-response pattern shortened, with the result that there was no significant

difference in shock counts. Behavior recovered in an hour. Harabuchi et al. (1993) also found little difference in shock avoidance in male Wistar rats exposed to toluene at 2,000 ppm for 4 h. At 4,000 ppm, lever presses in response to a warning sound were increased, but shock avoidance responses were significantly decreased soon after exposure began.

A biphasic recovery curve for a variable interval response schedule (lever press for food reward) was observed by Miyagawa et al. (1986). Young male Sprague-Dawley rats were exposed in groups of four to toluene at 1,700, 3,400, or 5,100 ppm for 4 h. The response rate was then assessed at recovery intervals of 0-30, 30-60, 60-90, and 90-120 min. The same rats were used at each concentration for the four response times (four different days). At 1,700 ppm, the behavioral response rate was increased by about 40% compared with baseline levels, and duration of recovery period did not influence activity. A decrease in responses compared with baseline was observed in the 3,400-ppm group immediately after exposure, but the response rate increased to greater than baseline during the next 30-120 min. Immediately after exposure at 5,100 ppm, an almost total decrease in responses was observed, followed by a linear increase with respect to duration of recovery period. The authors also noted that at low brain toluene concentrations an increase in response rate occurs, which is reversed at higher concentrations so that an inverted U-shaped curve is obtained for the relationship between lever-pressing behavior and toluene concentration in the brain.

A biphasic concentration-effect relationship was observed in male Long-Evans rats exposed to increasing concentrations of toluene by Hinman (1987). Six rats were used with some rats being exposed at several concentrations. Spontaneous locomotor activity was monitored continuously during inhalation of toluene at 0, 2,500, 5,000, 10,000, or 15,000 ppm for 60 min. Sham exposures resulted in a period of activity for approximately 30 min followed by period of low activity (habituation). Before each toluene exposure, the rats were allowed a 30-min habituation period during which they adjusted to their surroundings. The pattern of activity during the exposure at 2,500 ppm was the same as that of the control exposure (no increased activity during the exposure). At 5,000 ppm, locomotor activity increased monophasically during exposure and subsequently decreased in the same manner during recovery. At higher concentrations (10,000 and 15,000 ppm), locomotor activity initially increased, but decreased with continued exposure and eventually ceased. The highest concentrations of toluene produced a biphasic recovery, with time to maximum activity and time to recovery dependent on the concentration of toluene during exposure. No rats died during the exposures.

Lammers et al. (2005b) and van Asperen et al. (2002) exposed groups of eight male WAG/RijCrlBR rats to toluene at constant concentrations of 1,333 or 2,667 ppm for 7.5 h or to five peaks of 8,000 ppm for 15 or 30 min, alternating with toluene-free intervals, so that total exposures were to averages of 1,333 or 2,667 ppm, respectively. Visual discrimination was tested prior to, immediately after, and 24 h postexposure. Spontaneous motor activity was monitored continuously from preexposure to postexposure. All exposure scenarios resulted in

changes in visual discrimination performance, defined as a slowing of response speed and disinhibition of responding (results presented graphically). Short-term fluctuating exposure scenarios resulted in greater effects on behavior than exposures at a constant concentration. But effects were time- and exposure-scenario-related. Visual discrimination and activity returned to preexposure levels by 24 h postexposure.

3.3.3. Mice

Several studies in mice have focused on the neurobehavioral effects of acute toluene exposure (Table 6-6). Bushnell et al. (1985) exposed groups of eight male C57BL/6 mice to toluene at 0, 100, 1,000, 3,000, or 10,000 ppm for 72 min on successive days to measure effects on motor activity and carbon-dioxide production. The same group was used for all exposures (the first exposure was at 10,000 ppm). For the 10,000-ppm exposure, mice were placed into the chamber before the vapor was generated for safety reasons. The concentration climbed exponentially from 0 to 10,500 ppm over the course of the exposure ($t_{1/2}$ = 15 min). Activity was measured by interruptions of a photobeam in a computerized system. Activity was similar during exposure to air and to toluene at 100 ppm (activity followed by a gradual decline). At 1,000 ppm, motor activity began to increase above that of the control after 60 min. At 3,000 ppm, the increased activity began 12 min after the start of the experiment and continued throughout the exposure. At 10,000 ppm, activity was similar to that of the control group during the first 24 min, after which it declined precipitously, reaching 0 by 48 min. In the latter experiment, toluene was allowed to decline in the chamber over a period of 72 min. Carbon-dioxide production was initially suppressed at 1,000 ppm and higher. At vapor concentration below 6,000 ppm, animals recovered and became hyperactive 24 min post-exposure. In a second experiment, exposure of a separate group of mice to toluene at 3,000 ppm for 5 h/day for 5 days had no effect on activity when measured 30-90 min after exposure. In a third experiment, groups of eight mice were exposed to toluene at 0, 100, 1,000, or 3,000 ppm for 5 h/day, 5 days/week for 12 weeks. These exposures affected minute volume of expired carbon dioxide, but did not decrease postexposure locomotor activity or have an effect on body weight.

Using the inverted screen test to measure motor performance, Moser and Balster (1985) exposed groups of 12 CD-1 mice to several undefined concentrations of toluene for periods of 10, 30, or 60 min. Within 60 sec after exposure, mice were tested for the ability to hold onto or climb to the top of a screen rotated 180°. Significantly lower EC_{50} values were obtained at each increase in exposure duration; for the 10-, 30-, and 60-min durations, the EC_{50} values were 2,959, 2,012, and 1,445 ppm, respectively. The authors also presented recovery

TABLE 6-6 Neurobehavioral Effects of Acute Inhalation Exposure to Toluene in Mice

Concentration (ppm)	Duration	Effects	Reference
100	72 min	No effect on locomotor activity.	Bushnell et al. 1985
1,000	72 min	Increased activity after 60 min.	
3,000	72 min	Increased, sustained activity after 12 min.	
10,000	72 min	No effect on activity for 24 min followed by narcosis.	
200, 400, 800	30 min	No change in operant behavior.	Moser and Balster 1981
1,600	30 min	Increased responding, decreased reinforcement.	
3,200	30 min	Ataxia.	
6,400	30 min	Narcosis.	
2,959	10 min	EC_{50} for inverted screen test.	Moser and Balster 1985
2,012	30 min	EC_{50} for inverted screen test.	
1,445	60 min	EC_{50} for inverted screen test.	
≥2,000	20 min	Functional observational battery changes: abnormal posture, abnormal gait, decreased arousal, decreased rearing.	Tegeris and Balster 1994
100, 250, 500, 1,000, 2,000	30 min	Concentration-related increase in locomotor activity.	
4,000, 6,000, 8,000	30 min	Biphasic locomotor activity; overall concentration-related decrease in locomotor activity; narcosis at end of 30-min session at 8,000 ppm; slight concentration-related decrease in schedule-controlled behavior at 100-8,000 ppm.	Bowen and Balster 1998
500	4 h	No effect on schedule-controlled behavior.	Glowa 1981
1,000	4 h	Increased rate of responding.	
2,000	4 h	Decreased rate of responding.	
1,657	30 min	EC_{50} for decreased responding for schedule-controlled behavior.	Glowa et al. 1986
722-1193	4 h	31-74% decrease in immobility in “behavioral despair” swimming test.	De Ceaurriz et al. 1983
2,600	1-1.5 h	Ataxia, no loss of consciousness at 3 h.	Bruckner and Peterson 1981a, b
5,200	45 min	Immobility, loss of consciousness at 1.5 h.	
12,000	10 min	Loss of consciousness.	

times with respect to maximum concentrations tested for each duration. There was only a 5-min recovery time for a 10-min exposure at 5,000 ppm. However, for the 30- and 60-min exposures at 3,000 and 2,000 ppm, respectively, there was a 30-min recovery period.

In a study of operant behavior, Moser and Balster (1981) exposed groups of eight CD-1 mice individually to toluene at 200, 400, 800, 1,600, 3,200, or 6,400 ppm for 30 min in a static-exposure chamber. Tests were performed during a 15-min postexposure period. Diet was maintained at 80% free feeding weight, and sweetened milk was used as a reinforcer for lever-press responding. Reinforcement occurred only with a 10-sec pause between responses. Response rates increased in the groups exposed at up to 3,200 ppm; at 6,400 ppm, the response rate decreased below that of the control group. At concentrations above 800 ppm, the rate of reinforcement decreased in a concentration-dependent manner. When removed from the exposure cage, mice exposed at 1,600 ppm were excitable and mice exposed at 3,200 ppm had marked ataxia. Animals exposed at 6,400 ppm were almost anesthetized. As part of the same report, mice were exposed to toluene at 6,000 ppm for 30 min/day, 5 days/week for 7 weeks; operant testing was carried out with the acute exposures. All mice survived the repeated exposures and appeared in good health. Response rate was variable, and the reinforcement rate remained low. Operant behavior returned to baseline 3 days after exposure ended.

Tegeris and Balster (1994) exposed groups of eight male Swiss mice to toluene at 0, 2,000, 4,000, or 8,000 ppm for 20 min. During the last 2 min of the exposure, the mice were observed for neurologic deficits. A functional observational battery (FOB) was administered following exposures. Effects occurred both during and after exposures and were concentration-related. Motor incoordination (abnormal gait), decreased muscle tone, and equilibrium changes, as well as decreased rearing occurred at 2,000 ppm and higher. Loss of the righting reflex occurred at 4,000 ppm. By the end of the exposure at 8,000 ppm, all mice were essentially anesthetized. However, recovery was rapid when the rats were removed from exposure. Lacrimation was observed only after exposure at 8,000 ppm. The profile of neurobehavioral effects was similar to that induced by phenobarbital (intraperitoneal injections of 0-40 mg/kg).

In another study, Bowen and Balster (1998) tested locomotor activity and schedule-controlled behavior in adult male CFW mice exposed to toluene at 100, 250, 500, 100, and 2,000 ppm. During 30-min exposures, locomotor activity increased with increasing concentrations; the increases were significant different from controls at concentrations of 500 ppm and higher. Total locomotor activity decreased with increasing concentrations of 4,000, 6,000, and 8,000 ppm. Activity became biphasic, increasing and then decreasing at both 6,000 and 8,000 ppm. By the end of the 8,000-ppm exposure session, the mice were essentially immobile and appeared anesthetized. The effect of these concentrations on schedule-controlled behavior (pressing a lever for a liquid reward) was also studied. According to the authors, the expected increases in rates of behav-

ior were not observed. Instead, there was a concentration-related decrease in responding, which was most obvious at 4,000 ppm and higher.

The behavioral effects of toluene exposure in CD-1 mice were also evaluated by Glowa et al. (1986). A fixed-interval (FI) 60-sec schedule of milk delivery after a response (breaking a beam of light), with an alternating series of eight consecutive rewards followed by an inter-series time out of 30 min, was developed as a means of behavioral assessment. Nominal concentrations of toluene at 250 to 4,000 ppm were added to the sealed exposure chambers. Concentration-effect curves were constructed by exposing mice to incremental additions of toluene at 30-min intervals. The rate of responding in mice exposed to toluene at 700 ppm was increased, and higher concentrations progressively reduced responding. The calculated EC_{50} for a reduced rate of responses was 1,657 ppm.

In a similar study by Glowa (1981), the effects of 4-h exposures to toluene for 5 consecutive days produced similar results. The FI 60-sec milk presentation was again used, with 10-min sessions of milk availability followed by 25-min periods were responding had no consequences. The effects of toluene on schedule-controlled behavior were concentration-dependent: 500 ppm had little effect on the rate of responding, 1,000 ppm consistently increased rates of responding, and 2,000 ppm consistently decreased rates of responding.

Four different toluene exposure concentrations of 722, 785, 977, or 1,193 ppm were evaluated in a "behavioral despair" swimming test with male Swiss OF1 mice (De Ceaurriz et al. 1983). Rodents forced to swim in a restricted space became immobile after approximately 3 min. After 4-h exposures, all four toluene concentrations significantly decreased the mean duration of immobility (increased activity during a 3-min test period). A concentration-effect relationship was observed at the lowest concentration of toluene producing a 31% decrease in immobility and successively increasing concentrations producing 36, 54, and 74% decreases for exposures at 722, 785, 977, or 1,193 ppm, respectively. The concentration associated with a 50% decrease in immobility was 915 ppm.

Bruckner and Peterson (1981a) exposed groups of four male ICR mice to toluene at concentrations of 2,600, 5,200, or 12,000 ppm for up to 3 h to evaluate the narcotic potency, speed of onset, and duration of CNS-depressant effects of inhaled toluene. Five reflex tests (balance, visual placing, grip strength, tail pinch, and righting reflex) were used to evaluate the onset of loss of reflexes/narcosis during the exposures. Tests were performed at 5- to 15-min intervals. Seven-week-old mice exposed to toluene at 12,000 ppm became depressed very rapidly and were unconscious within 15 min. Mice exposed to toluene at 5,200 ppm became immobile within 45 min and unconscious after approximately 1.5 h. At 2,600 ppm, mice became ataxic in 1-1.5 h and, within 2 h, were immobile in the absence of stimulation, although consciousness was not lost within the 3-h test period. Four-week-old mice tested separately were slightly more sensitive to toluene-induced narcosis than were 8- and 12-week old mice. Rats, tested at the same concentrations, were slightly less sensitive than mice. Specific data were not provided for rats.

Bruckner and Peterson (1981a) also reported on recovery times of mice following 5-, 10-, or 20-min exposures to toluene at concentrations of 4,000, 8,000, or 12,000 ppm. Seven-week old mice were tested in groups of five. Minimal decrements in reflexes were observed at 4,000 ppm for up to 20 min. Recovery to preexposure performance and reflexes took 10 min or less. Depression was greater and recovery took longer with increasing concentrations and increasing exposure durations. For example, animals became immobile and lost consciousness during the 10- and 20-min exposures at 12,000 ppm, but full recovery took place after breathing fresh air for 12 and 37 min, respectively.

In exposures designed to approximate human solvent abuse episodes, mice and rats were subjected to seven consecutive inhalation cycles consisting of 10-min exposures to toluene at 12,000 ppm followed by a 20-min solvent-free recovery period (Bruckner and Peterson 1981b). Signs of ataxia characteristic of inebriation in humans were observed after 2-3 min and unconsciousness was observed in about 10 min. Although mice were depressed to a greater degree than rats, the mice exhibited marked recovery during each fresh air interval. Recoveries in rats progressively declined over the 190-min regimen. No deaths were reported.

3.3.4. Rabbits

Kobayashi (1985) described effects of toluene in rats exposed at 4,000 ppm either in air or mixed with oxygen. For both mixtures, the observed responses included Cheyne-Stokes respiration (within 2-3 min), arrhythmia, increased blood pressure, and slow wave hypersynchronies in cortical and subcortical EEGs which progressed to pH decreases and arousal reaction disappearance in the sensorimotor cortex and hippocampus. Most of these effects occurred within 15-20 min. Finally, grand mal seizures were followed by postictal depression. The respiratory acidosis shifted gradually to metabolic acidosis with continued exposure.

3.4. Developmental and Reproductive Toxicity

In a review of reproductive and developmental toxicity in animal models, reduction of late fetal body weight and retardation of skeletal development were the most consistent fetotoxic effects (Donald et al. 1991). Although intrauterine growth was retarded, there is little evidence that exposure to toluene causes teratogenic effects. Selected studies identified in the literature are summarized in Table 6-7.

Although continuous exposures and 12-h exposures to toluene at low concentrations appeared to be maternally toxic in rat and mice (Hudak and Ungvary 1978; Tatrai et al. 1980; Ungvary and Tatrai 1985), the lowest concentration that retarded fetal growth in the rat was 1,200 ppm when administered under developmental and reproductive guidelines suggested by EPA (6 h/day during organogenesis) (Thiel and Chahoud 1997).

TABLE 6-7 Reproductive and Developmental Toxicity of Toluene in Animals

Concentration (ppm)	Duration	Effects	Reference
Rat			
266	GD 1-21 (8 h/d)	Slightly reduced fetal body weights.	Hudak and Ungvary 1978
399	GD 1-8 (24 h/d)	Reduced fetal body weight; maternal deaths.	
399	GD 9-14 (24 h/d)	No effect on fetuses; maternal deaths.	
100, 400	GD 6-15 (6 h/d)	No effect at either concentration.	LBI 1978
266	GD 7-14 (24 h/d)	Delayed skeletal development.	Tatrai et al. 1980
100, 500, 2,000	80 d before mating and through lactation	Reduced fetal body weight (by 8%) at 2,000 ppm; no evidence of maternal toxicity.	API 1985
750, 1,500, 3,000	GD 6-15 (6 h/d)	No fetal effects at 750 ppm; minimal reduction in mean litter and fetal weights and unossified sternebrae at 1,500 and 3,000 ppm; maternal clinical signs at all concentrations.	API 1993
300, 600, 1,000, 1,200	GD 9-21 (6 h/d)	Reduced fetal and dam body weights at 1,200 ppm; higher mortality up to weaning at 1,200 ppm; no neurobehavioral or reproductive deficits in F_1 generation.	Thiel and Chahoud 1997
1,200, 1,800	GD 7-19	No effects on reproductive parameters.	Dalgaard et al. 2001
1,800	GD 7-20 (6 h/d)	Increased neuronal apoptosis in brain of male offspring at PND 21.	
1,500	GD 7-20 (6 h/d)	Reduced fetal birth weight and lower maternal weight gain.	Hougaard et al. 2003
600, 2,000	GD 7-17 (6 h/d)	No effect at 600 ppm. At 2,000 ppm: fetal and dam body weight decreases; no anomalies or neurobehavioral effects on offspring but fetal mortality and growth retardation.	Ono et al. 1995
600, 2,000	6 h/d; females: 14 d pre-gestation to GD 7; males: 90 d (60 d prior to mating)	Fertility and mating performance unaffected at both concentrations. Males: no clinical signs at 2,000 ppm. Females: salivation, lacrimation, and decreases in body weight and food consumption; increased fetal mortality at 2,000 ppm.	Ono et al. 1996

(Continued)

TABLE 6-7 Continued

Concentration (ppm)	Duration	Effects	Reference
Mouse			
133, 399	GD 6-13 (24 h/d)	Significantly reduced fetal weight at 133 ppm; all dams died at 399 ppm.	Hudak and Ungvary 1978
133, 266, 399	GD 6-15 (12 h/d)	Significantly reduced fetal weight at 266 ppm; all dams died at 399 ppm.	Ungvary and Tatrai 1985
200, 400	GD 7-16 (7 h/d)	Increased incidence of dilated renal pelves at 200 ppm but not at 400 ppm; increase in fetuses with 13 ribs (normal number for mice).	Courtney et al. 1986
100, 1,000	GD 1-17 (6 h/d)	Significant increase in incidence of fetuses with extra (14) ribs at 1,000 ppm.	Shigeta et al. 1981
Rabbit			
30, 100, 300, 500	GD 6-18 (6 h/d)	No effects on dams or fetuses at any concentration.	Klimisch et al. 1992

Abbreviations: GD, gestation day; PND, postnatal day.

Male F344/N rats and B6C3F$_1$ mice evaluated in the toluene inhalation studies of NTP (1990) exhibited no compound-related effects on sperm count or motility when exposed at concentrations of 3,000 ppm or less for 14 weeks or at 1,200 ppm or less for 2 years. No histopathologic lesions were observed in the epididymis, prostate, or testes either species.

Male SD rats exposed to toluene at 600 ppm for 6 h/day for 90 days exhibited a decrease in sperm count of 13%; when exposed at 2,000 ppm under the same protocol, the sperm count decreased significantly by 26% and the weight of the epididymis declined by 15% (Ono et al. 1996); these changes had no effect on mating performance or fertility as characterized by fertility and copulation indices.

3.5. Genotoxicity

Toluene has been extensively studied for genetic toxicity both in vitro and in vivo. There is an overwhelming body of evidence that indicates that toluene is not genotoxicy. Very few positive studies exist, and the few that are positive have confounding factors which limit their reliability and relevance (NTP 1990). These confounding factors include the purity of the toluene in the case of in vitro studies and the presence of other chemicals and smoking habits in studies of workers. The metabolites of toluene, such as benzyl alcohol, are also nongenotoxic (NTP 1990). While the majority of toluene metabolites are nongenotoxic, the minor metabolite, o-cresol, has shown genotoxicity in some in vitro tests with Chinese hamster ovary cells (ATSDR 2008). Selected studies reviewed in CIR (1987), NTP (1990), IARC (1999), and ATSDR (2000) are discussed below.

Toluene was assayed for mutagenicity using the Ames Salmonella/microsome assay by Bos et al. (1981). In this study, toluene was unable to revert *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 either with or without metabolic activation by S9 mix derived from livers of rats either untreated or induced with Aroclor 1254. Several other studies in *S. typhimurium* were also negative for gene mutation and growth inhibition due to DNA damage (Mortelmans and Riccio 1980; Anderson and Styles 1978; LBI 1978; Florin et al. 1980; Nestmann et al. 1980; Snow et al. 1981; Spanggord et al. 1982; Haworth et al. 1983). Studies in *Bacillus subtilis* (McCarroll et al. 1981a), *Escherichia coli* (Fluck et al. 1976; McCarroll et al. 1981b; Mortelmans and Riccio 1980), and *Saccharomyces cerevisiae* (LBI 1978; Mortelmans and Riccio 1980) were also negative for genotoxic effects.

In vitro studies using mouse lymphoma L5178Y cells (LBI 1978; McGregor et al. 1988) or Chinese hamster ovary cells (Evans and Mitchell 1980) were also negative.

Mammalian in vivo studies in rats have produced some positive, yet questionable, results. In one inhalation study, rats that were exposed to toluene at 80 ppm for 4 h/day for 4 months (Dobrokhotov and Enikeev 1975) had an increased incidence of chromosomal aberrations. Three oral studies in rats (Dobrokhotov 1972; Lyapkalo 1973; and Sina et al. 1983) also observed chromoso-

mal aberrations or DNA single-strand breaks. However, three of these studies used toluene preparations of unspecified purity and could have been contaminated with benzene (a known clastogen). The results observed in the study by Sina et al. (1983) were probably due to cell lysis, because the single-strand breaks were only observed when cytotoxicity was greater than 30% (NTP 1990).

In vivo studies in the mouse have produced negative results. Several studies in the mouse were negative for genotoxic effects when several different parameters were evaluated. These included micronucleus induction (Kirkhart 1980; Gad-El-Karim et al. 1984), sperm-head abnormalities (Topham 1980), dominant-lethal mutations (LBI 1981), sister-chromatid exchange (Tice et al. 1982), and chromosomal aberrations (Gad-El-Karim et al. 1984).

3.6. Subchronic and Chronic Toxicity and Carcinogenicity

Jenkins et al. (1970) exposed Sprague-Dawley rats to repeated or continuous concentrations of toluene to study long-term effects on mortality, body weight, and hematology parameters. A group of 15 male and female rats was exposed to toluene at 1,085 ppm for 8 h/day, 5 days/week for 6 weeks, and a group of 13 male and female rats exposed continuously at 107 ppm for 90 days. A control group was composed of 14 rats. No rats died in the repeated-exposure study. Two rats continuously exposed to toluene died, one on day 28 and the second on day 56. Rats in both treatment groups gained more weight than the control group; however, rats in the treatment groups were heavier than the controls at the start of the study. There were no apparent effects on hemoglobin, hematocrit, or leucocyte count. No further details were reported.

Poon et al. (1994) exposed groups of 10 male and 10 female Sprague-Dawley rats to toluene at 30 or 300 ppm for 6 h/day, 5 days/week for 4 weeks. The higher concentration caused mild biochemical changes (increased serum alkaline phosphatase activity in males), an occasional moderate reduction in follicle size of thyroid gland cells, and subepithelial nonsuppurative inflammation of the nasal passages.

There is no evidence to indicate toluene produces increased incidences of tumors in rats or mice. Gibson and Hardisty (1983) conducted a chronic toxicity and carcinogenicity inhalation study in male and female F344 rats. Groups of 120 animals were exposed to toluene at 0, 30, 100, or 300 ppm for 6 h/day for 5 days/week for up to 2 years. Subgroups of animals were killed after 6, 12, and 18 months for interim evaluations. There were no treatment-related effects on hematology or clinical-chemistry parameters and no tissue or organ lesions attributable to treatment. No increases in the incidences of neoplasms in treated rats compared with controls were found. Because IARC (1989) judged that the test concentrations may have been low, NTP (1990) conducted a second series of oncogenic bioassays in rats and mice. In those studies, groups of 60 male and 60 female F344/N rats and 60 male and 60 female $B6C3F_1$ mice were exposed to toluene at 120, 600, or 1,200 ppm for up to 2 years (6.5 h/day, 5 days/week).

The results revealed no evidence of carcinogenicity in treated animals compared with concurrent controls. Mild degeneration of the nasal cavity olfactory and respiratory epithelium was observed at 600 and 1,200 ppm. Because these effects on the respiratory system were not observed at a higher concentration (3,000 ppm) in a 15-week study, also conducted by NTP (1990), they can be attributed to the repeated nature of the chronic exposure regime. The NOAELs for carcinogenicity and survival were both 1,200 ppm in rats and mice. In addition, no clinical signs were observed in rats or mice. In 1999, IARC concluded that there is evidence suggesting a lack of carcinogenicity in experimental animals treated with toluene.

3.7. Summary

Lethality data on toluene were available for only the rat and mouse. Based on LC_{50} values, the mouse is slightly more sensitive to toluene than the rat. Mouse LC_{50} values ranged from 38,465 ppm for 10 min to 5,320 ppm for 7 h. The highest nonlethal concentrations were 12,000 ppm for 20 min (Bruckner and Peterson 1981a), 5,000 and 6,250 ppm for 2 h (Kojima and Kobayashi 1973; Mullin and Krivanek 1982), and 6,000 ppm for 4 h (Wada et al. 1989).

Toluene, like all CNS depressants and anesthetics, produces an initial excitatory stage followed by narcosis. Except for increased activity, concentrations below 1,000 ppm have little or no effect on gross manifestations of animal behavior (NRC 1981; WHO 1987). At approximately 2,000 ppm, increased motor activity and an increased rate of responding in neurobehavioral tests occur. Higher concentrations suppress activity. In neurotoxicity tests, increased motor activity and response rates (excitation) at low concentrations and decreased activity and responses at higher concentrations are the result of CNS depression (Moser and Balster 1981, 1985; Wood et al. 1983). Increases in activity with no or minor decrements in accuracy on tasks occurred in rats and mice exposed to toluene at 1,000-2,000 ppm (Mullin and Krivanek 1982; Kishi et al. 1988; Wood and Cox 1995). Mice exposed at approximately 2,000 ppm for short periods of time began to fail equilibrium tests in some studies (Moser and Balster 1985; Tegeris and Balster 1994), but had increased activity in others (Kishi et al. 1988; Wada et al. 1989). Mice exposed at 5,200 ppm became immobile after 45 min and lost consciousness after 1.5 h (Bruckner and Peterson 1981a). The neurologic deficits are similar to those observed in humans. Unfortunately, the onset of neurobehavioral deficits is not readily observable in rodents, so extrapolation to humans is difficult. Furthermore, the increased activity of rodents at low concentrations is not clearly observable in humans.

A number of developmental studies have reported fetotoxicity, including reduced fetal weight and retarded skeletal development, but no evidence of teratogenicity. Continuous exposures and 12-h exposures to relatively low concentrations of toluene appeared to be more toxic to pregnant rat and mice (Hudak and Ungvary 1978; Tatrai et al. 1980; Ungvary and Tatrai 1985) than 6- to 8-h

exposures at higher concentrations. The lowest concentration that retarded fetal growth of the rat was 1,200 ppm when administered under developmental and reproductive guidelines suggested by EPA (6 h/day during organogenesis) (Thiel and Chahoud 1997). These rodent studies duplicate the developmental delays associated with gross toluene exposures in humans.

Studies of acute exposures to toluene at high concentrations and of repeated and chronic exposures show that toluene is relatively nontoxic. Toluene at concentrations that produced unconsciousness failed to produce residual organ damage (Svirbely et al. 1943; Bruckner and Peterson 1981b; NTP 1990). Repeated and chronic exposures at moderately high concentrations (e.g., 1,200 ppm) also failed to produce organ damage (Gibson and Hardisty 1983; NTP 1990). Effects appeared to be limited to reversible liver enzyme-activity changes (Bruckner and Peterson 1981b). In concordance with the available human epidemiologic data, evidence of carcinogenicity from inhalation exposure to toluene has not been substantiated in well-conducted rodent studies. IARC (1999) concluded that there is evidence suggesting lack of carcinogenicity of toluene in experimental animals.

4. SPECIAL CONSIDERATIONS

4.1. Uptake, Metabolism, and Disposition

As shown in controlled-exposure studies with humans and animals, toluene is readily absorbed through the respiratory tract. Uptake is proportional to the concentration in the inspired air, length of exposure, and pulmonary ventilation (Astrand et al. 1972; Astrand 1975; Veulemans and Masschelein 1978; Bruckner and Peterson 1981a). Blood:air partition coefficients of 15-21, measured both in vitro at 37°C and in vivo in humans and laboratory animals, indicate that toluene is readily absorbed into the blood (Astrand et al. 1972; Sherwood 1976; Sato and Nakajima 1979a; Gargas et al. 1989; Pierce et al. 1996a). The pulmonary retention percentage of toluene (measured by concentrations in inspired and expired air) was 50% in healthy male subjects exposed at 50 ppm with a workload of 50 W or at 80 ppm under sedentary conditions (Lof et al. 1990, 1993). Because uptake depends on respiratory rate and cardiac output, both of which increase during exercise, uptake increases during exercise compared with that at rest (Astrand et al. 1972; Carlsson and Lindqvist 1977; Veulemans and Masschelein 1978; Carlsson 1982; Nadeau et al. 2006). In humans, dermal absorption, measured during atmospheric exposures, is about 1% of that measured after respiratory absorption (Kezic et al. 2000).

Toluene can be detected in human blood within 10-15 sec of initiation of an exposure, and reaches 60% of maximum arterial concentrations within 10-15 min at concentrations as low as 100-200 ppm (Astrand et al. 1972; Benignus 1981). During a 4-h exposure to toluene at 80 ppm under sedentary conditions, approximately 90% of the 4-h blood value was attained at 2 h; steady-state was reached more rapidly under exercise conditions (Hjelm et al. 1988; Lof et al.

1990, 1993). In a study of mice exposed to toluene at 4,000 ppm, arterial blood concentrations did not reach maximum values until about 2 h after the onset of exposure (Bruckner and Peterson 1981a). After the first 20-30 min of inhalation, the ratio of toluene concentration in the brain and blood is constant (Benignus et al. 1981).

Distribution of toluene to body tissues depends on blood flow to the tissue or organ, lipid content of the tissue, rate of metabolism, and duration of exposure. After absorption, toluene is rapidly distributed to highly vascularized tissues, such as the liver, kidneys, and brain. It rapidly accumulates and affects the brain due to that organ's high lipid content (Bruckner and Warren 2001). It is eventually absorbed and stored in adipose tissue; consequently, obese people tend to accumulate more toluene than do lean people (Carlsson and Lindqvist 1977). Male Sprague-Dawley rats exposed to toluene at 550 ppm for 1 h had the following concentrations of toluene in their tissues immediately after exposure: adipose tissue, 87 µg/g; adrenal glands, 56 µg/g; kidneys, 55 µg/g; liver 21 µg/g; and brain, 15 µg/g (Carlsson and Lindqvist 1977).

Absorbed toluene undergoes rapid, extensive metabolism, primarily in the liver (Low et al. 1988; ATSDR 2000). The major pathway of toluene detoxification and elimination is methyl hydroxylation to form benzoic acid followed by dehydrogenation to benzoic acid and conjugation with glycine to form hippuric acid which is excreted in the urine (Figure 6-1). In humans, oxidation of the methyl group by the hepatic cytochrome isozyme CYP2E1 yields benzyl alcohol (Liira et al. 1991; Nakajima et al. 1997). Benzyl alcohol is rapidly oxidized by alcohol dehydrogenase to benzaldehyde, which in turn is converted to benzoic acid by aldehyde dehydrogenases. About 75-80% of the absorbed dose of toluene is metabolized to benzoic acid, which is also a common food constituent. Following conjugation with glycine, benzoic acid is excreted in the urine as hippuric acid (75-80% of the absorbed dose in humans); smaller amounts of benzoic acid are excreted as the sulfate or glucuronide conjugate. Toluene can also be hydroxylated to form *o*-, *m*-, or *p*-cresol, which are conjugated with sulfate or glucuronide and excreted in the urine. The cresols are minor urinary metabolites (less than 1% of the absorbed dose). The remainder of the absorbed dose, about 18%, is eliminated via the lungs as unchanged toluene. Studies with rat liver microsomes indicate that pathways are the same in humans and rats.

Pierce et al. (1999, 2002) measured exhaled toluene and excreted metabolites in 25 men, ages 20-62, who were exposed to ^{2}H-toluene at 50 ppm and unlabeled toluene at 50 ppm through a gated mouthpiece for 2 h while at rest. Metabolites were evaluated for 4 days, and the disposition was as follows: exhaled toluene, 13 ± 6.2%; hippuric acid, 75 ± 6.4%; *o*-cresol, 0.31 ± 0.22%; *m*-cresol, 0.53 ± 0.44%; and *p*-cresol, 11 ± 3.8%. The exhalation rate of toluene was exponentially triphasic, whereas metabolite excretion rates were biphasic. ^{2}H-toluene was cleared slightly faster than unlabeled toluene, but the difference was small compared with individual differences in toluene kinetics. Body weight, adipose tissue fraction, and blood:air partition coefficient were correlated with

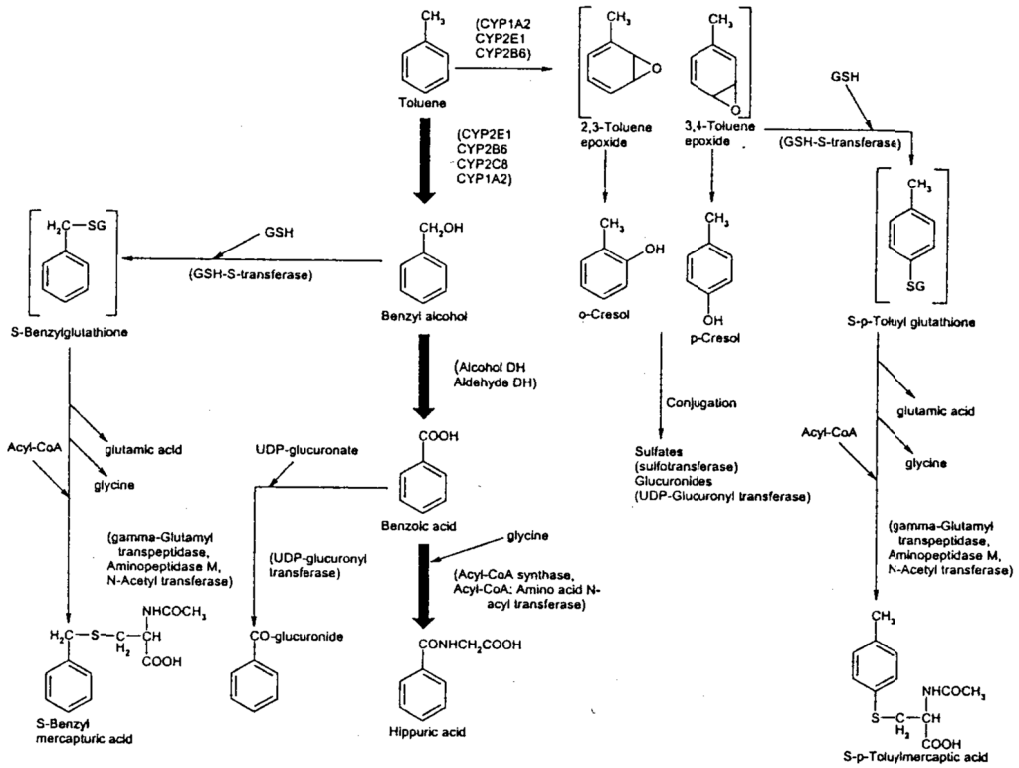


FIGURE 6-1 Metabolism of toluene in mammalian systems (heavy arrows indicate major pathways of metabolism). Source: ATSDR 2000.

terminal half-life, steady-state volume of distribution, and terminal volume of distribution (Pierce et al. 1996a). During the 2-h exposure, a 10-fold interindividual range in venous blood concentrations of toluene was found between the highest and lowest values (ventilation rate differed between these two subjects by a factor of two).

Benoit et al. (1985) reported that following a 90-min exposure of seven human subjects to toluene at 50 ppm, retention at steady-state (measured by elimination in exhaled air) was 83%. In the postexposure period, toluene was eliminated occurred by first order kinetics, with a half-life of 25 min. Lof et al. (1993) found that toluene elimination from the blood of nine human volunteers after exposure at 53 ppm for 2 h was triphasic, with half-lives of 3, 40, and 738 min. The longer half-life is presumed to be representative of the mobilization of toluene from adipose tissue, given the chemical's high lipophilicity. Brugnone (1985) reported half-lives of 1.8 and 29 min in vessel-rich tissue and muscle of humans, respectively, and 36 and 2.7 h in fat and vessel-poor tissues.

Metabolism and excretion of toluene are rapid, as indicated by recovery from behavioral deficits in rodents and rapid elimination from the brain following exposure (Gospe and Calaban 1988). ^{14}C-Labeled toluene decayed in an exponential manner from brain compartments of male Long-Evans rats, with negligible amounts detected at 4 h. At 15 min postexposure, concentrations were half of those at the end of exposure. Nonvolatile metabolites were not detected in the brain, and the CNS-depressant activity was attributed to toluene. Initial activity was highest in the lipid-rich medulla/pons followed by the mid-brain. However, elimination coefficients were not correlated with regional lipid content. The atmospheric concentration during the 10-min exposure was not specified. Radiolabeled toluene, injected into the antecubital vein, was cleared from the brain of baboons with a half-life of 10-20 min (Gerasimov et al. 2002).

Several factors influence rate and pathway of metabolism in humans (Nakajima et al. 1992; ATSDR 2000). The cytochrome P-450 isozymes responsible for toluene metabolism influence the relative production of benzyl alcohol, *o*-cresol, and *p*-cresol. There are two cytochrome P-450 isozymes that play major roles in the metabolism of toluene in rats: CYP2C11 and CYP2E1. The former has a high Km (metabolic rate constant) and becomes increasingly important with increasing exposure concentrations of toluene. The latter has a low Km and is induced by fasting and ethanol. CYP2B1 is induced by toluene concentrations as low as 500 ppm and is important for the formation of the genotoxic *o*-cresol (Wang et al. 1993). The action of these isozymes is influenced by factors, such as age, sex, and pregnancy (Nakajima eta l. 1992). Therefore, extrinsic and intrinsic factors can influence the relative amounts of the various urinary metabolites that are produced after toluene exposure.

Several studies indicated that measurement of hippuric acid in the urine could be used as an indicator of toluene exposure (Ogata et al. 1970; Nomiyama

and Nomiyama 1978; Hasegawa et al. 1983; Ogata 1984). However, measurement of hippuric acid may not be a good indicator of toluene exposure, as metabolism of other substances to hippuric acid may override the levels from toluene alone (NIOSH 1973; Stewart et al. 1975). When volunteers were exposed to deuterium-labeled toluene at 50 ppm and nonlabeled toluene at 50 ppm, there was little variation in labeled hippuric acid excretion among individuals (78% excreted after 20 h) (Lof et al. 1993). However, unlabeled hippuric-acid excretion varied widely among subjects and was about four times greater than what would have been generated by toluene exposure alone. In humans there are large variations in the amounts of toluene metabolites; therefore, monitoring of urinary metabolites can serve only as a qualitative marker for toluene exposure (Andersen et al. 1983; Hasegawa et al. 1983; Baelum et al. 1987).

The concentration of toluene in blood and tissues is proportional to the concentration in alveolar air, which in turn is proportional to the atmospheric concentration. Numerous investigators have reported on the exposure and alveolar concentration of toluene in relation to tissue content during controlled exposures in human subjects (Astrand et al. 1972; Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Carlsson 1982; Hjelm et al. 1988; Tardif et al. 1991) and animal models (Benignus et al. 1981, 1984; Bruckner and Peterson 1981a; Tardif et al. 1992; van Asperen et al. 2002). Nadeau et al. (2006) reported that toluene concentrations in alveolar air of human subjects exercising at 50-100 W were 1.4- to 2.0-fold greater than from when exposures administered at rest. Several of the studies also measured toluene concentrations in the brain of rodents. With the exception of concentrations above 5,200 ppm in a study with the mouse (Bruckner and Peterson 1981a), all of the studies demonstrated a linear relationship between concentrations in both atmospheric and alveolar air and blood concentrations. At concentrations above 5,200 ppm, the metabolism of toluene may be saturated in the mouse. Although values appear comparable among some of the studies, differences in analytic techniques and the use of arterial rather than venous blood samples allow only general comparisons to be made.

Selected studies of toluene in human subjects and animal models are presented in Table 6-8 and presented graphically in Figure 6-2 (human studies) and Figure 6-3 (animal studies). The clinical studies represent different exposure situations, ranging from sedentary subjects to exercising subjects (Astrand et al. 1972; Lof et al. 1990; 1993) and to routine working conditions (von Oettingen et al. 1942). Steady-state may not have been reached for blood concentrations during the successive 20-min exposures in the study of Gamberale and Hultengren (1972). Where several studies involving the same species are available, there is relatively good agreement among peak blood concentrations. In general, for similar air concentrations, peak blood concentrations are inversely related to body size, being greatest in the mouse, followed by the rat and then the dog.

TABLE 6-8 Relationship between Ambient Air and Blood Concentrations of Toluene

Species	Exposure Duration	Air Concentration (ppm) (level of work)	Blood Concentration (mg/L)	Reference
Human	–	Background, general population	Up to 0.015	ACGIH 2001
Human	8 h (occupational)	40-54	0.41	Brugnone et al. 1986
Human	7 h	33	0.20	Tardif et al. 1997
Human	6.5 h 3.5 h	50 95	0.77 1.36	Tardif et al. 1991
Human	4.5 h	0 (control) 50	0.01 0.50	Muttray et al. 2005
Human	2 h	80 (rest) 80 (50 W)[b]	0.6 (mg/L, arterial)[a] 0.4 (mg/L, venous) 2.1 (mg/L, arterial) 1.2 (mg/L, venous)	Carlsson 1982
Human	4 h	53	0.28[c]; 0.52-0.64	Wallen et al. 1985
Human	4 h	80	0.47	Hjelm et al. 1988
Human	4 h	80 (no exercise)	0.52	Lof et al. 1990
Human	2 h	50 (exercise, 50 W)	0.92	Lof et al. 1993
Human 8 men 7 men	 4 h 4 h	 80 80	 1.17 0.98	Cherry et al. 1983; Waldron et al. 1983
Human	4 h (four 50-min exposures)	50 100 150	0.2 0.4 0.6	Veulemans and Masschelein 1978
Human	8 h 8 h	100 200	1.3 3.4	Angerer et al. 1980

(Continued)

TABLE 6-8 Continued

Species	Exposure Duration	Air Concentration (ppm) (level of work)	Blood Concentration (mg/L)	Reference
Human	6 h (occupational)	50-100	0.85-1.70	Neubert et al. 2001a
Human	20 min[d]	100	0.6	Gamberale and Hultengren 1972
	20 min	300	1.8	
	20 min	500	3.0	
	20 min	700	4.5	
Human	30, 60 min	100 (no exercise)	1.0	Astrand et al. 1972
	30 min	200 (no exercise)	2.0	
	30, 60 min	100 (exercise, 50 W)	2.3	
	30 min	200 (exercise, 50 W)	4.8	
Human	8 h (occupational)	Nonexposed	0.004	Foo et al. 1988
		32 (50 W)	0.56	
		65 (50 W)	0.99	
		86 (50 W)	1.3	
		115 (50 W)	1.5	
		132 (50 W)	1.9	
		196 (50 W)	2.6	
Dog	1 h	700	27	Hobara et al. 2000
	1 h	1,500	56	
	1 h	2,000	67	
Rat	1 h	2,000	100[b]	Oshiro et al. 2007
Rat	1 h	2,000 (sedentary)	31.5-42.8	Bushnell et al. 2007b;
		2,000 (active)	36.5-50.4	Kenyon et al. 2008
		2,000 (free fed)	25-31.7	
		2,000 (weight maintained)	16.7-28.1	
Rat	7 h	100	1.3	Korsak et al. 1991
Rat	5 h	75	0.7	Tardif et al. 1992
	5 h	150	2.7	
	5 h	225	5.1	

Rat	4 h	50	0.5	Haddad et al. 1999a
		100	1.3	
		200	5.0	
Rat	3 h	50	0.45	Benignus et al. 1984
	3 h	100	0.89	
	3 h	500	10.2	
	3 h	1,000	30.6	
Rat	2 h	1,000	58	Rees et al. 1985
	2 h	1,780	94	
	2 h	3,000	120	
Rat	4 h	125	2.5	Kishi et al. 1988
	4 h	250	7	
	4 h	500	17	
	4 h	1,000	27	
	4 h	2,000	70	
	4 h	4,000	120	
Rat	7.5 h	1,333	45	van Asperen et al. 2003;
	7.5 h	2,667	79	Lammers et al. 2005b
Mouse	2 h	1,300	97	Bruckner and Peterson 1981a
	2 h	2,600	147	
	3 h	4,000	200	
	2 h	5,200	242	
	2 h	10,400	315	

[a]Blood concentrations were reported in mg/kg or µg/g.
[b]W, watts exercise (1 W = 4.2 calories/h).
[c]Concentrations reached a peak at 2.5 h and then decreased during the last 1.5 h.
[d]These were successive exposures of 20 min each; steady-state may not have been reached at the higher concentrations.

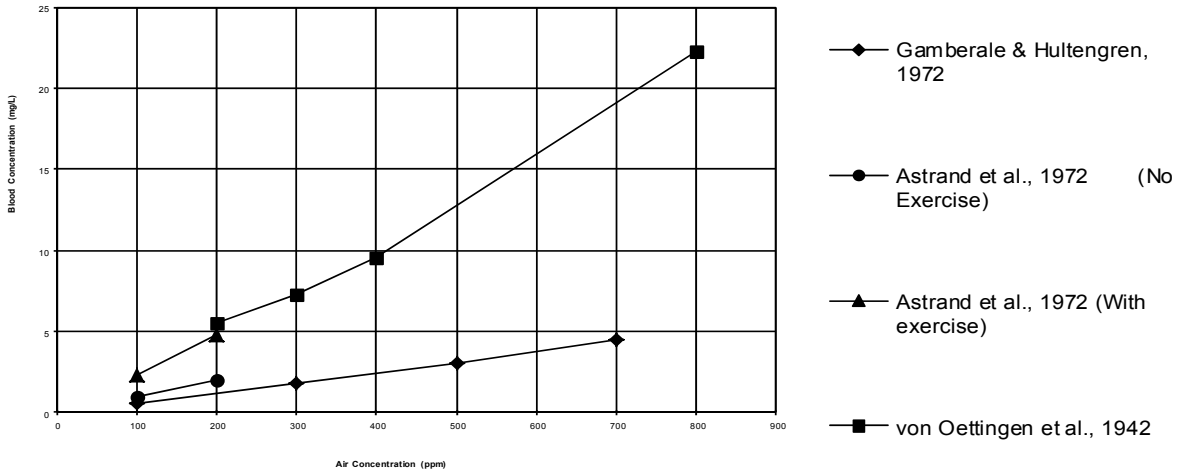


FIGURE 6-2 Relationship between air and blood concentrations of toluene in humans under different exposure conditions.

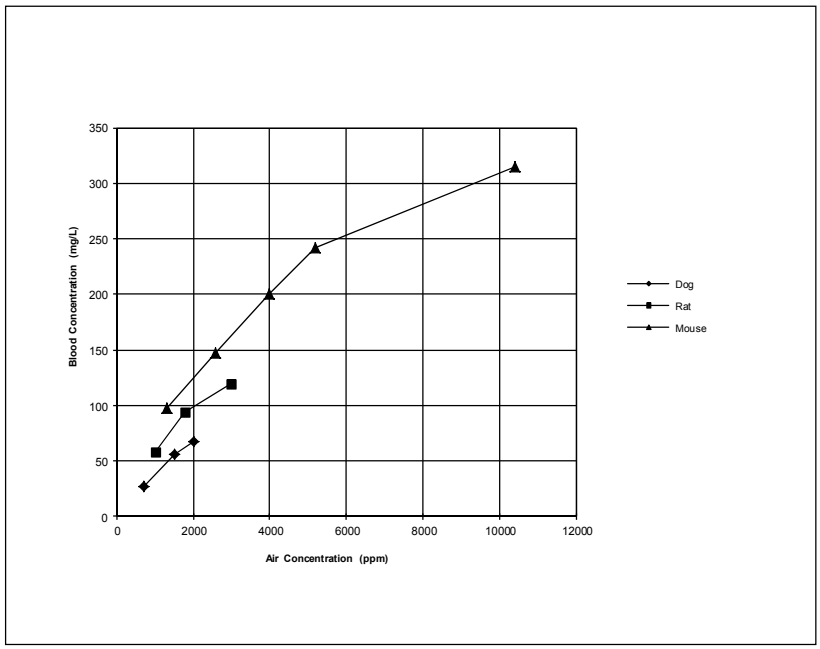


FIGURE 6-3 Relationship between air and blood concentrations of toluene in different animal species. Data for the dog, rat, and mouse are from studies by Hobara et al. (2000), Rees et al. (1985), and Bruckner and Peterson (1981a), respectively.

Using a single exposure concentration, Benignus et al. (1981) showed that blood and brain concentrations of toluene reach an asymptote fairly rapidly (Figure 6-4). The authors measured venous blood and brain concentrations of Long-Evans rats (gender unspecified) exposed to toluene at 575 ppm for 240 min. Animals were killed serially at 15, 30, 60, 120, and 240 min both during exposure and during a 240-min post-exposure period. The investigators fit the raw data to one-compartment, three-parameter models as shown in Figure 6-4. Blood and brain toluene concentrations achieved 95% of estimated asymptotes in 53 and 58 min, respectively. Estimated asymptotes were 10.5 ppm (mg/L) for venous blood and 18.0 ppm (mg/L) for brain. Blood and brain toluene concentrationss rose and fell at similar rates, although toluene in the brain fell slightly more rapidly than in the blood. The above value for brain concentration following exposure to toluene at 575 ppm is essentially the same as that of Carlsson and Lindqvist (1977), who measured a brain concentration of 15 µg/g (mg/L) in rats exposed at 550 ppm for 1 h. In studies of higher concentrations, 1,700, 3,400, and 5,100 ppm, Miyagawa et al. (1986) measured brain concentrations of approximately 120, 267, and 400 µg/g (mg/L), respectively (numbers read from graph) in young male Sprague-Dawley rats. Concentrations were measured immediately after 4-h exposures.

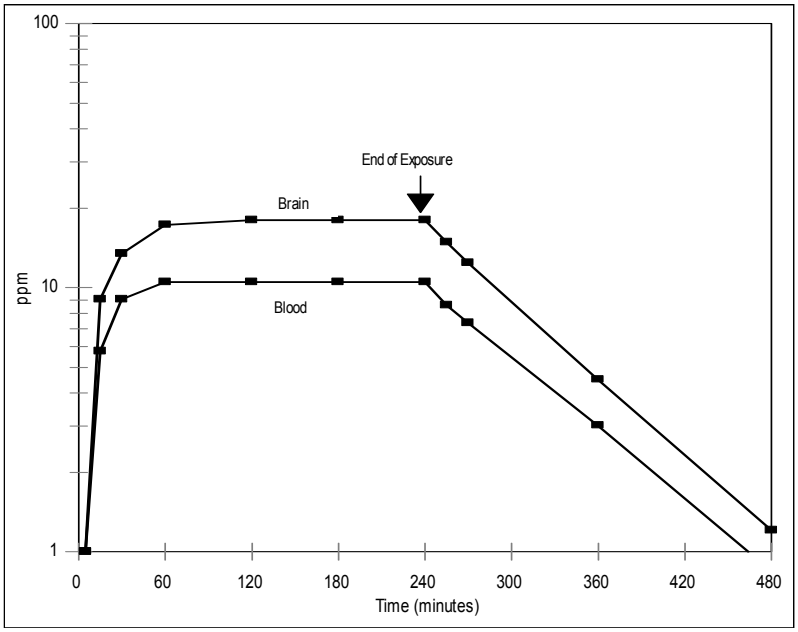


FIGURE 6-4 Toluene concentrations in the brain and venous blood of Long-Evans rats during and after exposure to toluene at 575 ppm for 4 h. (Blood concentrations of toluene given in ppm = mg/L.) Source: Adapted from Benignus et al. 1981.

A few studies reported blood toluene concentrations associated with coma in humans. Two workers admitted to the hospital in comas due to an accidental occupational exposure to mixed solvents had blood toluene concentrations of 823 and 1,122 µg/L at 36 h after the end of exposure (Brugnone et al. 1983). Respective alveolar air toluene concentrations were 53 and 38 µg/L. Calculated blood:air partition coefficients were 23 and 28, respectively. The decline in both compartments over the ensuing 5-day period allowed calculation of blood half-lives of 27.1 and 17.1 h in the respective workers and alveolar half-lives of 20.8 and 17.5 h. The authors noted that these half-lives were for the decline of toluene in fat and other poorly perfused tissues, as the half-life from well-perfused tissues would be on the order of 2 min. Extrapolation to the end of exposure gave blood concentration of 6.2 and 8.4 mg/L, respectively.

Toluene concentrations have also been measured in fatalities, but measurements were taken several hours after exposure in most cases. In 1983, Paterson and Sarvesvaran reported a fatality involving a 16-year-old Caucasian male who was found dead with a plastic bag over his head. The trachea and bronchi of the deceased contained inhaled stomach contents. His toluene blood concentration was 20.6 µg/mL, and the brain and liver concentrations were 297 and 89 µg/mg of tissue, respectively. The authors determined the cause of death to be

toluene poisoning; they also stated that using a plastic bag to "concentrate" the vapors and direct inhalation from the bag contributed to the fatality. A painter who died following a fall had tissue concentrations of toluene in blood, lungs, liver, and brain of 48, 35, 65, and 80 μg/g, respectively (Takeichi et al. 1986). The authors stated that these concentrations were not definitely lethal, but were high enough to anesthetize the CNS.

Kojima and Kobayashi (1973) measured toluene in blood of rats that died during 30-50 min exposures at 20,000 ppm. Average toluene concentrations were 890 μg/g in the brain, 700 μg/g in the liver, and 330 μg/g in the blood. During additional exposures, no rats died when brain concentrations were less than 760 μg/g. No deaths occurred during a 120-min exposure at 5,000 ppm; average toluene concentrations in blood, liver, and brain during exposure were 220, 510, and 480 μg/g. Miyagawa et al. (1984) observed increased response rates of rats to a variable interval schedule-controlled operant task when the brain toluene concentrations were less than 200 μg/g and decreased response rates when brain toluene concentrations were between 200 and 350 μg/g. However, van Asperen et al. (2003) found that repeated high-dose spikes producing peak brain concentrations in rats up to 248 mg/L did not predict the level of behavioral impairment observed across different exposure scenarios.

Bruckner and Peterson (1981a) related the following blood concentrations in mice to states of CNS depression: 40-75 μg/g, ataxia; 75-125 μg/g, immobility in the absence of stimulation; 125-150 μg/g, hypnosis with arousal difficult; and >150 μg/g, unconsciousness. A good correlation between brain toluene concentrations and the extent of CNS depression was also found. Exposures were to toluene at 4,000 ppm for 3 h or 10,600 ppm for 10 min.

4.2. Mechanism of Toxicity

The most common consequence associated with toluene exposure at concentrations historically found in the workplace is CNS depression. CNS depression and narcosis are thought to involve the reversible interaction of toluene (not its metabolites) and lipid or protein components of nervous system membranes. Bruckner and Warren (2001) summarized present theories on mechanisms of action. These involve (1) a change in membrane fluidity, thereby altering intercellular communication and normal ion movements, (2) interaction with hydrophobic regions of proteins, thereby altering membrane-bound enzyme activity or receptor specificity, (3) enhancement of the neurotransmitter gamma-aminobutyric acid ($GABA_A$) receptor function, and (4) activation of the dopaminergic system. Two mechanisms of toxicity have been proposed for CNS effects due to repeated exposure: 1) interaction of toluene with membrane proteins and/or phospholipids in brain cells changes the activities of enzymes involved in the synthesis or degradation of neurotransmitters, which in turn may produce subtle neurologic effects, and (2) toluene may change the binding of neurotransmitters to membrane receptors (ATSDR 2000).

Intentional exposure to excessively high concentrations of toluene results in feelings of euphoria, which progress to lethargy and neurobehavioral deficits; these effects resemble those produced by anesthetics. Toluene is highly lipophilic and, as a nonpolar, planar molecule, can behave as an anesthetic by dissolving in the interior lipid matrix of a membrane. Increasing toluene concentration produces membrane expansion as well as changes in membrane structure and fluidity. Following an acute exposure, toluene diffuses out of the membrane, original integrity is regained, and functional characteristics can be restored (ATSDR 2000).

Renal toxicity with metabolic acidosis may be experienced at high concentrations of toluene. Distal renal tubular acidosis is an established consequence of toluene abuse and has been reported in numerous studies. In life-threatening cases, patients present with severe generalized muscle weakness, nausea and vomiting, and neuropsychiatric derangements (Streicher et al. 1981; Batlle et al. 1988; Marjot and McLeod 1989). The disorder results from the inability of the distal tubule of the nephron to secrete hydrogen ions through the active transport pathway of the collecting tubule of the kidney, resulting in metabolic acidosis with respiratory compensation and production of alkaline urine and hyperchloremia. The high anion gap of the blood may be due to the accumulation of the acidic metabolites of toluene, namely benzoic acid and hippuric acid.

The mechanism(s) of action at the molecular level for hearing loss and impairment of color vision are poorly understood (ATSDR 2000). In hearing loss, toluene exposure leads to a loss of outer hair cells in the ear. There may also be an effect on neural cell membranes. The postulated mechanism of action for color vision impairment involves toluene interference with dopaminergic mechanisms of retinal cells or demyelinization of optic nerve fibers.

4.3. Structure-Activity Relationships

No structure-activity issues have been identified with regard to toluene toxicity. In a summary statement based on the studies of benzene, toluene, and mixed xylenes, NTP (1990) states that methyl and dimethyl substitution on the benzene ring eliminates the carcinogenic activity in rodents. The toxicity of toluene resembles that of benzene except that toluene is devoid of benzene's chronic hematopoietic toxicity (Henderson 2001).

Because many alkylbenzenes have the same CNS depressant effect, similar to that of CNS-depressant drugs and ethanol, their relative potency as CNS depressants might be of relevance. In their study of the effects of toluene on the functional observational battery in mice, Tegeris and Balster (1994) compared the effects of benzene and five alkylbenzenes with that of phenobarbital (5-40 mg/kg, intraperitoneal). The alkylbenzenes were toluene, ethylbenzene, propylbenzene, xylenes, and cumene. All exposures were to concentrations of 2,000, 4,000, or 8,000 ppm for 20 min. All agents decreased arousal, increased the ease of handling, decreased muscle tone, produced psychomotor impairment, and reduced reactivity to stimuli. At the two highest concentrations, the alkylbenzenes pro-

duced an anesthesia-like effect with loss of righting reflex (for phenobarbital, the loss of righting reflex occurred at 30 mg/kg). Both propylene and *m*-xylene required slightly higher concentrations to produce effects comparable to those of benzene, toluene, ethylbenzene, and cumene, although insufficient concentrations were studied to allow precise comparisons. The converse appears to be true for lethality. Where data on toluene and xylenes were available for the same species, LC_{50} values were slightly lower for xylene. For the mouse, the 6-h LC_{50} values for xylene isomers qwew 3,907-5,267 ppm, whereas the 6-h LC_{50} for toluene was 6,940 ppm (Bonnet et al. 1979).

4.4. Other Relevant Information

4.4.1. Interspecies Variability

Uptake of toluene by dogs (Hobara et al. 2000) appears to be more rapid and the blood concentrations attained slightly higher than those in several human studies (Figures 6-2 and 6-3). Uptake is somewhat greater in the rat than in humans, on the basis of blood: air partition coefficients and higher respiratory rate and cardiac output. The blood:air partition coefficient of 21.0 in rats is higher than that of humans (13.9) (Thrall et al. 2002).

Physiologically-based pharmacokinetic (PBPK) modeling was done in rats and humans (see Appendix C). PBPK modeling allows a comparison of the internal dose that is received in both species receiving identical external exposures. As can be seen in Figures 6-2 and 6-3, rats achieve higher blood toluene concentrations than humans. This is primarily due to the higher respiration rate and cardiac output, as well as a slightly higher blood:air partition coefficient in rats (13-21) (Sato and Nakajima 1979a; Gargas et al. 1989; Thrall et al. 2002; van Asperen et al. 2003) compared to humans (10-18; Thrall et al. 2002; Sato and Nakajima 1979a; Fiserova-Bergerova and Diaz 1986; Pierce et al. 1996a).

The interspecies factor is comprised of a pharmacodynamic component as well. A review of the data indicate little difference in interspecies sensitivity to toluene. Comparison of LC_{50} values for the rat and mouse shows that the mouse is slightly more sensitive than the rat. The 1-h LC_{50} in rats was 26,700 ppm (Pryor et al. 1978). In the mouse the 1-h LC_{50} was 19,018 ppm (confidence limits: 17,350-20,846 ppm) (Moser and Balster 1985). The sequelae of death was similar in both species with observations of lacrimation, hyperactivity, hypoactivity, lethargy, and shallow respiration followed by death. The greater uptake of toluene in mice compared with rats, on the basis of respiratory rate and cardiac output, is offset to some degree by more rapid toluene metabolism by the mouse.

Neurotoxicity end points at the same concentration of toluene were also similar for rats and mice. For both species, 1,200 ppm was a chronic no-adverse-effect level (NTP 1990); for short-term exposures, motor activity was increased in rodents exposed at 1,000 ppm (see Tables 6-5 and 6-6). For rats and mice, 2,000 ppm may be the threshold for CNS depression, but a 50-min exposure at 2,000 ppm failed to produce an attention deficit in monkeys (Taylor and Evans

1985). At the same target tissue dose, humans may experience effects similar to those observed in animals, although it would take longer to attain the effects in humans due to a lower breathing rate per kilogram of body weight. In animals, death is preceded by increased activity, followed by narcosis, and is likely the result of depression of the CNS resulting in respiratory arrest. CNS depression with narcosis has also been observed in several accidental and intentional human exposures. Thus, nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and CNS effects at high concentrations of toluene.

Benignus et al. (2007) compared the acute neurotoxicity of toluene in rats and humans. A meta-analysis of dose-effect functions for variables such as choice reaction time in humans and reaction time in rats suggested that sensitivity to toluene is equivalent in humans and rats if both species performed behaviors that were controlled to the same extent.

4.4.2. Intraspecies Variability

Toluene produces CNS dysfunctions that are similar to those produced by other anesthetics (Bruckner and Warren 2001). Studies indicate that children, and particularly infants, are more resistant than adults to the effects of various volatile anesthetics (Gregory et al. 1969; Stevens et al. 1975; Lerman et al. 1983; LeDez and Lerman 1987; Katoh and Ikeda 1992; Chan et al. 1996). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lungs which produce "anesthesia" (lack of movement) have been measured. Values are usually reported as the minimum alveolar concentration which produces lack of movement in 50% of persons exposed at that concentration. Minimum alveolar concentrations for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest minimum alveolar concentration) in newborns, particularly premature infants, pregnant women, and the elderly. The least sensitive (highest minimum alveolar concentration values) occur in older infants, toddlers, and children compared with normal adults. The total range of sensitivity is 2-3 fold. On the basis of this knowledge, it is not unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for toluene.

In healthy adult male volunteers exposed to toluene at 40 ppm for 2 h (number of subjects not specified), blood toluene concentration differed by no more than 2-fold (Bessems et al. 2004). Small standard deviations in additional studies also indicate little inter-individual variation for a constant level of activity (Astrand et al. 1972; Carlsson 1982; Rahill et al. 1996). In one study, Pierce et al. (1999) reported an approximate 10-fold interindividual range in venous concentrations in two individuals exposed to toluene at 100 ppm for 2 h. The ventilation rate of these two subjects differed by a factor of two. A PBPK model indicates that there are no adult-children differences in tissue dose during inhalation (Pelekis et al. 2001).

4.4.3. Concentration-Response Relationship

The two primary effects of toluene exposure are irritation and CNS depression. Irritation is considered a threshold (concentration related) effect and therefore should not vary over time. CNS depression is also a concentration-related effect, with duration of exposure also a factor at higher exposures and short durations (less than 8 h). At low concentrations of 80 to 200 ppm, toluene approaches steady-state in the blood within 15-30 min (Astrand et al. 1972; Carlsson 1982). At higher concentrations, steady-state is approached in a concentration-related manner within one to several hours (Benignus et al. 1981; Gospe and Al-Bayati 1994). Storage would take place in lipid-rich tissues, but elimination is rapid. Once steady-state is reached, concentration is the prime determinant of toluene-induced CNS effects. Thus, concentrations that are not irritating or narcotic to humans within 30 min are assumed to have no greater effect with prolonged exposure.

Although blood concentrations can be used as a surrogate for brain concentrations, the target tissue for toluene, steady-state is not reached and there is much variability in the brain:blood ratio across durations at higher concentrations and the short durations relevant to AEGL derivation. As noted by Bushnell et al. (2007a), momentary brain concentration is most predictive of CNS effects. For higher exposure concentrations, PBPK modeling was used to determine human equivalent AEGL values from the animal data. PBPK modeling was used to calculate the internal dose (BrTC) in several studies with the rat. The general physiological and toxicokinetic (GPAT) human model for toluene was then used to determine the exposure concentrations in humans that yields the same concentration (Benignus et al. 2006). PBPK modeling allows a determination of the internal dose for the experimental species, and a determination of the external exposure which would lead to the same internal dose in the human. As can be seen in Figures 6-2 and 6-3, rats achieve higher blood toluene concentrations than humans. This is primarily due to the higher respiration rate and cardiac output, as well as a slightly higher blood:air partition coefficient in rodents.

4.4.4. Concurrent Exposure Issues

Toluene and a number of other volatile organic compounds are competitive metabolic inhibitors, as they are oxidized by some of the same P450 isozymes. The net effect is an increase in the blood and tissue (for example, brain) concentrations of each parent compound (despite some increase in exhalation) and an increase in the degree and duration of CNS depression. This may occur at "high concentrations," but at lower concentrations in both man (100 ppm) and rats (25 ppm), no significant interaction occurred (Ikeda 1974; Sato and Nakajima 1979b).

Tardif et al. (1992) reported that, compared with single 5-h exposures to toluene or xylene, the simultaneous exposure of adult male Sprague-Dawley rats

to toluene (75, 150, and 225 ppm) and xylene (225, 150, and 75 ppm) resulted in interactive effects on metabolism. The interaction was evidenced by higher toluene concentrations in the blood and lower amounts of excreted metabolites over 24 h. There was some dependence of this effect on the ratio of the two chemicals. Furthermore, the effect was not observed at 50 ppm of toluene and 40 ppm xylene (Tardif et al. 1991).

Studies of toluene exposure (100 ppm) in combination with alcohol ingestion report delayed metabolism of toluene (Dossing et al. 1984), but there were no additive effects in neurobehavioral tests (4-h exposure at 80 ppm) (Cherry et al. 1983).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Twenty controlled human studies that describe the threshold for irritation and CNS effects from acute exposures to toluene or toluene concentrate have been conducted (Table 6-3). The effects in these studies include slight sensory irritation, accompanied by headache in some cases, subtle impairment on some sensitive cognitive-function tasks, and occasional slight dizziness. The more recent studies involved exposure durations of up to 4 h at 80 ppm, 7.5 h at 100 ppm, and 7 h at 200 ppm. Although slight sensory irritation was reported in subjects exposed to toluene at 80-200 ppm in some studies (Andersen et al. 1983; Baelum et al. 1985, 1990; Echeverria et al. 1989, 1991), these concentrations were not irritating in other studies (Stewart et al. 1975; Cherry et al. 1983; Olson et al. 1985; Rahill et al. 1996) and the exposures were generally considered acceptable (no annoyance). True sensory irritation from toluene was reported at concentrations of 20,000 ppm or higher in human studies (Cometto-Muniz and Cain 1995; Abraham et al. 1996), but could not be determined in the mouse (Nielsen and Alarie 1982). No differences in performance on neurobehavioral tests were found in some studies, and others found only subtle differences that indicated slight reductions in alertness (Ogata et al. 1970; Gamberale and Hultengren 1972; Stewart et al. 1975; Winneke 1982; Andersen et al. 1983; Cherry et al. 1983; Dick et al. 1984; Olson et al. 1985; Baelum et al. 1985, 1990; Echeverria et al. 1989, 1991; Rahill et al. 1996). There were no biologically significant pulmonary or cardiovascular effects (Astrand et al. 1972; Gamberale and Hultengren 1972; Suzuki 1973) and no indications of renal damage (Nielsen et al. 1985). The studies by Rahill et al. (1996), Astrand et al. (1972), and Baelum et al. (1990) found that exercise doubled the uptake of toluene by blood. The study by Stewart et al. (1975) involved repeated exposure to toluene, and found no greater effects over time. Baelum et al. (1990) also tested concentrations that ranged between 50 and 300 ppm (repeated 14 times during a 7-h exposure) with a TWA of 100 ppm; the subjects exercised during the peak exposures at 300 ppm. Gamberale and Hultengren (1972) tested higher concentrations of toluene, but the exposure durations were relatively short and toluene was delivered via

breathing tube. Concentrations of toluene above 300 ppm were associated with subtle differences in the speed of reacting to a stimulus or completing a task. For example, during a 20-min exposure at 700 ppm, it took subjects approximately 30 sec longer than controls to match three-digit numbers in 60 columns with numbers appearing at the top of the column (the test was two pages in length).

In metabolism studies, subjects were routinely exposed to toluene at 78-200 ppm for several hours, with and without exercise (Nomiyama and Nomiyama 1978; Veulemans and Masschelein 1978; Carlsson 1982; Dossing et al. 1984; Wallen et al. 1985; Hjelm et al. 1988). These studies did not evaluate subjective effects, because they were undertaken to study the toxicodynamics and toxicokinetics of toluene in people exposed in the workplace.

Occupational-monitoring studies indicate that workers presumed to be healthy have been exposed to toluene at a TWA of 100 ppm or higher without adverse effects. In a comprehensive, well-conducted occupational-monitoring study involving more than 1,000 workers, Neubert et al. (2001a) failed to find alterations in motor performance or increased subjective complaints in workers exposed to toluene at TWA concentrations of 50-100 ppm compared with matched control groups. Workers exposed chronically to toluene at concentrations greater than 100 ppm (66-800 ppm) did not have greater attention deficits or sensory symptoms in neurologic tests than those exposed acutely (Foo et al. 1990; Zavalic et al. 1998; Neubert et al. 2001a). Irritation of the conjunctiva and upper respiratory tract was found in only one of 11 workers exposed at 200-800 ppm (Parmeggiani and Sassi 1954). Occupational exposures to toluene at concentrations up to 300 ppm (Bauchinger et al. 1982), 350 ppm (Ovrum et al. 1978), and 467 ppm (Deschamps et al. 2001) have also been reported.

5.2. Animal Data Relevant to AEGL-1

Few animal studies of end points relevant to AEGL-1 values for toluene were found. Toluene at 1,200 ppm was a NOAEL for overt behavior changes in rodents exposed chronically (NTP 1990). Subtle changes in rodent behavior are not possible to observe, and the effects on rat and mouse behavior described in Tables 6-5 and 6-6, respectively, are sometimes conflicting. Motor activity either remained unchanged or increased at concentrations below 1,000 ppm; this stimulatory effect was accompanied by either an increase or decrease in positive responses in subtle neurobehavioral tests.

5.3. Derivation of AEGL-1 Values

Multiple clinical, occupational-monitoring, and metabolism studies found effects below the definition of the AEGL-1 (notable discomfort). It is not feasible to model notable discomfort, so AEGL-1 values were based on the preponderance of data from clinical and occupational studies and from metabolism studies with human subjects that indicated that an 8-h exposure to toluene at 200

ppm is a NOAEL for notable discomfort, but elicited subjective, low-severity, nonsensory effects in some studies. More than 300 individuals were involved in the clinical studies summarized in Table 6-3. Several thousand workers were surveyed in the occupational-monitoring studies. Although these populations are presumed to be composed of healthy individuals, they represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions) and individual differences in metabolism rates (Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Brugnone et al. 1986; Hjelm et al. 1988). Although slight respiratory irritation was reported at 100 and 200 ppm in several studies, toluene is not a respiratory irritant as evidenced by the high RD_{50} value of 5,300 ppm (Nielsen and Alarie 1982). In addition, the severity of the irritation and the neurobehavioral effects reported in these studies was generally below the definition of AEGL-1.

The highest NOAELs for notable discomfort were 200 ppm for 60 min (Astrand et al. 1972), 300 ppm for 15 min (Baelum et al. 1990), and 700 ppm for 20 min (Gamberale and Hultengren 1972). NOAELs for nonsensory (neurobehavioral) effects were 100 ppm for 4 h (Dick et al. 1984), 6 h (Rahill et al. 1996), and 6.5 h (Baelum et al. 1985, 1990; Nielsen et al. 1985); 150 ppm for 7 h (Echeverria et al. 1989, 1991); and 200 ppm for 3 h (Ogata et al. 1970). Exercise during the studies of Astrand et al. (1972) and Baelum et al. (1990) takes into account the increased uptake that may occur during an emergency situation. Although a steady-state in blood and brain toluene concentrations would be approached but not attained during the 15-and 20-min exposures, the blood concentration of toluene has been shown to increase approximately two-fold with moderate exercise of 50 W (Astrand et al. 1972). Therefore, the preponderance of data indicates that an 8-h exposure to toluene at 200 ppm is a NOAEL for AEGL-1 effects; however, some subjective neurobehavioral effects have been reported. Although there was no notable discomfort and only mild irritation (effects expected to be concentration dependent and not subject to changes in activity level), headaches (potentially related to CNS effects), reports of dizziness, and nonmeasurable neurologic effects have been reported at 100-200 ppm in controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983). Neurologic effects would be expected to be affected by an increase in activity level, leading to higher concentrations of toluene in the brain. As noted earlier, moderate physical activity may double the blood concentration of toluene.

Empirical data as well as pharmacokinetic modeling in humans and rodents indicate that venous-blood and brain concentrations of toluene rapidly increase during the first 15-20 min of exposure, followed by relatively modest increases in blood concentrations with continuing exposure (Gamberale and Hultengren 1972; Tardif et al. 1993, 1995). At low concentrations, toluene reaches an asymptote in the blood within 20-30 min (Gamberale and Hultengren 1972; Carlsson 1982). Although storage of toluene would take place in lipid-rich tissues (including those of the brain), elimination is also rapid. On the basis of the range of alveolar concentrations among humans exposed to anesthetic gases

(see Section 4.4.2), an uncertainty factor of 3 for intraspecies variability was applied to derive a value of 67 ppm. That concentration was used for all of the AEGL durations, because a steady-state of at 67 ppm is reach fairly rapidly. The AEGL-1 values for toluene are presented in Table 6-9, and the calculations in Appendix A. The relationship between the AEGL-1 values and human exposures is shown in Appendix B.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In humans and animals, the primary effect associated with inhalation of "high concentrations" is CNS depression. Few studies of controlled or accidental exposures to toluene evaluated CNS depression of a severity that would inhibit the ability to escape. Gamberale and Hultengren (1972) exposed volunteers to toluene at 700 ppm for 20 min, following successive 20-min exposures at 100, 300, and 500 ppm (total exposure duration 85 min). The work by Benignus et al. (2011) shows a useful comparative analysis equating decrements in neurologic functioning associated with blood ethanol levels across exposures to a number of volatile solvents, including toluene.

There was one case report of accidental human exposure to toluene, which was appropriate as a basis for deriving AEGL-2 values (Meulenbelt et al. 1990). Two men used toluene to remove excess glue from tiles in the bottom of a swimming pool. The men were barely conscious when they were found; they were confused and unable to walk. They also suffered paresis, ocular irritation, amnesia, and had increased anion gaps, presumably from the onset of distal renal tubular acidosis from the metabolites, hippuric and benzoic acid. The toluene concentration measured above the site several hours later was greater than 1,842 ppm, although the victims were likely exposed at higher concentrations at the bottom of the pool. The duration of exposure was approximately 2.5 h.

6.2. Animal Data Relevant to AEGL-2

Except for increased locomotor activity, toluene concentrations below 1,000 ppm have little or no effect on gross manifestations of animal behavior (NRC 1981; WHO 1987). At concentration of 2,000 ppm lower, increased motor activity and an increased rate of responding in neurobehavioral tests were found in rodents (Glowa 1981; De Ceaurriz et al. 1983; Bushnell et al. 1985; Miyagawa et al. 1986; Hinman 1987; Kishi et al. 1988; Wada et al. 1989; Wood and

TABLE 6-9 AEGL-1 Values for Toluene

10 min	30 min	1 h	4 h	8 h
67 ppm (250 mg/m^3)	67 ppm 250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)

Cox 1995) and monkeys (Taylor and Evans 1985). Higher concentrations of toluene suppress activity. Rats exposed to toluene at 2,400 ppm for 70 min performed more poorly on a signal detection task than controls (Oshiro and Bushnell 2004). The rats were described as sleepy but arousable. Adult female macaque monkeys were affected little by a 50-min exposure to toluene at 2,000 ppm or lower; an attention deficit was found during a 50-min exposure at 3,000 ppm, and failure to respond occurred during the second half of a 50-min exposure at 4,500 ppm (presumably indicating narcosis) (Taylor and Evans 1985). The NOAEL for clinical signs, survival, and carcinogenicity in mice and rats after chronic inhalation exposure to toluene is 1,200 ppm (NTP 1990). Exposures in the NTP study were for 6.5 h/day, 5 days/week for 2 years.

6.3. Derivation of AEGL-2 Values

AEGL-2 values for toluene are based on a notable increase in reaction time. The point of departure was a NOAEL of 1,600 ppm based on doubling of reaction time in Long-Evans rats exposed for 34 min (Bushnell et al, 2007a). This point of departure is supported by modeling that shows that a similar magnitude of behavioral impairment is caused by oral ingestion of ethanol to the point of legal intoxication (Benignus et al. 2007, 2011). The CNS effects observed following toluene exposure are assumed to be directly related to concentrations of the parent chemical in the brain at the time the effects were measured. Therefore, the BrTC at the 34-min exposure would be expected to provide an internal dose correlating with the NOAEL.

The PBPK model of Kenyon et al. (2008) was used to calculate the internal dose (BrTC) in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a value of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncertainty factor of 3 was applied because the minimum alveolar concentration (lowest concentration causing an anesthetic effect) for volatile anesthetics should not vary by more than 2- to 3-fold among humans (see Section 4.4.2).

The GPAT model developed by Benignus et al. (2006) is a human whole-body differential equation-based model for simulating the function of the various organs in response to realistic situations, such as exercise, environment, and diet. The environmental aspects include temperature, humidity, and, in this application, toluene uptake and elimination for each organ. Thus, toluene uptake and elimination under various exposures was estimated for each organ, most notably the brain, and for various exercise levels. In addition, estimates were made of the exposure concentrations that would lead to specific organ concentrations (BrTC) in humans based on output from the Kenyon et al. (2008) rat PBPK model. The target internal dose metric in humans (human BrTC) was calculated by dividing the rat BrTC by the total uncertainty factor of 3. The hu-

man GPAT model (Benignus et al. 2006) was then used to determine the equivalent exposure concentration that yields the human BrTC at each of the AEGL exposure durations.

Similar types of neurobehavioral effects are caused by ethanol intoxication and have been well documented. Comparisons of the effects caused by the modeled levels of toluene and similar effects caused by ethanol intoxication (using blood ethanol concentration as the indicator) have been included in Appendix C (Table C-4), Appendix D, and in the paper by Benignus et al. (2011) to further support the approach taken in deriving the AEGL-2 values.

Time-scaling calculations are presented in Appendix A and the PBPK modeling methods are explained in Appendix C. AEGL-2 values for toluene are presented in Table 6-10, and are shown graphically in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human data on toluene concentrations that are the threshold for lethality are sparse. In a shipboard accident, workers lost consciousness after being exposed to estimated concentrations of toluene that ranged from 5,000 to 30,000 ppm (Longley et al. 1967). The exposure was at least 75 min in duration. Because toluene is heavier than air, the higher concentration was most likely near the floor where a kneeling worker rapidly lost consciousness. All workers recovered. Press and Done (1967) estimate the concentration of toluene achieved when inhaling directly from a paper bag containing gauze soaked with toluene (abuse situation) at 10,000 ppm. One of the authors inhaled from the bag for 5 min, and reported dizziness, blurred vision, roaring and buzzing in the ears, and slurred speech.

7.2. Animal Data Relevant to AEGL-3

On the basis of LC_{50} values, the mouse is slightly more sensitive to the effects of toluene than the rat. LC_{50} values for the mouse for 10, 30, and 60 min are 38,465, 21,872, and 19,018 ppm, respectively (Moser and Balster 1985). The 3-h LC_{50} was 8,600 ppm (Bruckner and Peterson 1981a). A 6-h LC_{50} of 6,940 ppm was calculated by Bonnet et al. (1979) and a 7-h LC_{50} of 5,320 was calculated by Svirbely et al. (1943). For the rat, LC_{50} values ranged from 26,700 ppm for 1 h to 12,500 ppm for 2-2.5 h (Pryor et al. 1978; Kojima and Kobayashi 1973). Death was caused by severe CNS depression and respiratory failure.

Data were also available on the highest concentrations of toluene that did not result in lethality. No deaths occurred in mice exposed to toluene for 20 min at 12,000 ppm (Bruckner and Peterson 1981a), in rats exposed for 2 h at 5,000 or 6,250 ppm (Kojima and Kobayashi 1973; Mullin and Krivanek 1982), or in rats exposed for 4 h at 6,000 ppm (Wada et al. 1989). Mice exposed at 6,000

ppm for 30 min/day, 5 days/week for 7 weeks and that were deprived of food survived the exposures in apparent good health (Moser and Balster 1981). Additionally, mice and rats tolerated toluene at 1,200 ppm for 2 years without an effect on mortality (NTP 1990).

7.3. Derivation of AEGL-3 Values

The AEGL-3 values are based on a NOAEL for lethality in the rat. A 2-h exposure at 6,250 ppm was not lethal but produced prostration in rats (Mullin and Krivanek 1982). CNS effects observed following toluene exposure were assumed to be directly related to concentration of parent chemical in the brain at the time effects were observed. Therefore, the PBPK model of Kenyon et al. (2008) was used to calculate the BrTC in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a factor of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncertainty factor of 3 was applied to account for intraindividual variability, as was done for the AEGL-2. A human GPAT model (Benignus et al. 2006) was used to determine the equivalent exposure concentration in humans for each of the AEGL exposure durations.

Time-scaling calculations are presented in Appendix A, and the PBPK modeling methods are explained in Appendix C. AEGL-3 values are presented in Table 6-11, and shown graphically in Appendix B.

TABLE 6-10 AEGL-2 Values for Toluene

10 min	30 min	1 h	4 h	8 h
1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)

[a]Concentration is one-tenth of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

TABLE 6-11 AELG-3 Values for Toluene

10 min	30 min	1 h	4 h	8 h
–[a]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6800 mg/m^3)	1,400 ppm[b] (5300 mg/m^3)

[a]The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

Workers lost consciousness after being accidentally exposed to toluene at an estimated concentration of 5,000 ppm or greater for an undefined period of time (Longley et al. 1967). In rodent studies, concentrations of 5,000 ppm for 2 h (Kojima and Kobayashi 1973), 12,000 ppm for 20 min (Bruckner and Peterson 1981a), and 6,000 ppm for 30 min/day, 5 day/week for 7 weeks (Moser and Balster 1981) were all nonlethal.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for toluene are presented in Table 6-12.

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures to toluene are presented in Table 6-13. The Occupational Health and Safety Administration recommends a 10-min maximum exposure of 500 ppm. The National Institute for Occupational Safety and Health's immediately dangerous to life or health (IDLH) value is also 500 ppm. The IDLH is based on the human data of Gamberale and Hultengren (1972), von Oettingen et al. (1942), and Wilson (1943), and was established at a concentration lower than both the 30-min AEGL-2 and AEGL-3 values. The IDLH is based on a weight-of-evidence approach from human data only, with the final value based on a consensus from a panel of experts. No quantitative analysis or application of PBPK models to approximate the human exposure which would lead to a NOAEL in the rat was used to determine the IDLH concentration whereas a quantitative approach was used in the development of the AEGL-2 and AEGL-3 values. The emergency response planning guideline (ERPG) values of the American Industrial Hygiene Association (AIHA 2013) are lower than the AEGL values. The ERPG-1 is based on controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983) in which exposure at 100 ppm produced mild symptoms, such as fatigue, drowsiness, headache, dizziness, and feeling of intoxication without measurable neurotoxic effects; these studies were considered in the derivation of the AEGL-1 values in the context of 20 relevant human studies. The final resulting AEGL-1 value of 67 ppm was deemed protective for these low-level, subjective effects. The ERPG-2 was based on controlled human studies in which exposure at 300 ppm for 8 h did not result in muscular weakness or incoordination (von Oettingen et al. 1942). This is an old study and was not considered for AEGL development. The ERPG-3 was based on the 1-h LC_{50} of 26,700 ppm in rats (Pryor et al. 1978), divided by approximately 20 and the reported loss of consciousness in humans exposed at 5,000 ppm for a few minutes (Longley et al. 1967). The National Research Council (NRC) 1-h emergency exposure guidance level for toluene is 200 ppm for workplace conditions (NRC 2008).

TABLE 6-12 AEGL Values for Toluene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)
AEGL-2 (disabling)	1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)
AEGL-3 (lethal)	–[b]	5,200 ppm[a] 20,000 mg/m^3)	3,700 ppm[a] (14,000 mg/m^3)	1,800 ppm[a] (6,800 mg/m^3)	1,400 ppm[a] (5300 mg/m^3)

[a]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

TABLE 6-13 Standards and Guidelines for Toluene

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	67 ppm	–	67 ppm	67 ppm	67 ppm	67 ppm
AEGL-2	1,400 ppm[a]	–	760 ppm	560 ppm	310 ppm	250 ppm
AEGL-3	–[b]	–	5,200 ppm[a]	3,700 ppm[a]	1,800 ppm[a]	1,400 ppm[a]
ERPG-1 (AIHA)[c]	–	–	–	50 ppm	–	–
ERPG-2 (AIHA)	–	–	–	300 ppm	–	–
ERPG-3 (AIHA)	–	–	–	1,000 ppm	–	–
EEGL (NRC)[d]	–	–	–	200 ppm	–	–
SMAC (NRC)[e]	–	–	–	16 ppm	–	–
IDLH (NIOSH)[f]	–	–	500 ppm	–	–	–
TLV-TWA (ACGIH)[g]	–	–	–	–	–	50 ppm
PEL-TWA (OSHA)[h]	–	–	–	–	–	200 ppm
REL-TWA (NIOSH)[i]	–	–	–	–	–	100 ppm
REL-STEL (NIOSH)[j]	–	150 ppm	–	–	–	–
PEL-C (OSHA)[k]	300 ppm	300 ppm	300 ppm	300 ppm	300 ppm	300 ppm
PEL-peak (OSHA)[l]	500 ppm	–	–	–	–	–
MAK (Germany)[m]	–	–	–	–	–	50 ppm
MAK peak exposure (Germany)[n]	–	–	250 ppm	–	–	–
MAC (The Netherlands)[o]	–	–	–	–	–	40 ppm

[a]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

[c]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013).
ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for toluene is based on controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983) in which exposure at 100 ppm produced mild symptoms, such as fatigue, drowsiness, headache, dizziness, and feeling of intoxication without neurotoxic effects.
ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for toluene was based on controlled human studies in which exposure at 300 ppm for 8 h did not result in muscular weakness or incoordination (von Oettingen et al. 1942).
ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for toluene was based on the LC_{50} in rats (Pryor et al. 1978), divided by approximately 20, and the reported loss of consciousness in humans exposed at 5,000 ppm for a few minutes (Longley et al. 1967).
[d]EEGL (emergency exposure guidance levels, National Research Council) (NRC 2008). The EEGL is the concentration of a contaminant that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects, and long-term or chronic injury.
[e]SMAC (spacecraft maximum allowable concentration, National Research Council) (NRC 2008). SMACs are intended to provide guidance on chemical exposures during normal operations of spacecraft, as well as emergency situations. The 1-h SMAC is a concentration of an airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects, such as dermal or ocular irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.
[f]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The IDLH for toluene is based on the human studies of Gamberale and Hultengren (1972), von Oettingen et al. (1942) and Wilson (1943).
[g]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2005) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. There is a skin notation for the TLV for toluene.
[h]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is a time-weighted average concentration that must not be exceeded during any 8-h workshift of a 40-h workweek.
[i]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is a time-weighted average concentration for up to a 10-h workday during a 40-h workweek.

[h]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday.
[j]PEL-C (permissible exposure limit – ceiling, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is a ceiling value that should not be exceeded during any part of the workday. If instantaneous monitoring is not feasible, the ceiling must be assessed as a 15-min time-weighted average exposure.
[l]PEL-peak (permissible exposure limit – peak, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is the acceptable 10-min maximum peak above the acceptable ceiling value.
[m]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 1999) is defined analogous to the ACGIH TLV-TWA.
[n]MAK spitzenbegrenzung (peak limit [Category II, 2], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 1999) is the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than two excursions per work shift; total exposure may not exceed 8-h MAK.
[o]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

Exposure limits for chronic exposures are lower than for emergency guidelines. The American Conference of Governmental Industrial Hygienists (ACGIH 2005) occupational exposure limit for toluene is 50 ppm, as is the German MAK (German Research Association (DFG 1999). The Dutch MAC is 40 ppm (MSZW 2004). The 8-h AEGL-1 for toluene is 200 ppm. The previous ACGIH TWA value of 200 ppm was lowered in 1991 on the basis of slight irritation at 100 ppm, described in the studies of Andersen et al. (1983), Baelum et al (1985), Wilson (1943), and Echeverria et al. (1989). The AEGL-1 value is higher than the TLV because slight irritation is acceptable under acute (once-in-a-lifetime) conditions. Furthermore, it is unlikely that an intolerable level of annoyance of sensory irritation was reached in the Andersen et al. (1983) study, given the inability to attain an RD_{50} (Nielsen and Alarie 1982).

The NRC (2008) spacecraft maximum allowable concentration for toluene is 16 ppm for 1 and 24 h. The SMAC values were based on a single study (Andersen et al. 1983), rather than the preponderance of the evidence from 20 published studies.

8.3. Data Adequacy and Research Needs

Because toluene is a commonly used solvent, its effects on humans have been extensively studied. Numerous controlled studies with human subjects that addressed effects meeting the definition of the AEGL-1 were available. The data base of neurotoxicity studies with animals is extensive, and the supporting animal data were in good agreement with the AEGL values based on the human studies. Toluene is fatal to humans only after exposure at extremely high con-

centrations. Although the animal data base on lethality was limited to rodents (rats and mice), the agreement between these two species was good.

The anesthetic effects and metabolism of toluene are well documented and well understood. Although specific sensitive populations were not identified, the mechanism of action of CNS depression is the same for all mammalian species, and the concentration at which this effect occurs after toluene inhalation does not differ greatly among individuals.

Although an abundance of empirical data exists concerning the toxicity of toluene in several species (including humans), there is a lack of good concentration-effect data for the exposure-time relationships. This data gap is particularly prominent with respect to human exposures. While there are several well-conducted, controlled, chamber studies involving human subjects, the exposure concentrations are limited to those that produce very little if any impairment or anesthetic effects in humans. Therefore animal data extrapolated to humans via PBPK modeling were used to calculate exposure-duration-specific AEGL values.

9. REFERENCES

Abbate, C., C. Giogianni, F. Munao, and R. Brecciaroli. 1993. Neurotoxicity induced by exposure to toluene: An electrophysiologic study. Int. Arch. Occup. Environ. Health 64(6):389-392.

Abraham, M.H., J. Andonian-Haftvan, J. Enrique Cometto-Muniz, and W.S. Cain. 1996. An analysis of nasal irritation thresholds using a new solvation equation. Fundam. Appl. Toxicol. 31(1):71-76.

ACGIH (American Conference of Governmental Industrial Hygienists, Inc). 2001. Toluene (CAS No. 108-88-3). Recommended BEI. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists, Inc). 2005. Toluene. Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. Fairfax, VA: AIHA.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013 ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Ali, N., and R. Tardif. 1999. Toxicokinetic modeling of the combined exposure to toluene and n-hexane in rats and humans. J. Occup. Health 41(2):95-103.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-289.

Andersen, I., G.R. Lundqvist, L. Molhave, O.F. Pedersen, D.F. Proctor, M. Vaeth, and D.P. Wyon. 1983. Human response to controlled levels of toluene in 6-h exposures. Scand. J. Work Environ. Health 9(5):405-418.

Anderson, D., and J.A. Styles. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. The bacterial mutation test. Br. J. Cancer 37:924-930.

Angerer, J., K. Behling, and G. Lehnhart. 1980. Biological workplace tolerance values: BAT value for toluene. Arbeitsmed. Sozialmed. Praeventivmed. 16:161-164.

API (American Petroleum Institute). 1985. Two-Generation Inhalation Reproduction/Fertility Study on a Petroleum Derived Hydrocarbon with Toluene. Study conducted by Internal Research and Development Corporation. API Medical Research Publication No. 32-32854. Washington, DC: American Petroleum Institute.

API (American Petroleum Institute.). 1993. Toluene: The Effect on Pregnancy of the Rat. (Inhalation Exposure). Washington, DC: American Petroleum Institute.

Astrand, I. 1975. Uptake of solvents in the blood and tissues of man: A review. Scand. J. Work Environ. Health 1(4):199-218.

Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Work Environ. Health 9:119-130.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for Toluene (Update). U.S. Department of Health and Human Services. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp56.pdf [accessed Apr. 4, 2014].

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. Toxicological Profile for Cresols. U.S. Department of Health and Human Services. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp34.pdf [accessed Apr. 4, 2014].

Baelum, J., I. Andersen, G.R. Lundqvist, L. Mohave, O.F. Pedersen, M. Vaeth, and D.P. Wyon. 1985. Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work Environ. Health 11(4):271-280.

Baelum, J., M. Dossing, S.H. Hansen, G.R. Lundqvist, and N.T. Andersen. 1987. Toluene metabolism during exposure to varying concentrations combined with exercise. Int. Arch. Occup. Environ. Health 59(3):281-294.

Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72.

Bass, M. 1970. Sudden sniffing death. J. Am. Med. Assoc. 212(2):2075-2079.

Batlle, D.C., S. Sabatini, and N.A. Kurtzman. 1988. On the mechanism of toluene-induced renal tubular acidosis. Nephron 49(3):210-218.

Bauchinger, M., E. Schmid, J. Dresp, J. Kolin-Gerresheim, R. Hauf, and E. Suhr. 1982. Chromosome change in lymphocytes after occupational exposure to toluene. Mutat. Res. 102(4):439-445.

Benignus, V.A. 1981. Health effects of toluene: A review. Neurotoxicology 2(3):567-588.

Benignus, V.A., K.E. Muller, C.N. Barton, and J.A. Bittikofer. 1981. Toluene levels in blood and brain of rats during and after respiratory exposure. Toxicol. Appl. Pharmacol. 61(3):326-334.

Benignus, V.A., K.E. Muller, J.A. Graham, and C.N. Barton. 1984. Toluene levels in blood and brain of rats as a function of toluene level in inspired air. Environ. Res. 33(1):39-46.

Benignus, V.A., W.K. Boyes, and P.J. Bushnell. 1998. A dosimetric analysis of behavioral effects of acute toluene exposure in rats and humans. Toxicol. Sci. 43(2):186-195.

Benignus, V.A., T. Coleman, C.R. Eklund, and E.M. Kenyon. 2006. A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol. Mech. Methods 16(1):27-36.

Benignus, V.A., W.K. Boyes, E.M. Kenyon, and P.J. Bushnell. 2007. Quantitative comparison of the acute neurotoxicity of toluene in rats and humans. Toxicol. Sci. 100(1):146-155.

Benignus, V.A., P.J. Bushnell, W.K. Boyes, C. Eklund, and E.M. Kenyon. 2009. Neurobehavioral effects of acute exposure to four solvents: Meta-analyses. Toxicol. Sci. 109(2):296-305.

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2011. Estimated rate of fatal automobile accidents attributable to acute solvent exposure at low inhaled concentrations. Risk Anal. 31(12):1935-1948.

Benoit, F.M., W.R. Davidson, A.M. Lovett, S. Nacson, and A. Nago. 1985. Breath analysis by API/MS human exposure to volatile organic solvents. Int. Arch. Occup. Environ. Health 55(2):113-120.

Bessems, J., J. Lammers, G. Schaafsma, T. Bouwman, L. Ravensberg, and A. Friedig. 2004. Impact of Peak Exposure and Biological Variability on the Kinetics of Toluene in Man - a PBTK Analysis. Poster Presented at the Society of Toxicology Meeting, March 25, 2004, Baltimore, MD.

Billings, C.E., and L.C. Jonas. 1981. Odor thresholds in air as compared to threshold limit values. Am. Ind. Hyg. J. 42(6):479-480.

Boey, K.W., S.C. Foo, and J. Jeyaratnam. 1997. Effects of occupational exposure to toluene: A neuropsychological study on workers in Singapore. Ann. Acad. Med. Singapore 26(2):184-187.

Bonnet, P., G. Raoult, and D. Gradiski. 1979. Concentration lethales 50 des principaux hydrocarbures aromatiques. Arch. Mal. Prof. Med. Trav. Secur. Soc. 40:805-810 (as cited in ACGIH 2005).

Boor, J.W., and H.I. Hurtig. 1977. Persistent cerebellar ataxia after exposure to toluene. Ann. Neurol. 2(5):440-442.

Bos, R.P., R.M. Brouns, R. Van Doorn, J.L.G. Theuws, and P.T. Henderson. 1981. Nonmutagenicity of toluene, o-, m-, and p-xylene, o-methylbenzyl alcohol and o-methylbenzyl sulfate in the Ames assay. Mutat. Res. 88(3):273-279.

Bowen, S.E., and R.L. Balster. 1998. A direct comparison of inhalant effects on locomotor activity and schedule-controlled behavior in mice. Exp. Clin. Psychopharmacol. 6(3):235-247.

Brown, R.P., M.D. Delp, S.L. Lindstedt, L.R. Rhomberg, and R.P. Beliles. 1997. Physiological parameter values for physiologically based pharmacokinetic models. Toxicol. Ind. Health 13(4):407-484.

Bruckner, J.V., and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol. Appl. Pharmacol. 61(1):27-38.

Bruckner, J.V., and R.G. Peterson. 1981b. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61(3):302-312.

Bruckner, J.V., and D.A. Warren. 2001. Toxic effects of solvents and vapors. Pp. 891-892 in Casarett & Doull's Toxicology: The Basic Science of Poisons, 6th Ed, C.D. Klaassen, ed. New York: McGraw-Hill.

Bruckner, J.V., D.A. Keys, and J.W. Fisher. 2004. The Acute Exposure Guideline Level (AEGL) program: Applications of physiologically based pharmacokinetic modeling. J. Toxicol. Environ. Health A 67(8-10):621-634.

Brugnone, F. 1985. Uptake of solvents from the lungs. Br. J. Ind. Med. 42(8):569.

Brugnone, F., L. Perbellini, P. Apostoli, M. Locatelli, and P. Mariotto. 1983. Decline of blood and alveolar toluene concentration following two accidental human poisonings. Int. Arch. Occup. Environ. Health 53(2):157-165.

Brugnone, F., E. De Rosa, L. Perbellini, and G.B. Bartolucci. 1986. Toluene concentrations in the blood and alveolar air of workers during the workshift and the morning after. Br. J. Ind. Med. 43(1):56-61.

Bushnell, P.J., H.L. Evans, and E.D. Palmes. 1985. Effects of toluene inhalation on carbon dioxide production and locomotor activity in mice. Fundam. Appl. Toxicol. 5(5):971-977.

Bushnell, P.J., K.L. Kelly, and K.M. Crofton. 1994. Effects of toluene inhalation on detection of auditory signals in rats. Neurotoxicol. Teratol. 16(2):149-160.

Bushnell, P.J., W.M. Oshiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A Dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.

Bushnell, P.J., J. W.M. Oshiro, T.E. Samsam, and R. Klinger. 2007b. The role of physical activity and feeding schedule on the kinetics of inhaled and oral toluene in rats. J. Toxicol. Environ. Health A 70(21):1806-1814.

Cameron, G.R., J.H. Paterson, G.W. de Saram, and J.C. Thomas. 1938. The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal tar. J. Pathol. Bacteriol. 46(1):95-107.

Carder, J.R., and R.S. Fuerst. 1997. Myocardial infarction after toluene inhalation. Pediatr. Emerg. Care 13(2):117-119.

Carlsson, A. 1982. Exposure to toluene: Uptake, distribution and elimination in man. Scand. J. Work Environ. Health 8(1):43-55.

Carlsson, A., and T. Lindqvist. 1977. Exposure of animals and man to toluene. Scand. J. Work Environ. Health 3(3):135-143.

Carpenter, A.V., W.D. Flanders , E.L. Frome, W.G. Tankersley, and S.A. Fry. 1988. Chemical exposures and central nervous system cancers: A case-control study among workers at two nuclear facilities. Am. J. Ind. Med. 13(3):351-362.

Carpenter, C.P., C.B. Schaffer, C.S. Weil, and H.F. Smyth. 1944. Studies on the inhalation of 1,3-butadiene with a comparison of its narcotic effect with benzol, toluol, and styrene and a note on the elimination of styrene by the human. J. Ind. Hyg. Toxicol. 26(3):69-78.

Carpenter, C.P., D.L. Geary, R.C. Myers, D.J. Nachreiner, L.J. Sullivan, and J.M. King. 1976. Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. Toxicol. Appl. Pharmacol. 36(3):473-490.

Chan, M.T., P. Mainland, and T. Gin. 1996. Minimum alveolar concentration of halothane and enflurane are decreased in early pregnancy. Anesthesiology 85(4):782-786.

Chemical Week. 2000. Toluene. Chemical Week, P. 33. March 1, 2000.

Cherry, N., J.D. Johnston, H. Venables, H.A. Waldron, L. Buck, and C.J. MacKay. 1983. The effects of toluene and alcohol on psychomotor performance. Ergonomics 26(11):1081-1087.

CIR (Cosmetic Ingredient Review). 1987. Final report on the safety assessment of toluene. Int. J. Toxicol. 6(1):77-120.

Cohr, K.J., and J. Stockholm. 1979. Toluene: A toxicological review. Scand. J. Work Environ. Health 5(2):71-90.

Cometto-Muniz, J.E., and W.S. Cain. 1995. Relative sensitivity of the ocular trigeminal, nasal trigeminal and olfactory systems to airborne chemicals. Chem. Senses 20(2):191-198.

Courtney, K., J. Andrews, J. Springer, M. Memnache, T. Williams, L. Dalley, and J. Graham. 1986. A perinatal study of toluene in CD-1 mice. Fundam. Appl. Toxicol. 6(1):145-154.

Cunningham, S.R., G.W. Dalzell, P. McGirr, and M.M. Khan. 1987. Myocardial infarction and primary ventricular fibrillation after glue sniffing. Br. Med. J. 294(6574):739-740.

Dalgaard, M., A. Hossaini, K.S. Hougaard, U. Hass, and O. Ladefoged. 2001. Developmental toxicity of toluene in male rats: Effects on semen quality, testis morphology, and apoptotic neurodegeneration. Arch. Toxicol. 75(2):103-109.

De Ceaurriz, J.C., J.C. Micillino, P. Bonnet, and J.P. Guenier. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9(2):137-143.

De Ceaurriz Jr., J., J.P. Desiles, P. Bonnet, B. Marignac, J. Muller, and J.P. Guenier. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol. Appl. Pharmacol. 67(3):383-389.

DeJongh, J., and B. J. Blaauboer. 1996. Simulation of toluene kinetics in the rat by a physiologically based pharmacokinetic model with application of biotransformation parameters derived independently in vitro and in vivo. Fundam. Appl. Toxicol. 32(2):260-268.

Dennison, J.E., C.M. Troxel, and R. Benson. 2010. PBPK modeling white paper: Addressing the use of PBPK models to support derivation of acute exposure guideline levels. Pp. 381-446 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

Deschamps, D., C. Geraud, and S. Dally. 2001. Cognitive functions in workers exposed to toluene: Evaluation at least 48 hours after removal from exposure. Int. Arch. Occup. Environ. Health 74(4):285-288.

DFG (Deutsche Forschungsgemeinschaft). 1999. List of MAK and BAT Values, 1999. Maximum Concentarations and Biological Tolerance Value at the Workplace Report No. 35. Weinheim, Federal Republic of Germany: Wiley-VCH.

Dick, R.B., J.V. Setzer, R. Wait, M.B. Hayden, B.J. Taylor, B. Tolos, and V. Putz-Anderson. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health 54(2):91-109.

Dobrokhotov, V.B. 1972. Mutagenic effect of benzene and toluene under experimental conditions [in Russian]. Gig. Sanit. 37(10):36-39.

Dobrokhotov, V.B., and M.I. Enikeev. 1975. The mutagenic effect of benzene, toluene, and a mixture of these hydrocarbons in a chronic experiment [in Russian]. Gig. Sanit. 1:32-34.

Donald, J.M., K. Hooper, and C. Hopenhayn-Rich. 1991. Reproductive and developmental toxicity of toluene: A review. Environ. Health Perspect. 94:237-244.

Dossing, M, J. Baelum, S.H. Hansen, and G.R. Lundqvist. 1984. Effect of ethanol, crimetidine and propranolol on toluene metabolism in man. Int. Arch. Occup. Environ. Health 54(4):309-315.

DuPont (E.I. du Pont de Nemours and Company). 1966. Acute Inhalation Toxicity: Toluene. Haskell Laboratory Report 4427. EPA Document No. 878220472. Microfiche No. OTS0215044.

Echeverria, D., L. Fine, G. Langolf, A. Schork, and C. Sampaio. 1989. Acute neurobehavioral effects of toluene. Br. J. Ind. Med. 46(7):483-495.

Echeverria, D., L. Fine, G. Langolf, T. Schork, and C. Sampaio. 1991. Acute behavioral comparisons of toluene and ethanol in human subjects. Br. J. Ind. Med. 48(11):750-761.

Eller, N., B. Netterstrom, and P. Laursen. 1999. Risk of chronic effects on the central nervous system at low toluene exposure. Occup. Med. 49(6):389-395.

EPA (U.S. Environmental Protection Agency). 1990. Drinking Water Criteria Document for Toluene. Environmental Criteria and Assessment, Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Cincinnati, OH. July 1990.

EPA (U.S. Environmental Protection Agency). 2007. Toluene. Integrated Risk Information System. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/iris/subst/0118.htm [accessed Apr. 5, 2014].

Evans, E.L., and A.D. Mitchell. 1980. An Evaluation of the Effect of Toluene on Sister Chromatid Exchange Frequencies in Cultured Chinese Hamster Ovary Cells. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Fischman, C.M., and J.R. Oster. 1979. Toxic effect of toluene: A new cause of high anion gap metabolic acidosis. J. Am. Med. Assoc. 241(16):1713-1715.

Fiserova-Bergerova, V., and M.L. Diaz. 1986. Determination and prediction of tissue-gas partition coefficients. Int. Arch. Occup. Environ. Health 58(1):75-87.

Florin, I., L. Rutberg, M. Curvall, and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15(3):219-232.

Fluck, E.R., L.A. Poirier, and H.W. Ruelius. 1976. Evaluation of a DNA polymeraedeficient mutant of E. coli for the rapid detection of carcinogens. Chem. Biol. Interact. 15(3):219-231.

Foo, S.C., W.O. Phoon, and N.Y. Khoo. 1988. Toluene in blood after exposure to toluene. Am. Ind. Hyg. Assoc. J. 49(5):255-258.

Foo, S.C., J. Jeyarathnam, and D. Koh. 1990. Chronic neurobehavioral effects of toluene. Br. J. Ind. Med. 47(7):480-484.

Forni, A., E. Pacifico, and A. Limonta. 1971. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health 22(3):373-378.

Gad-El-Karim, M.M., B.L. Harper, and M.S. Legator. 1984. Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3-methylcholanthrene, Aroclor 1254 and SKF-252A. Mutat. Res. 135(3):225-243.

Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health 9(3):131-139.

Garcia, H.D. 2008. Toluene. Pp. 329-347 in Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 5. Washington, DC: The National Academies Press.

Gargas, M.L., R.J. Burgess, D.E. Voisard, G.H. Cason, and M.E. Andersen. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

Geller, I., R. Hartmann, S. Randle, and E.M. Gause. 1979. Effects of acetone and toluene vapors on multiple schedule performance of rats. Pharmacol. Biochem. Behav. 11(4):395-399.

Gerasimov, M.R., R.A. Ferrieri, W.K. Schiffer, J. Logan, S.J. Gatley, A.N. Gifford, D.A. Alexoff, D.A. Marsteller, C. Shea, V. Garza, P. Carter, P. King, C.R. Ashby, Jr., S. Vitkun, and S.L. Dewey. 2002. Study of brain uptake and biodistribution of [^{11}C]toluene in non-human primates and mice. Life Sci. 70(23):2811-2828.

Gericke, C., B. Henke, G. Beckmann, M.M. Baltes, K.P. Kuhl, and D. Neubert. 2001. Multicenter field trial on possible health effects of toluene. III. Evaluation of effects after long-term exposure. Toxicology 168(2):185-209.

Gerner-Smidt, P., and U. Friedrich. 1978. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 58(2-3):313-316.

Gibson, J.E., and J.F. Hardisty. 1983. Chronic toxicity and oncogenicity bioassay of inhaled toluene in Fischer-344 rats. Fundam. Appl. Toxicol. 3(4):315-319.

Glowa, J. 1981. Some effects of sub-acute exposure to toluene on schedule-controlled behavior. Neurobehav. Toxicol. Teratol. 3(4):463-465.

Glowa, J.R., J. DeWeese, M.E. Natole, J.J. Holland, and P.B. Dews. 1986. Behavioral toxicology of volatile organic solvents. I. Methods: acute effects of toluene. J. Environ. Pathol. Toxicol. Oncol. 6(5-6):153-158.

Gospe, S.M., and M.A.S. Al-Bayati. 1994. Comparison of oral and inhalation exposure to toluene. J. Am. Coll. Toxicol. 13(1):21-32.

Gospe, S.M., and M.J. Calaban. 1988. Central nervous system distribution of inhaled toluene. Fundam. Appl. Toxicol. 11(3):540-545.

Greenberg, L., M.R. Mayers, H. Heiman, and S. Moskowitz. 1942. The effects of exposure to toluene in industry. J. Am. Med. Assoc. 118(8):573-578.

Gregory, G.A., E.I. Eger, and E.S. Munson. 1969. The relationship between age and halomethane requirements in man. Anesthesiology 30(5):488-491.

Gupta, R.K., J. van der Meulen, and K.V. Johny. 1991. Oliguric acute renal failure due to glue-sniffing. Scand. J Urol. Nephrol. 25(3):247-250.

Haddad, S.R. Tardif, G. Charest-Tardif, and K. Krishnan. 1999a. Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. Toxicol. Appl. Pharmacol. 161(3):249-257.

Hammer, K.D. 2002. Metabolite ratio of toluene-exposed rotogravure printing plant workers reflects individual mutagenic risk by sister chromatid exchanges. Mutat. Res. 519(1-2):171-177.

Harabuchi, I, R. Kishi, T. Ikeda, H. Kiyosawa, and H. Miyake. 1993. Circadian variations of acute toxicity and blood and brain concentrations of inhaled toluene in rats. Br. J. Ind Med. 50(3):280-286.

Hasegawa, K., S. Shiojima, A. Koizumi, and M. Ikeda. 1983. Hippuric acid and o-cresol in the urine of workers exposed to toluene. Int. Arch. Occup. Environ. Health. 52(3):197-208.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(suppl. 1):1-142.

Hellman, T.M., and F.H. Small. 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. J. Air Pollut. Control Assoc. 24(10):979-982.

Henderson, R. 2001. Aromatic hydrocarbons - benzene and other alkylbenzenes. Pp. 231-301 in Patty's Toxicology, Vol. 4, 5th Ed. New York: John Wiley & Sons.

Hinman, D. 1987. Biphasic dose-response relationship for effects of toluene inhalation on locomotor activity. Pharmacol. Biochem. Behav. 26(1):65-69.

Hjelm, E.W., P.H. Naslund, and M. Wallen. 1988. Influence of cigarette smoking on the toxicokinetics of toluene in humans. J. Toxicol. Environ. Health 25(2):155-163.

Hobara, T. M. Okuda, M. Gotoh, K. Oki, H. Segawa, and I. Kunitsugu. 2000. Estimation of the lethal toluene concentration from the accidental death of painting workers. Ind. Health 38(2):228-231.

Horvath, M., E. Frantik, and P. Krekule. 1981. Diazepam impairs alertness and potentiates the similar effect of toluene. Homeostasis 23:177-179.

Hougaard, K.S., A.M. Hansen, U. Hass, and S.P. Lund. 2003. Toluene depresses plasma corticosterone in pregnant rats. Pharmacol. Toxicol. 92(3):148-152.

Hudak, A., and G. Ungvary. 1978. Embryotoxic effects of benzene and its methyl derivatives: Toluene, xylene. Toxicology 11(1):55-63.

IARC (International Agency for Research on Cancer). 1989. Toluene. Pp. 79-123 in Some Organic Solvents, Resin Monomers, and Related Compounds, Pigments, and

Occupational Exposures in Paint Manufacture and Painting. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 47. Lyon, France: IARC Press [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol47/mono47.pdf [accessed Apr. 4, 2014].

IARC (International Agency for Research on Cancer). 1999. Toluene. Pp. 829-864 in Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol. 71(Part 2). Lyon France: IARC Press [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol71/mono71.pdf [accessed Apr. 4, 2014].

Ikeda, M. 1974. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. Int. Arch. Arbeitsmed. 33(2):125-133.

Ikeda, N., H. Takahashi, K. Umetsu, and T. Suzuki. 1990. The course of respiration and circulation in "toluene-sniffing". Forensic Sci. Int. 44(2-3):151-158.

Iregren, A. 1982. Effects on psychological test performance of workers exposed to a single solvent (toluene) - A comparison with effects of exposure to a mixture of organic solvents. Neurobehav. Toxicol. Terat. 4(6):695-701.

Iregren, A., T. Akerstedt, B.A. Olsen, and F. Gamberale. 1986. Experimental exposure to toluene in combination with ethanol intake. Scand. J. Work Environ. Health 12(2):128-136.

Jenkins, L.J., R.A. Jones, and J. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16(3):818-823.

Johnson, A.C., and B. Canlon. 1994. Progressive hair cell loss induced by toluene exposure. Hear. Res. 75(1-2):201-208.

Jone, C.M., A.H. Wu. 1988. An unusual case of toluene-induced metabolic acidosis. Clin. Chem. 34(12):2596-2599.

Jonsson, F., F. Bois, and G. Johanson. 2001. Physiologically based pharmacokinetic modeling of inhalation exposure of humans to dichloromethane during moderate to heavy exercise. Toxicol. Sci. 59(2):209-218.

Juntunen, J., E. Matikainen, M. Antti-Poika, H. Suoranta, and M. Valle. 1985. Nervous system effects of long-term occupational exposure to toluene. Acta Neurol. Scand. 72(5):512-517.

Kamijima, M., Y. Nakazawa, M. Yamakawa, E. Shibata, N. Hisanaga, Y. Ono, M. Toida, and Y. Takeuchi. 1994. Metabolic acidosis and renal tubular injury due to pure toluene inhalation. Arch. Environ. Health 49(5):410-413.

Katoh, T., and K. Ikeda. 1992. Minimum alveolar concentration of seroflurane in children. Br. J. Anaesth. 68(2):139-141.

Kenyon, E.M., V. Benignus, C. Eklund, J.W. Highfill, W.M. Oshiro, T.E. Samsam, and P.J. Bushnell. 2008. Modeling the toxicokinetics of inhaled toluene in rats: Influence of physical activity and feeding status. J. Toxicol. Environ. Health A 71(4):249-265.

Kezic, S., A.C. Monster, J. Kruse, and M.M. Ververk. 2000. Skin absorption of some vaporous solvents in volunteers. Int. Arch. Occup. Environ. Health 73(6):415-422.

King, M.D., R.E. Day, J.S. Oliver, M. Lush, and J.M. Watson. 1981. Solvent encephalopathy. Br. Med. J. 283(6292):663-665.

Kirkhart, B. 1980. Micronucleus Test on Toluene. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Kishi, R., I. Harabuchi, T. Ikeda, H. Yokota, and H. Miyake. 1988. Neurobehavioral effects and pharmacokinetics of toluene in rats and their relevance to man. Br. J. Ind. Med. 45(6):396-408.

Klimisch, H.J., J. Hellwig, and A. Hoffman. 1992. Studies on the prenatal toxicity of toluene in rabbits following inhalation exposure and proposal of a pregnancy guidance value. Arch. Toxicol. 66(6):373-381.

Kobayashi, K. 1985. Experimental studies on acute toluene poisoning. Shikoku Acta Med. 41:82-94.

Kobayashi, H., T. Hobara, and T. Sakai. 1989. Effects of inhalation of several organic solvents on left ventricular dp/dt [in Japanese]. Sangyo Igaku 31(3):136-141.

Kojima, T., and H. Kobayashi. 1973. Toxicological study on toluene poisoning by inhalation - correlation of toluene concentration for exposure with mortality and toluene tissue level. Nippon Hoigaku Zasshi 27:282-296.

Korsak, Z., J. Sokal, and R. Swiercz. 1991. The toxic effects of combined exposure to toluene and m-xylene in animals. II. Blood toluene and m-xylene during single and combined exposure in rats. Pol. J. Occup. Med. Environ. Health 4(4):377-382.

Krewski, D., K. Bakshi, R. Garrett, E. Falke, G. Rusch, and D. Gaylor. 2004. Development of acute exposure guideline levels for airborne exposures to hazardous substances. Regul. Toxicol. Pharmacol. 39(2):184-201.

Kroeger, R.M., R.J. Moore, T.H. Lehman, J.D. Giesy, and C.E. Skeeters. 1980. Recurrent urinary calculi associated with toluene sniffing. J. Urol. 123(1):89-91.

Lammers, J.H., W.J. Meuling, H. Muijser, A.P. Freid, and J.G. Bessems. 2005a. Neurobehavioral evaluation and kinetics of inhalation of constant or fluctuating toluene concentrations in human volunteers. Environ. Toxicol. Pharmacol. 20(3):431-442.

Lammers, J.H., J. van Asperen, D. de Groot, and W.R. Rijcken. 2005b. Behavioural effects and kinetics in brain in response to inhalation of constant or fluctuating toluene concentration in the rat. Environ. Toxicol. Pharmacol. 19(3):625-634.

LBI (Litton Bionetics, Inc). 1978. Mutagenicity Evaluation of Toluene. Final Report. LBI Project No. 20847. Washington, DC: American Petroleum Institute.

LBI (Litton Bionetics, Inc). 1981. Mutagenicity Evaluation of Toluene-Mouse Dominant Lethal Assay. Final Report. LBI Project No. 20847. Washington, DC: American Petroleum Institute.

LeDez, K.M., and J. Lerman. 1987. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 67(3):301-307.

Lee, B.K., S.H. Lee, K.M. Lee, K.S. Cho, K.D. Ahn, S.B. Kim, H. Ukai, H. Nakatsuka, T. Watanabe, and M. Ikeda. 1988. Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. Ind. Health 26(1):11-23.

Lerman, J., S. Robinson, M.M. Willis, and G.A. Gregory. 1983. Anesthetic requirements for halothane in young children 0-1 months and 1-6 months of age. Anesthesiology 59(5):421-424.

Liira, J., E. Elovaara, H. Raunio, V. Riihimaki, and K. Engstrom. 1991. Metabolic interaction and disposition of methyl ethyl ketone and m-xylene in rats at single and repeated inhalation exposures. Xenobiotica 21(1):53-63.

Litt, I.F., M.L. Cohen, S.K. Schonberg, and I. Spigland. 1972. Liver disease in the drug-using adolescent. J. Pediatr. 81(2):238-242.

Lof, A., M. Wallen, and E.W. Hjelm. 1990. Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. Pharmacol. Toxicol. 66(2):138-141.

Lof, A., E.W. Hjelm, A. Colmsjo, B.O. Lundmark, A. Norström, and A. Sato. 1993. Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to ^{2}H-toluene. Br. J. Ind. Med. 50(1):55-59.

Longley, E.O., A.T. Jones, R. Welch, R., and O. Lomaev. 1967. Two acute toluene episodes in merchant ships. Arch. Environ. Health 14(3):481-487.

Low, L.K., J.R. Meeks, and C.R. Mackerer. 1988. Health effects of the alkylbenzenes. I. Toluene. Toxicol. Ind. Health 4(1):49-75.

Luderer, U., M.S. Morgan, C.A. Brodkin, D.A. Kalman, and E.M. Faustman. 1999. Reproductive endocrine effects of acute exposure to toluene in men and women. Occup. Environ. Med. 56(10):657-666.

Lyapkalo, A.A. 1973. Genetic activity of benzene and toluene [in Russian]. Gig. Tr. Prof. Zabol. 17(3):24-28.

Magos, G.A., M. Lorenzana-Jimenez, and H. Vidrio. 1990. Toluene and benzene inhalation influences on ventricular arrhythmias in the rat. Neurotoxicol. Teratol. 12(2):119-124.

Maki-Paakkanen, J. K. Husgafvel-Pursiainen, P.L. Kalliomaki, J. Tuominen, and M. Sorsa. 1980. Toluene-exposed workers and chromosome aberrations. J. Toxicol. Environ. Health 6(4):775-781.

Marjot, R., and A.A. McLeod. 1989. Chronic non-neurological toxicity from volatile substance abuse. Hum. Toxicol. 8(4):301-306.

Massengale, O.N., H.H. Glaser, R.E. LeLievre, J.B. Dobbs, and M.E. Klock. 1963. Physical and psychologic factors in glue sniffing. N. Engl. J. Med. 269:1340-1344.

McCarroll, N.E., B.H. Keech, and C.E. Piper. 1981a. A microsuspension adaptation of the Bacillus subtilis "rec" assay. Environ. Mutagen. 3(6):607-616.

McCarroll, N.E., C.E. Piper, and B.H Keech. 1981b. An E coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ. Mutagen. 3(4):429-444.

McGregor, D.B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Riach, and W.J. Caspary. 1988. Responses of the L5178Ytk^{+}/tk^{-} mouse lymphoma cell forward mutation assay. III. 72 coded chemicals. Environ. Mole. Mutagen. 12(1):85-154.

Mergler, D., and B. Beauvais. 1992. Olfactory threshold shift following controlled 7-hour exposure to toluene and/or xylene. Neurotoxicology 13(1):211-215.

Meulenbelt, J., G. de Groot, and T.J. Savelkoul. 1990. Two cases of acute toluene intoxication. Br. J. Ind. Med. 47(6):417-420.

Miyagawa, M., T. Honma, M. Sato, and H. Hasegawa. 1984. Effects of a single exposure to toluene on operant behavior and brain toluene levels in rats. Ind. Health 22(2):127-131.

Miyagawa, M., T. Honma, M. Sato, and H. Hasegawa. 1986. Behavioral change after single exposure to toluene, and brain toluene levels in rats. Ind. Health 24(3):157-161.

Morata, T.C., A.C. Fiorini, F.M. Fischer, S. Colacioppo, K.M. Wallingford, E.F. Krieg, D.E. Dunn, L. Gozzoli, M.A. Padrão, and C.L. Cesar. 1997. Toluene-induced hearing loss among rotogravure printing workers. Scand. J Work Environ. Health 23(4):289-298.

Mortelmans, K.E., and E.S. Riccio. 1980. In vitro Microbiological Genotoxicity Assays of Toluene. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Moser, V.C., and R.L. Balster. 1981. The effects of acute and repeated toluene exposure on operant behavior in mice. Neurobehav. Toxicol. Teratol. 3(4):471-475.

Moser, V.C., and R.L. Balster. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol. Appl. Pharmacol. 77(2):285-291.

Moss, A.H., P.A. Gabow, W.D. Kaehny, W.D. Goodman, L.L. Haut, and M.R. Hassler. 1980. Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. Ann. Intern. Med. 92(1):69-70.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Tolueen. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Apt 5, 2014].

Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.

Murata, K., S. Araki, K. Yokoyama, T. Tanigawa, K. Yamashita, F. Okajima, T. Sakai, C. Matsungag, and K. Suwa. 1993. Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction. Ind. Health 31(3):79-90.

Muttray, A., U. Spelmeyer, G. Hommel, F. Oesch, D. Jung, D.M. Rose, O. Mayer-Popken, B. Rossbach, and S. Letzel. 2005. Acute exposure to 50 ppm toluene does not increase sleepiness. Environ. Toxicol. Pharmacol. 19(3):665-669.

Nadeau, V., G. Truchon, M. Brochu, and R. Tardif. 2006. Effect of physical exertion on the biological monitoring of exposure of various solvents following exposure by inhalation in human volunteers: I. Toluene. J. Occup. Environ. Hyg. 3(9):481-489.

Nakajima, T., R.S. Wang, Y. Katakura, R. Kishi, E. Elovaara, S.S. Park, H.V. Gelboin, and H. Vainio. 1992. Sex-, age-, and pregnancy-induced changes in the metabolism of toluene and trichloroethylene in rat liver in relation to the regulation of cytochrome P45011E1 and P45011C11 content. J. Pharmacol. Exp. Ther. 261(3):869-874.

Nakajima, T., R.S. Wang, E. Elovaara, F.J. Gonzalez, H.V. Gelboin, H. Raunio, O. Pelkonen, H. Vainio, and T. Aoyama. 1997. Toluene metabolism by cDNA-expressed human hepatic cytochrome P450. Biochem. Pharmacol. 53(3):271-277.

Nestmann, E.R., E.G.H. Lee, T.I. Matula, G.R. Douglas, and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79(3):203-212.

Neubert, D., C. Gericke, B. Hanke, G. Beckmann, M.M. Baltes, K.P. Kuhl, G. Bochert, and J. Hartmann. 2001a. Multicenter field trial on possible health effects of toluene. II. Cross-sectional evaluation of acute low-level exposure. Toxicology 168(2):159-183.

Neubert, D., G. Bochert, C. Gericke, B. Hanke, and G. Beckmann. 2001b. Multicenter field trial on possible health effects of toluene. I. Toluene body burdens in workers of the rotogravure industry. Toxicology 168(2):139-157.

Ng, T., S. Foo, and T. Yoong. 1992. Menstrual function in workers exposed to toluene. Br. J. Ind. Med. 49(11):799-803.

Nielsen, G.D., and Y. Alarie. 1982. Sensory irritation, pulmonary irritation and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodyamic properties. Toxicol. Appl. Pharmacol. 65(3):457-477.

Nielsen, H.K., L. Krusell, J. Baelum, G. Lundqvist, O. Omland, M. Vaeth, M., S.E. Husted, C.E. Mogensen, and E. Geday. 1985. Renal effects of acute exposure to toluene: A controlled clinical trial. Acta Med. Scand. 218(3):317-321.

NIOSH (National Institute for Occupational Safety and Health). 1973. Criteria for a Recommended Standard... Occupational Exposure to Toluene. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/docs/1970/73-11023.html [accessed Apr. 4, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1985. FACE Report: Confined Space Incident Kills Two Workers Company Employee and Rescuing Fireman. Report No. FACE-85-5. U.S. Department of Health and Hyman Services,

Morgantown, WV [online]. Available: http://www.cdc.gov/niosh/fire/reports/face8505.html [accessed Apr. 4, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs): Toluene. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/108883.html [accessed Apr. 7, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Toluene. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0619.html [accessed Apr. 4, 2014].

Nomiyama, K., and H. Nomiyama. 1978. Three fatal cases of thinner-sniffing and experimental exposure to toluene in humans and animals. Int. Arch. Occup. Environ. Health 41(1):55-64.

NRC (National Research Council). 1981. The Alkyl Benzenes. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2008. Toluene. Pp. 230-275 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NTP (National Toxicology Program). 1990. Toxicology and Carcinogenesis Studies of Toluene. (CAS No. 108-88-3) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). NTP-TR-371. NIH 90-2826. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC [online]. Available: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr371.pdf [accessed Apr. 4, 2014].

O'Brien, E.T., W.B. Yeoman, and J.A.E. Hobby. 1971. Hepatorenal damage from toluene in a "glue sniffer." Br. Med. J. 2(5752):29-30.

Ogata, M. 1984. Estimation of solvent concentrations in ambient air from urinary metaboliste levels of workers expsed to solvents. Ind. Health 22(4):319-324.

Ogata, M., K. Tomokuni, and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and m- and p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- and p-xylene as a test of exposure. Br. J. Ind. Med. 27(1):43-50.

Olson, B.A., F. Gamberale, and A. Iregren. 1985. Coexposure to toluene and p-xylene in man: Central nervous functions. Br. J. Ind. Med. 42(2):117-122.

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2006. Toluene. P.1638 inThe Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th ed. Whitehouse Station, NJ: Merck.

Ono, A., K. Sekita, K. Ohno, A. Hirose, Y. Ogawa, M. Saito, K. Naito, T. Kaneko, T. Furuya, K. Matsumoto, S. Tanaka, and Y. Kurokawa. 1995. Reproductive and developmental toxicity studies of toluene. I. Teratogenicity study of inhalation exposure in pregnant rats. J. Toxicol. Sci. 20(2):109-134.

Ono, A., K. Sekita, Y. Ogawa, A. Hirose, S. Suzuki, M. Saito, K. Naito, T. Kaneko, T. Furuya, K. Kawashima, K. Yasuhara, K. Matsumoto, S. Tanaka, T. Inoue, and Y. Kurokawa. 1996. Reproductive and developmental toxicity studies of toluene. II.

Effects of inhalation exposure on fertility in rats. J. Environ. Path. Toxicol. Oncol. 15(1):9-20.

Oshiro, W.M., and P.J. Bushnell. 2004. Acute and repeated inhalation of toluene by rats performing a signal detection task leads to behavioral tolerance on some performance measures. The Toxicologist 98:296. (Poster presented at the Society of Toxicology, March 22, 2004, Baltimore, MD).

Oshiro, W.M., Q.T. Krantz, and P.J. Bushnell. 2007. Repeated inhalation of toluene by rats performing a signal detection task leads to behavioral tolerance on some performance measures. Neurotoxicol. Teratol. 29(2):247-254.

Ovrum, O., M. Hultengren, and T. Lindqvist. 1978. Exposure to toluene in a photogravure printing plant. Concentration in ambient air and uptake in the body. Scand. J. Work Environ. Health 4(3):237-245.

Ozokwelu, E.D. 1997. Toluene. Pp. 350-389 in Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 24, 4th Ed. New York: John Wiley & Sons.

Parmeggiani, L., and C. Sassi. 1954. Occupational hazards from toluene: Atmospheric investigation and clinic findings in chronic poisoning [in Italian]. Med Lav. 45(11):574-583.

Patel, R., and J. Benjamin. 1986. Renal disease associated with toluene inhalation. J. Toxicol. Clin. Toxicol. 24(3):213-223.

Paterson, D.C., and R. Sarvesvaran. 1983. Plastic bag death: A toluene fatality. Med. Sci. Law 23(1):64-66.

Pelekis, M., L.A. Gephart, and S.E. Lerman. 2001. Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. Regul. Toxicol. Pharmacol. 33(1):12-20.

Pierce, C.H., R.L. Dills, M.S. Morgan, G.L. Nothstein, D.D. Shen, and D.A. Kalman. 1996a. Interindividual differences in ^{2}H-toluene toxicokinetics assessed by a semiempirical physiologically based model. Toxicol. Appl. Pharmacol. 139(1):49-61.

Pierce, C.H., R.L. Dills, M.S. Morgan, P. Vicini, and D.A. Kalman. 1998. Biological monitoring of controlled toluene exposure. Int. Arch. Occup. Environ. Health 71(7):433-444.

Pierce, C.H., T.A. Lewandowski, R.L. Dills, M.S. Morgan, M.A. Wessels, D.D. Shen, and D.A. Kalman. 1999. A comparison of $^{1}H_8$ and $^{2}H_8$-toluene toxicokinetics in men. Xenobiotica 29(1):93-108.

Pierce, C.H., Y. Chen, R.L. Dills, D.A. Kalman, and M.S. Morgan. 2002. Toluene metabolites as biological indicators of exposure. Toxicol. Lett. 129(1-2):65-76.

Poon, R., I. Chu, S. Bjarnason, M. Potvin, R. Vincent, R.B. Miller, and V.E. Valli. 1994. Inhalation toxicity study of methanol, toluene, and methanol/toluene mixtures in rats: Effects of 28-day exposure. Toxicol. Indust. Health 10(3):231-245.

Press, E., and A.K. Done. 1967. Solvent sniffing: Physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents. I. Pediatrics 39(3):451-461.

Pryor, G.T., R.A. Howd, R. Malik, R., R.A. Jensen, and C.S. Rebert. 1978. Biomedical Studies on the Effects of Abused Inhalant Mixtures. Annual Progress Report prepared by SRI International (Contract No. 271-77-3402) for the National Institute on Drug Abuse, Rockville, MD (as cited in ACGIH 2005).

Pryor, G.T., J. Dickinson, E. Feeney, and C.S. Rebert. 1984. Hearing loss in rats first exposed to toluene as weanlings or as young adults. Neurobehav. Toxicol. Teratol. 6(2):111-119.

Purcell, K.J., G.H. Cason, M.L. Gargas, M.E. Andersen, and C.C. Travis. 1990. In vivo metabolic interactions of benzene and toluene. Toxicol. Lett. 52(2):141-152.

Rahill, A.A., B. Weiss, P.E. Morrow, M.W. Frampton, C. Cox, R. Gibb, R. Gelein, D. Speers, and M.J. Utell. 1996. Human performance during exposure to toluene. Aviat. Space Environ. Med. 67(7):640-647.

Reddy, M., R.S.H. Yang, H.J. Clewell, III, and M.E. Andersen. 2005. Physiologically Based Pharmacokinetics: Science and Applications. John Wiley & Sons. 420 pp.

Rees, D.C., R.W. Wood, J.P. McCormick, and C. Cox. 1985. Toxicokinetics of toluene in the rat. Scand. J. Work Environ. Health 11(4):301-306.

Reisin, E., A. Teicher, R. Jaffe, and H.E. Eliahou. 1975. Myoglobinuria and renal failure in toluene poisoning. Br. J. Ind. Med. 32(2):163-164.

Richer, C.L., S. Chakrabarti, M. Senecal-Quevillon, M.A. Duhr, X.X. Zhang, and R. Tardif. 1993. Cytogenic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. Int. Arch. Occup. Environ. Health 64(8):581-585.

Ron, M. 1986. Volatile substance abuse: A review of possible long-term neurological, intellectual and psychiatric sequelae. Br. J. Psychiatry 148:235-246.

Russ, G., A.R. Clarkson, A.J. Woodroffe, A.E. Seymour, and I.K. Cheng. 1981. Renal failure from "glue sniffing". Med. J. Aust. 2(3):121-122.

Ruth, J.H. 1986. Odor threshold and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Sato, A., and T. Nakajima. 1979a. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br. J. Ind. Med. 36(3):231-234.

Sato, A., and T. Nakajima. 1979b. Dose-dependent metabolic interaction between benzene and toluene in vivo and in vitro. Toxicol. Appl. Pharmacol. 48(2):249-256.

Schaper, M., P. Demes, M. Zupanic, M. Blaszkewicz, and A. Seeber. 2003. Occupational toluene exposure and auditory function: Results from a follow-up study. Ann. Occup. Hyg. 47(6):493-502.

Seeber, A., P. Demes, E. Kiesswetter, M. Schaper, C. van Thriel, and M. Zupanic. 2005. Changes of neurobehavioral and sensory functions due to toluene exposure below 50 ppm? Environ. Toxicol. Pharmacol. 19(3):635-643.

Shell Oil Company. 1982. Test Standardization Inhalation Toxicity Testing of 8 Chemicals According to the OECD Inhalation Hazard Test with Cover Letter. EPA Document No. 878212113, Microfiche No. OTS0205969.

Sherwood, R.J. 1976. Ostwald solubility coefficients of some industrially important substances. Br. J. Ind. Med. 33(2):106-107.

Shigeta, S., H. Aikawa, T. Misawa, and A. Kondo. 1978. Effect of single exposure to toluene on Sidman avoidance response in rats. J. Toxicol. Sci. 3(4):305-312.

Shigeta, S., H. Aikawa, and T. Misawa. 1981. Effects of toluene exposure during pregnancy on mice fetuses. J. Toxicol. Sci. 6:254-255.

Simmons, J.E., W.K. Boyes, P.J. Bushnell, J.H. Raymer, T. Limsakun, A. McDonald, Y.M. Sey, and M.V. Evans. 2002. A physiologically based pharmacokinetic model for trichloroethylene in the male long-evans rat. Toxicol. Sci. 69(1):3-15.

Sina, J.F., C.L. Bean, G.R. Dysar, V.I. Taylor, and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5):357-391.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel, and J.S. Nycum. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30(5):470-476.

Snow, L., P. MacNair, and B.C. Casto. 1981. Mutagenesis Testing of Toluene in Salmonella Strains TA100 and TA98. Prepared by Northrop Services, Inc., for U.S. Environmental Protection Agency, Research Triangle Park, NC.

Spanggord, R.J., K.E. Mortelmans, A.F. Griffin, and V.F. Simmon. 1982. Mutagenicity in *Salmonella typhimurium* and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. Environ. Mutagen. 4(2):163-179.

Stevens, W.C., W.M. Dolan, R.T. Gibbons, A. White, E.I. Eger, R. Miller, R.H. deJong, and R.M. Elashoff. 1975. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 42(2):197-200.

Stewart, R.D., C.L. Hake, H.V. Forster, A.J. Lebrun, J.E. Peterson, and A.Wu. 1975. Toluene: Development of a Biologic Standard for the Industrial Worker by Breath Analysis. NIOSH-00080663. PB-82154220. National Institute for Occupational Safety and Health, Cincinnati, OH.

Streicher, H.Z., P.A. Gabow, A.H. Moss,, D. Kono, and W.D. Kaehny. 1981. Syndromes of toluene sniffing in adults. Ann. Int. Med. 94(6):758-762.

Suzuki, H. 1973. Autonomic nervous responses to experimental toluene exposure in humans [in Japanese]. Sangyo Igaku 15:379-384.

Svensson, B.G., G. Nise, V. Englander, R. Attewell, S. Skerfving, and T. Moller. 1990. Deaths and tumours among rotogravure printers exposed to toluene. Br. J. Ind. Med. 47(6):372-379.

Svensson, B.G., G. Nise, E.M. Erfurth, A. Nilsson, and S. Skerfving. 1992. Hormone status in occupational toluene exposure. Am. J. Ind. Med. 22(1):99-107.

Svirbely, J.L., R.C. Dunn, and W.F. von Oettingen. 1943. The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J. Ind. Hyg. Toxicol. 25(8):366-373.

Taher, S.M., R.J. Anderson, R. McCartney, M. Popovtzer, and R.W. Schrier. 1974. Renal tubular acidosis associated with toluene sniffing. N. Engl. J. Med. 290:765-768.

Takeichi, S., T. Yamada, and I. Shikata. 1986. Acute toluene poisoning during painting. Forensic Sci. Int. 32(2):109-115.

Takeuchi, T., and N. Hisanaga. 1977. The neurotoxicity of toluene: EEG changes in rats exposed to various concentrations. Br. J. Ind. Med. 34(4):314-324.

Tanaka, K., T. Maeda, T. Kobayashi, M. Tanaka, and T. Fukushima. 2003. A survey of urinary hippuric acid and subjective symptoms among occupational low toluene exposed workers. Fukushima J. Med. Sci. 49(2):129-139.

Tardif, R., S. Lapare, G.L. Plaa, and J. Brodeur. 1991. Effect of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. Int. Arch. Occup. Health 63(4):279-284.

Tardif, R., G.L. Plaa, and J. Brodeur. 1992. Influence of various mixtures of inhaled toluene and xylene on the biological monitoring of exposure of these solvents in rats. Can. J. Physiol. Pharmacol. 70(3):385-393.

Tardif, R., S. Lapare, K. Krishnan, and J. Brodeur. 1993. Physiologically based modeling on the toxicokinetic interaction between toluene and m-xylene in the rat. Toxicol. Appl. Pharmacol. 120(2):266-273.

Tardif, R., S. Lapare, G. Charest-Tardif, J. Brodeur, and K. Krishnan. 1995. Physiologically-based pharmacokinetic modeling of a mixture of toluene and xylene in humans. Risk. Anal. 15(3):335-342.

Tardif, R., G. Charest-Tardif, J. Brodeur, and K. Krishnan. 1997. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicol. Appl. Pharmacol. 144(1):120-134.

Tardif, R., P.O. Droz, G. Charest-Tardif, G. Pierrehumbert, and G. Truchon. 2002. Impact of human variability on the biological monitoring of exposure to toluene: I. Physiologically based toxicokinetic modelling. Toxicol. Lett. 134(1-3):155-163.

Tatrai, E., K. Rodics, and G.Y. Ungvary. 1980. Embryotoxic effects of simultaneously applied exposure of benzene and toluene. Folia Morphol. (Praha) 28(3):286-289.

Taylor, J.D., and H.L. Evans. 1985. Effects of toluene inhalation on behavior and expired carbon dioxide in macaque monkeys. Toxicol. App. Pharmacol. 80(3):487-495.

Tegeris, J.S., and R.L. Balster. 1994. A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fundam. Appl. Toxicol. 22(2):240-250.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Thiel, R., and I. Chahoud. 1997. Postnatal development and behavior of Wistar rats after prenatal toluene exposure. Arch. Toxicol. 71:258-265.

Thrall, K.D., R.A. Gies, J. Muniz, A.D. Woodstock, and G. Higgins. 2002. Route-of-entry and brain tissue partition coefficients for common superfund contaminants. J. Toxicol. Environ. Health A 65(24):2075-2086.

Tice, R.R., T.F. Vogt, and D.L. Costa. 1982. Cytogenic effects of inhaled benzene in murine bone marrow. Environ. Sci. Res. 25:257-275.

Topham, J.C. 1980. Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? Mutat. Res. 74(5):379-387.

Ukai, H., T. Watanabe, H. Nakatsuka, T. Satoh, S.J. Liu, X. Qiao, Y. Hong, C. Jin, G.L. Li, and M. Ikeda. 1993. Dose-dependent increase in subjective symptoms among toluene-exposed workers. Environ. Res. 60(2):274-289.

Ungvary, G., and E. Tatrai. 1985. On the embryonic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. (Suppl) 8:425-430.

U.S. Air Force. 1989. Equilibrium partitioning calculations for toluene in model environments. Pp. 19-1 to 19-37 in The Air Force Installation Restoration Program Toxicology Guide, Vol. 2. Wright-Patterson Air Force Base, OH.

van Asperen, J., W.R. Pels Rijcken, V.J. Feron, and J.H.C.M. Lammers. 2002. Physiologically-Based Toxicokinetic Modelling of Peak Exposure Versus Constant Exposure to Toluene in the Rat. Poster Presented at the Society of Toxicology Meeting, March 17-21, 2002, Nashville, TN.

van Asperen, J., W.R. Rijcken, and J.H. Lammers. 2003. Application of physiologically based toxicokinetic modelling to study the impact of the exposure scenario on the toxicokinetics and the behavioural effects of toluene in rats. Toxicol. Lett. 138(1-2):51-62.

Veulemans, H., and R. Masschelein. 1978. Experimental human exposure to toluene. II. Toluene in venous blood during and after exposure. Int. Arch. Occup. Environ. Health 42(2):105-117.

Vicini, P., C.H. Pierce, R.L. Dills, M.S. Morgan and D.A. Kalman. 1999. Individual prior information in a physiological model of 2H8-toluene kinetics: An empirical Bayes estimation strategy. Risk. Anal. 19(6):1127-1134.

Vidrio, H., G.A. Magos, and M. Lorenzana-Jones. 1986. Electrocardiographic effects of toluene in the anesthetized rat. Arch. Int. Pharmacodyn. 279(1):121-129.

von Oettingen, W.F., P.A. Neal, and D.D. Donahue. 1942. The toxicity and potential dangers of toluene with special reference to its maximal permissible concentration. J. Am. Med. Assoc. 118(8):579-584.

Vrca, A., D. Bozicevic, V. Karacic, R. Fuchs, D. Prpic-Majic, and M. Malinar. 1995. Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch. Toxicol. 69(5):337-340.

Wada, H., T. Hosokawa, and K. Saito. 1989. Single toluene exposure and changes of response latency in shock avoidance performance. Neurotoxicol. Teratol. 11(3):265-272.

Waldron, H.A., N. Cherry, and J.D. Johnson. 1983. The effects of ethanol on blood toluene concentrations. Int. Arch. Occup. Environ. Health 51(4):365-369.

Wallen, M., S. Holm, and M. Nordqvist. 1985. Coexposure to toluene and p-xylene in man: Uptake and elimination. Br. J. Ind. Med. 42(2):111-116.

Wang, R.S., T. Nakajima, and S.S. Park. 1993. Monoclonal antibody-directed assessment of toluene induction of rat hepatic cytochrome P450 isozymes. Biochem. Pharmacol. 46(3):413-419.

Weisenberger, B.L. 1977. Toluene habituation. J. Occup. Med. 19(8):569-570.

Weiss, B., R.W. Wood, and D.A. Macys. 1979. Behavioral toxicology of carbon disulfide and toluene. Environ. Health Perspect. 30:39-45.

Weiss, G. 1980. Toluene. P. 870 in Hazardous Chemicals Data Book. Park Ridge NJ: Noyes Data Corporation.

WHO (World Health Organization). 1985. Toluene. Environmental Health Criteria 52. Geneva: World Health Organization [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc52.htm [accessed Apr. 5, 2014].

WHO (World Health Organization). 1987. Toluene. Pp. 137-147 in Air Quality Guidelines for Europe. WHO Regional Publications, European Series 21. Copenhagen, Denmark: World Health Organization.

Wilson, R.H. 1943. Toluene poisoning. J. Am. Med. Assoc. 123(17):1106-1109.

Winneke, G. 1982. Acute behavioral effects of exposure to some organic solvents - psychophysiological aspects. Acta Neurol. Scand. 92 (suppl.):117-129.

Wiseman, M.N., and S. Banim. 1987. "Glue sniffer's" heart? Br. Med. J 294(6574):739.

Wood, R., and C. Cox. 1995. A repeated measures approach to the detection of the acute behavioral effects of toluene at low concentrations. Fundam. Appl. Toxicol. 25(2):293-301.

Wood, R.W., D.C. Rees, and V.G. Laties. 1983. Behavioral effects of toluene are modulated by stimulus control. Toxicol. Appl. Pharmacol. 68(3):462-472.

Wood, R., J.B. Coleman, R. Schuler, and C. Cox. 1984. Anticonvulsant and antipunishment effects of toluene. J. Pharmacol. Exp. Ther. 230(2):407-412.

Yin, S., G. Li, Y. Hu, X. Zhang, C. Jin, O. Inoue, K. Seiji, M. Kasahara, H. Nakatsuka, and M. Ikeda. 1987. Symptoms and signs of workers exposed to benzene, toluene or the combination. Ind. Health 25(3):113-130.

Zavalic, M., Z. Mandic, R. Turk, A. Bogadi-Sare, and D. Plavec. 1998. Quantitative assessments of color vision impairment in workers exposed to toluene. Am. J. Ind. Med. 33(3):297-304.

APPENDIX A

DERIVATION OF AEGL VALUES FOR TOLUENE

Derivation of AEGL-1 Values

Key studies:

Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Scand. Work Environ. Health 9:119-130.

Baelum J., I. Andersen, G.R. Lundqvist, L. Mohave, O. F. Pedersen, M. Vaeth, and D.P. Wyon. 1985. Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work Environ. Health 11(4):271-280.

Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72.

Dick, R.B., J.V. Setzer, R. Wait, R., M.B. Hayden, B.J. Taylor, B. Tolos, and V. Putz-Anderson. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health 54(2):91-109.

Echeverria, D., L. Fine, G. Langolf, A. Schork, and C. Sampaio. 1989. Acute neurobehavioral effects of toluene. Br.. J Ind. Med. 46(7):483-495.

Echeverria, D., L. Fine, G. Langolf, T. Schork, and C. Sampaio. 1991. Acute behavioral comparisons of toluene and ethanol in human subjects. Br.. J. Ind. Med. 48(11):750-761.

Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health 9(3):131-139.

Nielsen, H.K., L. Krusell, J. Baelum, G. Lundqvist, G. O. Omland, M. Vaeth, M., S.E. Husted, C.E. Mogensen, and E. Geday. 1985. Renal effects of acute exposure to toluene. Acta Med. Scand. 218(3):317-321.

Ogata, M., K. Tomokuni, and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and m- and p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- and p-xylene as a test of exposure. Br. J. Ind. Med. 27(1):43-50.

Stewart, R.D., C.L. Hake, H.V. Forster, and A.J. Lebrun. 1975. Toluene: development of a biologic standard for the industrial worker by breath analysis. NIOSH-00080663; National Institute for OccupationalSafety and Health, Cincinnati, OH.

Toxicity end point:	200 ppm for short- and long-exposure durations; effects would not exceed the definition of an AEGL-1
Time scaling:	None applied; toluene rapidly approaches steady-state in the blood at low concentrations.
Uncertainty factors:	3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-1:	200 ppm ÷ 3 = 67 ppm
30 min AEGL-1:	200 ppm ÷ 3 = 67 ppm
1-h AEGL-1:	200 ppm ÷ 3 = 67 ppm
4-h AEGL-1:	200 ppm ÷ 3 = 67 ppm
8-h AEGL-1:	200 ppm ÷ 3 = 67 ppm

Derivation of AEGL-2 Values

Key studies:	Bushnell, P.J., W.M. Oshiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.
Toxicity end point:	No-observed-adverse-effect level of 1,600 ppm for 34 min based on doubling of reaction time in rats; concentration-related decrease in accuracy and increase in response time in a signal detection task with food reward.

Time scaling:	CNS effects observed after toluene exposure were assumed to be directly related to parent material reaching the brain. Therefore, a physiologically-based pharmacokinetic (PBPK) model for the rat (see Appendix C) was used to calculate the internal dose (BrTC) correlating with the exposure. A human PBPK model was then used determine the equivalent exposure concentration that would produce the target BrTC in humans at each AEGL duration.
Uncertainty factors:	1 for interspecies differences; PBPK modeling allows a comparison of the internal dose in both rats and humans from identical external exposures, and similar CNS effects were observed in rodents and humans. 3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-2:	1,400 ppm (based on results of PBPK model)
30-min AEGL-2:	760 ppm (based on results of PBPK model)
1-h AEGL-2:	560 ppm (based on results of PBPK model)
4-h AEGL-2:	310 ppm (based on results of PBPK model)
8-h AEGL-2:	250 ppm (based on results of PBPK model)

Derivation of AEGL-3 Values

Key study:	Mullin, L.S. and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.
Toxicity end point:	Threshold for lethality in rats of 6,250 ppm for 2 h
Time scaling:	CNS effects observed after toluene exposure were assumed to be directly related to parent material reaching the brain. Therefore, a PBPK model for the rat (see Appendix C) was used to calculate the internal dose (BrTC) correlating with the exposure. A human PBPK model was then used determine the equivalent exposure concentration that would produce the target BrTC in humans at each AEGL duration.

Uncertainty factors:	1 for interspecies differences; PBPK modeling allows a comparison of the internal dose in both rats and humans from identical external exposures, and similar CNS effects were observed in rodents and humans.
	3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-3:	10,000 ppm (based on results of PBPK model)
30-min AEGL-3:	5,200 ppm (based on results of PBPK model)
1-h AEGL-3:	3,700 ppm (based on results of PBPK model)
4-h AEGL-3:	1,800 ppm (based on results of PBPK model)
8-h AEGL-3:	1,400 ppm (based on results of PBPK model)

APPENDIX B

CATEGORY PLOT FOR TOLUENE

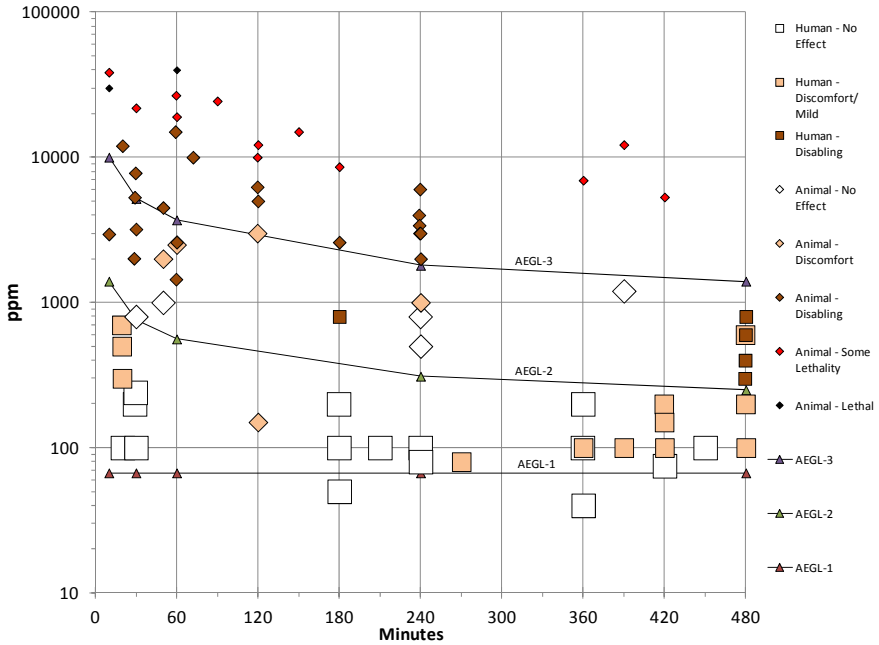


FIGURE B-1 Category plot of animal toxicity data and AEGL values for toluene.

TABLE B-1 Data Used in Category Plot for Toluene

Source	Species	ppm	Minutes	Category
AEGL-1		67	10	AEGL
AEGL-1		67	30	AEGL
AEGL-1		67	60	AEGL
AEGL-1		67	240	AEGL
AEGL-1		67	480	AEGL
AEGL-2		1,400	10	AEGL
AEGL-2		760	30	AEGL
AEGL-2		560	60	AEGL
AEGL-2		310	240	AEGL
AEGL-2		250	480	AEGL
AEGL-3		10,000	10	AEGL
AEGL-3		5,200	30	AEGL
AEGL-3		3,700	60	AEGL
AEGL-3		1,800	240	AEGL
AEGL-3		1,400	480	AEGL
Andersen et al. 1983	Human	40	360	0, no neurobehavioral effects
Andersen et al. 1983	Human	100	360	1, slight ocular and nasal irritation; no neurobehavioral effects
Cherry et al. 1983; Olson et al. 1985	Human	80	240	0, no neurobehavioral effects
Iregren et al. 1986	Human	80	270	1, subjective symptoms

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category
Winneke 1982	Human	100	210	0, no behavioral deficits in psychomotor tests
Dick et al. 1984	Human	100	240	0, no neurobehavioral deficits
Rahill et al. 1996	Human	100	360	0, slight latency, neurobehavioral tests
Baelum et al. 1985	Human	100	390	1, sensory irritation, sleepiness, behavioral deficits
Stewart et al. 1975	Human	100	450	0, no neurobehavioral deficits
Baelum et al. 1990	Human	100	420	1, sensory irritation
Echeverria et al. 1989	Human	75	420	0, no neurobehavioral effects
Echeverria et al. 1989	Human	150	420	1, ocular irritation, headache
Astrand et al. 1972	Human	100	30	0, no neurobehavioral effects
Astrand et al. 1972	Human	200	30	0, no neurobehavioral effects with exercise
Ogata et al. 1970	Human	100	180	0, no effects
Ogata et al. 1970	Human	200	180	0, no effects
von Oettingen et al. 1942	Human	100	480	1, moderate fatigue
von Oettingen et al. 1942	Human	300	480	2, increasing fatigue symptoms
von Oettingen et al. 1942	Human	400	480	2, increasing fatigue symptoms
von Oettingen et al. 1942	Human	600	480	2, increasing fatigue symptoms
von Oettingen et al. 1942	Human	800	180	2, incoordination
Gamberale and Hultengren 1972	Human	100	20	0, no effect on reaction time

Gamberale and Hultengren 1972	Human	300	20	0, increase in reaction time
Gamberale and Hultengren 1972	Human	500	20	0, increase in complex reaction time
Gamberale and Hultengren 1972	Human	700	20	0, decrease in perceptual speed at end of exposure
Carpenter et al. 1944	Human	200	420	1, mild irritation
Carpenter et al. 1944	Human	400	420	1, mild ocular irritation
Carpenter et al. 1944	Human	600	480	1, lassitude
Carpenter et al. 1944	Human	800	480	2, inebriation
Suzuki 1973	Human	200	360	0, no effect
Horvath et al. 1981	Human	240	30	0, no effect
von Oettingen et al.	Human	200	480	1, mild discomfort
Luderer et al 1999	Human	50	180	0, no symptoms
Pryor et al. 1978	Rat	26,700	60	SL, LC_{50}
Cameron et al. 1938	Rat	24,400	90	SL, 60% mortality
Cameron et al. 1938	Rat	12,200	390	SL, LC_{50}
Kojima and Kobayashi 1973	Rat	15,000	150	SL, 80% mortality
Kojima and Kobayashi 1973	Rat	12,200	120	SL, LC_{50}
Kojima and Kobayashi 1973	Rat	5,000	120	2, no mortality
Mullin and Krivanek 1982	Rat	6,250	120	2, no mortality
Moser and Balster 1985	Mouse	38,465	10	SL, LC_{50}
Moser and Balster 1985	Mouse	21,872	30	SL, LC_{50}

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category
Moser and Balster 1985	Mouse	19,018	60	SL, LC_{50}
Bruckner and Peterson 1981a	Mouse	12,000	20	2, no mortality
Bruckner and Peterson 1981a	Mouse	8,600	180	SL, LC_{50}
Bonnet et al. 1979	Mouse	6,940	360	SL, LC_{50}
Svirbely et al. 1943	Mouse	5,320	420	SL, LC_{50}
Bruckner and Peterson 1981a	Mouse	2,600	180	2, immobility in absence of stimulus
NTP 1990	Rat, mouse	1,200	390	0, no clinical signs
Moser and Balster 1985	Mouse	2,959	10	2, EC_{50}, inverted screen test
Moser and Balster 1985	Mouse	2,012	30	2, EC_{50}, inverted screen test
Moser and Balster 1985	Mouse	1,445	60	2, EC_{50}, inverted screen test
Moser and Balster 1981	Mouse	3,200	30	2, ataxia
Bruckner and Peterson 1981a	Mouse	2,600	60	2, ataxia
Glowa 1981	Mouse	500	240	0, no effects, scheduled controlled behavior
Glowa 1981; Takeuchi and Hisanga 1977	Mouse	2,000	240	2, changes in behavior
Shigeta et al. 1978; Takeuchi and Hisanaga 1977	Rat	1,000	240	1, no changes in behavior
Shigata et al. 1978	Rat	3,000	240	2, changes in avoidance response, ataxia
Hinman 1987	Mouse	2,500	60	1, no effect on motor activity
Mullin and Krivanek 1982	Mouse	800	240	0, threshold, unconditioned reflex change
Miyagawa et al. 1986	Rat	3,400	240	2, 31% activity decrease
Geller et al. 1979	Rat	150	120	1, reduced neurobehavioral performance

Hinman 1987	Rat	15,000	60	2, no mortality
Nielsen and Alarie 1982	Mouse	7,800	30	2, no mortality
Nielsen and Alarie 1982	Mouse	5,300	30	2, RD_{50}
Kojima and Kobayashi 1973	Rat	10,000	120	SL, 20% mortality
Pryor et al. 1978	Rat	40,000	60	3, lethal
Ikeda et al 1990	Dog	30,000	10	3, lethal
Kishi et al. 1988	Rat	4,000	240	2, ataxia
Taylor and Evans 1985	Monkey	1,000	50	0, no effect
Taylor and Evans 1985	Monkey	2,000	50	1, impairment, cognitive function
Taylor and Evans 1985	Monkey	4 500	50	2, failure to respond in cognitive function test
Wood and Cox 1995	Rat	3,000	120	1, increased activity
Wood et al. 1984	Rat	3,000	240	2, ataxia
Bushnell et al. 1985	Mouse	10,000	72	2, decrease in activity
Moser and Balster 1981	Mouse	800	30	0, no change in operant behavior
Wada et a. 1989	Rat	6,030	240	2, no mortality

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

APPENDIX C

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING OF TOLUENE

Summary

The method used in this appendix to determine human equivalent AEGL values is similar to that previously reported (Bruckner et al. 2004; Krewski et al. 2004) and follows the methodology described in the PBPK Modeling White Paper, Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels (AEGLs), (Dennison et al. 2010). The method reduces the uncertainty inherent in extrapolating rat toxicity data to humans and extrapolating toxicity data across time scales, by using validated PBPK models to perform the extrapolation based on an internal measure of dose. This reduces the uncertainty in the pharmacokinetic component of the extrapolation. Uncertainty in the pharmacodynamic component of the rat-to-human extrapolation is handled with standard uncertainty factors.

The end points found in the critical studies for AEGL 2 and AEGL 3 values can be reasonably associated with the blood concentration of toluene. The blood concentration is a superior measure of dose than the applied concentration (exposure concentration) because, as an internal measure of dose, pharmacokinetic alterations in tissue dosimetry are addressed in extrapolations by explicit quantification. In an extrapolation, for example, of a 1-h AEGL to an 8-h AEGL, the increase in blood concentration over time is explicitly compensated for by reducing the 8-h AEGL to the point where blood concentrations are equivalent. This obviates the need for the use of algorithms such as the ten Berge et al. (1986) equation, which can result in corresponding errors when the empirical parameters are unknown.

Fundamentally, the PBPK-based AEGL values are based on the same critical studies as the AEGL values established in the technical support document; only the method of extrapolating from rat to human (dosimetry replaces pharmacokinetic uncertainty factors) and over time (dosimetry replaces empirical formulas) differs. When the PBPK-based approach replaces pharmacokinetic uncertainty factors, the resulting AEGL value may be higher due to the reduction in the total uncertainty factor.

The AEGL 1 value for toluene was based on effects that could not feasibly be modeled, so modeling was not applied. Modeling was performed in deriving the AEGL-2 and AEGL-3 values. The PBPK assessment method involves the following specific steps:

Step 1) Determine an appropriate dose metric, the pharmacokinetic measure of internal dose that correlates with the critical effect. For toluene, the critical effect is CNS depression, and a dose metric of peak concentration of toluene in brain (BrTC) was used.

Step 2) Develop a PBPK model for that chemical that adequately describes the pharmacokinetics of toluene in rats and humans with respect to CV. Describe model equations, parameter value development, and evaluation using experimental data from the literature.

Step 3) Calculate the dose metric amount under conditions that correspond to the critical study. For example, for toluene's AEGL 3 values, the critical study point of departure was 6,250 ppm for 2 h in rats. Based on the PBPK model, the CV in rats is 165 mg/L (at 2 h and 6,250 ppm).

Step 4) Apply the uncertainty factors determined in the technical support document to the dose metric. For AEGL-3 values, the total uncertainty factor was 3, for intraspecies variability. As described in the technical support document, the interspecies factor was set at 1, for a total uncertainty factor of 3. This total uncertainty factor may have been higher if PBPK modeling was not used. After application of the uncertainty factor of 3, the target internal dose of CV becomes 55 mg/L for AEGL 3. The uncertainty factor can also be applied after derivation of the human equivalent concentration (HEC) as an alternative, and in the derivation section of this appendix, both approaches are provided.

Step 5) Scale the model to humans by changing body weight and other parameter values to human values.

Step 6) Run the PBPK model to determine the HEC that corresponds to the target internal dose of 55 mg/L for each AEGL.

This appendix has three parts. First, the structure and parameterization of the toluene PBPK model is described. Second, validation of the model is provided by showing model performance against rat and human data sets obtained from the literature. Third, derivation of recommended AEGL values is performed.

Introduction

The critical studies that provide the NOAEL used in this analysis (Table C-1) are the same as those used in the technical support document to calculate AEGL values. For the AEGL-2 values, both a clinical study and a study with rats were considered. The study with rats was chosen as the basis for the AEGL-2 values, because the effect in this study, threshold for narcosis, more closely meets the definition of the AEGL-2. Supporting studies were not used in any of the AEGL calculations.

TABLE C-1 Critical Studies for Deriving AEGL Values for Toluene

Level	Study	Species	NOAEL	Duration
AEGL-2	Gamberale et al. 1972	Human	700 ppm[a]	20 min
AEGL-2	Bushnell et al. 2007a	Rat	1,600 ppm	34 min
AEGL-3	Mullin and Krivanek 1982	Rat	6,250	2 h

[a]After initial exposures at 100-500 ppm.

Additional information and justification of these choices of critical studies is available in the technical support document. The target tissue dose (venous blood concentration) was determined from these studies.

Selection of the Dose Metric

The dose metric used for the PBPK-based assessment is the concentration of toluene in the brain (BrTC). The critical effect of toluene for the setting of AEGLs has been determined to be CNS depression, on the basis of toxicity studies presented in the technical support document. It has been generally suggested that CNS depression caused by organic solvents, such as toluene, is mediated by the action of the parent chemical and not metabolites (Bruckner and Warren 2001). The concentration of toluene in that target brain tissue is proportional to the concentration in venous blood (van Asperen et al. 2003) once steady state has been achieved. The PBPK models have been parameterized to provide CV as model output under the exposure conditions indicated for this assessment.

Model Selection

The present approach requires a validated PBPK model for rats and humans. Three options exist for developing or selecting a model to use: 1) develop a wholly new model, 2) modify an existing model, or 3) select an existing model and use in its present form. If an existing model would serve the needs of this assessment, option #3 is the preferred choice and was the first approach to be used. Ultimately, an existing model was used with minor modifications.

An evaluation of all existing models can in principle be performed to determine the best available model. However, this process is time consuming and can be arbitrary to some extent. Therefore, the method of selecting a model was to screen models for good candidates using specific criteria, and evaluate models one by one until an acceptable model was identified. The criteria used to screen models included: 1) the model should include the inhalation route of exposure (primarily), 2) development of the model should incorporate validation against venous blood data, 3) the model should be reported in the peer reviewed literature, and 4) the model should have as a primary purpose the goal of rat-to-human extrapolation.

A number of PBPK models have published for inhalation of toluene (Purcell et al. 1990; Tardif et al. 1993; Pierce et al. 1996a; Tardif et al. 1997; Benignus et al. 1998; Pierce et al. 1998; Ali and Tardif 1999; Haddad et al. 1999a; Pierce et al. 1999; Vicini et al. 1999; Jonsson et al. 2001; Tardif et al. 2002; van Asperen et al. 2003; Benignus et al. 2006; Kenyon et al. 2008). Several of these are variations of each other. Some were developed for rats, others for humans, and some for both (with modification of appropriate parameter values). The purpose for some of the models was evaluation of mixture interactions, although in each of these cases, a model was first developed for toluene as a single chemical. The two most recently published models that met the criteria described above are those of Kenyon et al. (2008) for the rat and that of Benignus et al. (2006) for the human.

Model Structure

The model structure is shown in Figure C-1. The tissue groups/compartments specified are consistent with models for other inhaled volatile organic solvents (Reddy et al. 2005). The individual compartments (lungs, brain, liver, gastrointestinal tissue, fat, and slowly and rapidly perfused tissue groups) are connected by the systemic circulation. The model has distinct arterial and venous blood compartments and tissues are described as homogeneous well-mixed compartments. Metabolism is described by a single metabolic pathway following saturable (Michaelis-Menten) kinetics in the liver. Brain is the target tissue of interest and fat is a major site for sequestration.

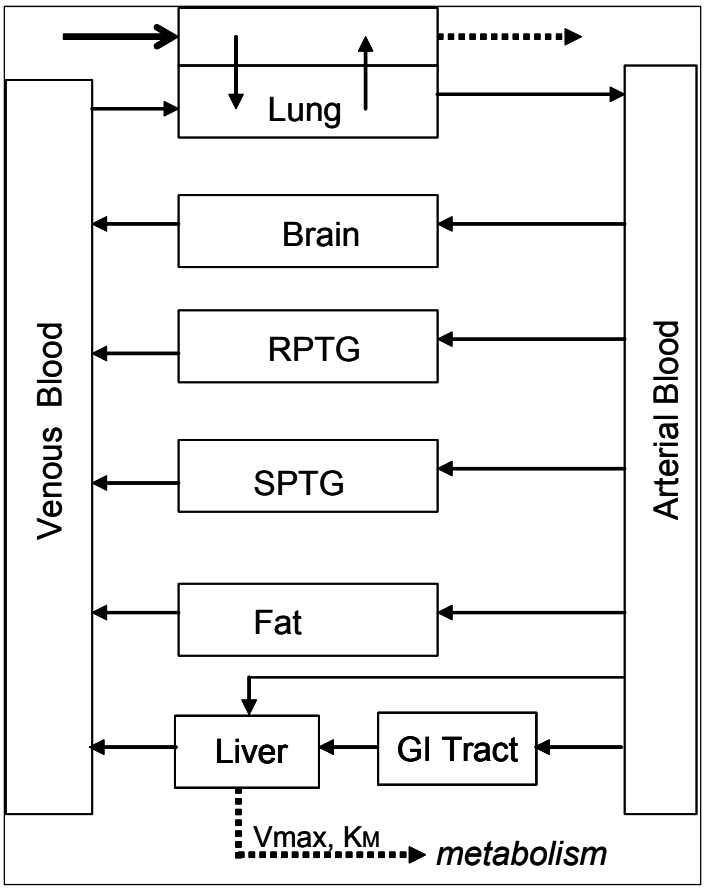


FIGURE C-1 Schematic diagram of the toluene PBPK model. Source: Kenyon et al. 2008. Reprinted with permission; copyright 2008, *Journal of Toxicology and Environmental Health, Part A: Current Issues*.

TABLE C-2 Physiologic Parameters for the Toluene Rat Model

Parameter, units	Symbol	Value	Footnote
Body weight, kg	BW	0.237-0.508	[1]
Cardiac output, L/h-kg$^{0.75}$	QCC		[2]
Normal		11.2	
Sedentary, day acclimated		11.2	
Active, day-acclimated		13.2	
Alveolar ventilation, L/h-kg$^{0.75}$	QPC		[2]
Normal		9.9	Ratio = 0.9
Sedentary, day-acclimated		12.2	Ratio = 1.1
Active, day-acclimated		22.4	Ratio = 1.7
Flow (fraction QC)[3]			
Lung	QCC	1.0	[4]
Liver	QLC	0.02	
Fat	QFC	0.082	
Brain	QBC	0.027	
Gut	QGC	0.16	
SPTG	QSC	0.257	
RPTG	QRC	1-ΣQi	
Volumes (fraction body weight)[5]			
Arterial blood	VABC	0.030	
Venous blood	VVBC	0.060	
Lung	VNC	0.0048	
Liver	VLC	0.0401	
Fat	VFC	0.08-0.16	[6]
Brain	VBC	0.0054	
Gut	VGC	0.0249	
SPTG	VSC	0.60	
RPTG	VRC	1-ΣVi	

[1]Body weight is an experiment-specific measurement.
[2]Experiment-specific based on type of acclimation and activity level of rat. "Normal" refers to rats with a normal diurnal cycle of being active and fed at night and studied during daylight hours, whether weight-maintained or free-fed. "Sedentary, day-acclimated" refers to rats acclimated to be fed and active during the light part of their diurnal cycle, but not performing a task. "Active, day-acclimated" refers to rats acclimated to be fed and active during the light part of their diurnal cycle and performing a lever pressing task. Ratio is the ratio of QPC/QCC, an approximation of ventilation-perfusion ratio.
[3]Values are from two main sources (Brown et al. 1997; Simmons et al. 2002).
[4]Lung receives all of cardiac output.
[5]Values that LE rat specific were calculated from regression equations (Simmons et al. 2002) for a 0.35 kg rat. Other values are from a standard reference (Brown et al. 1997). All calculated values were checked against reported ranges of reference values (Brown et al. 1997).
[6]Experiment-specific based on body weight of rat using regression equation from Simmons et al. (2002).

TABLE C-3 Chemical-Specific Parameters for the Toluene Rat Model

Parameter	Symbol	Units	Value	Reference
Partition coefficients				
Blood:air	PB	None	21.0	Thrall et al. 2002
Lung:blood	PN	None	1.14	
Liver:blood	PL	None	2.01	
Brain:blood	PBR	None	1.72	
Fat:blood	PF	None	86.19	
Gut:blood	PG	None	2.62	
RPTG:blood	PR	None	2.62	
SPTG:blood	PS	None	1.32	
Metabolism parameters				
V_{max}	VMAXC	$L/h/kg^{0.75}$	4.55	Tardif et al. 1993[a]
K_M	KM	mg/L	0.45	

[a]Metabolism parameters are consistent with the range of published values in the literature (DeJongh and Blaauboer 1996).

Physiological and Chemical-Specific Parameter Values

Physiological and chemical-specific parameter values used in the present model for rats are listed in Tables C-2 and C-3, respectively. Model code is provided in Attachment 1. All details concerning model calibration and evaluation for both the rat model and the human GPAT model can be obtained from the original publications (Benignus et al. 2006; Kenyon et al. 2008).

Derivation of AEGLs with PBPK-Based Approach

The AEGL-2 critical study was Bushnell et al. (2007a), in which the NOAEL for a doubling in choice reaction time in Long-Evans rats exposed to toluene was 1,600 ppm for 34 min. As shown in Table C-4, the internal dose metric of brain toluene concentration (BrTC) in the rat was determined using a PBPK model (Kenyon et al. 2008), and the determination of the HEC used the human GPAT model (Benignus et al. 2006). The BrTC in rats at the end of exposure, calculated by the PBPK model, was 49.2 mg/L. A total uncertainty factor of 3 was applied to the rat BrTC to arrive at the target internal dose in humans of 16.4 mg/L. The uncertainty factor of 3 was applied to the internal dose metric, as recommended by the Standing Operating Procedures (NRC 2001), to arrive at final human exposure values in the final row of Table C-4 which were rounded to obtain the final AEGL-2 values. The AEGL-2 values were also compared to the estimated toluene exposure concentrations (ppm) which would lead to decrements in reaction time similar to those associated with ethanol inebriation (0.08% and 0.10% blood ethanol level), with the AEGL-2 values are between those two estimates (lower portion of Table C-4).

TABLE C-4 Toluene Concentrations in Air Associated with Relevant Brain Toluene Concentrations in Rats and Humans as Determined by PBPK Modeling

	10 min	30 min	1 h	4 h	8 h
Duration extrapolation at the critical brain toluene concentration (BrTC) in rats, and extrapolation to humans using one-third of the critical internal dose (per guidance in NRC 2002)					
Rat internal dose metric (1,600 ppm for 34 min) ; BrTC = 49.2 mg/L	3,085 ppm	1,705 ppm	1,243 ppm	809 ppm	651 ppm
AEGL-2 values based on GPAT estimates in humans; BrTC = (49.2/3) = 16.4 mg/L	1,396 ppm	757 ppm	558 ppm	311 ppm	251 ppm
Toluene concentrations leading to effect levels comparable to blood ethanol levels (BELs) of 0.08% and 0.10%					
GPAT estimations of exposures comparable to BEL of 0.08% (standing); BrTC = 119 μM = 10.9 mg/L	930 ppm	520 ppm	390 ppm	230 ppm	190 ppm
GPAT estimations of exposures comparable to BEL of 0.10% (standing); BrTC = 241 μM = 24.1 mg/L	1,860 ppm	1,000 ppm	730 ppm	390 ppm	320 ppm

Source: Based on Bushnell et al. 2007a.

For comparative purposes, alternative AEGL-2 values were also calculated using the clinical study of Gamberale and Hultengren (1972) as shown in Table C-5. In this study, the threshold for narcosis was not approached as indicated by the failure to produce significant deficits in tests of perceptual speed and reaction time. In the Gamberale and Hultengren (1972) study, subjects were sequentially exposed to toluene at 100, 300, 500, and 700 ppm for 20 min at each level, with a short break in the middle. The venous blood concentration calculated by the PBPK model is much greater when the full exposure regimen was simulated compared with the concentration after only a 20 min exposure (about 6.5 versus 4.5 mg/L). The actual exposures were roughly equivalent to a 20-min exposure at about 1,000 ppm. Therefore, the CV determined for the actual experimental conditions was used to derive AEGL-2 values. According to the standing operating procedure for use of PBPK modeling in AEGL value development, the uncertainty factor can be applied to the HEC or to the dose metric of 6.54 mg/L, but the latter approach is generally preferred. If the total uncertainty factor is 1, the approaches become the same. The alternative AEGLs were deemed to be not as credible as the refined approach using the rat data extrapolated via the human GPAT model based on the comparisons with the toluene concentrations leading to effect levels comparable to blood ethanol levels of 0.08% and 0.10%, as shown in the lower portion of Table C-4.

TABLE C-5 AEGL-2 Values for Toluene Determined with PBPK Model of Human Data

	10 min	30 min	1 h	4 h	8 h
UF = 1	1,855	805	601	426	378
UF = 3, applied to human equivalent concentration	618	268	200	142	126
UF = 3, applied to dose metric	655	305	239	180	166

Source: Based on Gamberale and Hultengren 1972.

The AEGL-3 values were based on a rat NOAEL for lethality and were determined in the same manner as the AEGL-2 values: the determination of the internal dose metric used the rat PBPK model and the determination of the HEC used the human GPAT model. In Table C-6, the results in the first row are based on the target internal dose (BrTC) of 362 mg/L taken from the Mullin and Krivanek (1982) study in rats, then deriving the HEC with no adjustment with uncertainty factors using the GPAT model. In the second row, the HEC determined for an uncertainty factor of 1 (listed in the first row) were divided by 3. The results in the third row were obtained by dividing 362 mg/L by 3 (121 mg/L) as a new target internal dose, and then using the human GPAT model to determine the corresponding HECs.

TABLE C-6 Comparison of AEGL-3 Values for Toluene Determined by PBPK Modeling

	10 min	30 min	1 h	4 h	8 h
UF = 1, human BrTC = 362 mg/L	30,200 ppm	15,440 ppm	10,860 ppm	5,210 ppm	3,920 ppm
UF = 3, applied to human equivalent concentration	10,067 ppm	5,147 ppm	3,620 ppm	1,737 ppm	1,307 ppm
UF = 3, applied to dose metric	10,125 ppm	5,209 ppm	3,680 ppm	1,810 ppm	1,370 ppm

Source: Based on Mullin and Krivanek (1982), NOAEL for lethality of 6,250 ppm (2 h) in rats.

Attachment 1

PBPK Model Code for Toluene AEGL Rat Model

Models used were published models for the rat (Kenyon et al. 2008) and the human GPAT model (Benignus et al. 2006). All model calibration details and evaluation data and equations are available in these papers, except where otherwise noted (e.g., QPC and QCC values were set equal to 15 L/h-kg, so that the values for these highly influential parameters were equal to those used in the Dennison model originally used for AEGL derivation). The code below is for the Kenyon el. al. (2008) model realized in acslX 3.0.1.6 (Aegis Technologies Group, Austin, TX).

```
PROGRAM      TOLRAT1.CSL  !PBPK Model for Toluene (TOL)in rat
             !created by Elaina Kenyon 08/04/05
             !incl. explicit arterial and venous compt
             !& non-SS lung, both inhalation & oral routes

LOGICAL      TOLCHX
             !If TOLCHX = true, then check Toluene
             !mass balance
             TOLCHX = .TRUE.
LOGICAL      DPSITG
             !Integration control variable for
             !precision
             DPSITG = TRUE.

INITIAL      !STATEMENTS EXECUTED ONLY AT THE
             BEGINNING OF THE !SIMULATION, CONSTANT
             COMMANDS EXECUTED ONLY at BUILD

CONSTANT     LIMIT = 0.1   !Limit for unbal. cmpds when checking
             mass balance
CONSTANT     DUMMY = 0.00001

!***** Physiological Parameters ****

CONSTANT     QPC = 16.1        !Alveolar Ventilation Rate(l/hr-kg)
CONSTANT     QCC = 16.1        !Cardiac Output(l/hr-kg)
CONSTANT     QLC = 0.02        !Fract. Blood Flow to Liver
CONSTANT     QFC = 0.052       !Fract. Blood Flow to Fat
CONSTANT     QBC = 0.114       !Fract. Blood Flow to Brain
CONSTANT     QGC = 0.16        !Fract. Blood Flow to Gut
CONSTANT     QSC = 0.249       !Fract. Blood Flow to Poorly Perfused T.
QRC = 1.0 - QLC - QFC - QBC - QSC - QGC
!Fract. Blood Flow to Richly Perfused T.
```

```
CONSTANT      BW = 0.350      !Body Weight(kg)
CONSTANT      VLC = 0.026     !Volume Fraction Liver
CONSTANT      VFC = 0.2142    !Volume Fraction Fat
CONSTANT      VBC = 0.020     !Volume Fraction Brain
CONSTANT      VGC = 0.0249    !Volume Fraction GI Tract
CONSTANT      VSC = 0.4371    !Volume Fraction Poorly Perfused T.
CONSTANT      VNC = 0.0076    !Volume Fraction Lung
CONSTANT      VVBC = 0.0592   !Volume Fraction Venous Blood
CONSTANT      VABC = 0.0198   !Volume Fraction Arterial Blood

VRC = 1.0 - VLC - VFC - VBC - VSC - VNC - VVBC - VABC - VGC
!Volume Fraction Richly Perfused T.

!***** Chemical Specific Parameters for TOL *****

!Partition Coefficients from Thrall et al., 2002
CONSTANT      PL = 2.01       !Liver/Blood Partition Coefficient
CONSTANT      PF = 86.19      !Fat/Blood Partition Coefficient
CONSTANT      PBR = 1.72      !Brain/Blood Partition Coefficient
CONSTANT      PG = 2.62       !GI/Blood Partition Coefficient
CONSTANT      PS = 1.32       !Poorly/Blood Partition Coefficient
CONSTANT      PR = 3.04       !Richly/Blood Partition Coefficient
CONSTANT      PB = 21.0       !Blood/Air Partition Coefficient
CONSTANT      PN = 1.14       !Lung/Blood Partition Coefficient
CONSTANT      MW = 92.14      !Molecular Wt (g/mol)

!***** Metabolism Parameters - VMAX/KM from Pierce et al., 1996
CONSTANT      VMAXC = 4.8     !Max Rate TOL metabolism (mg/hr-kg)
CONSTANT      KM = 0.55       !Affinity Constant for TOL (mg/l)

!***** Dosing & Exposure Variables *****

CONSTANT   CONC = 250.   !Inhalation Concentration (ppm)

!***** Timing Commands *****

SCHEDULE DS1 .AT. TCHNG      !Use discrete at discontinuities
CIZONE = 1.0                 !Start with inhalation on

CONSTANT TSTOP = 8.          !Length of experiment (hrs)
CONSTANT TCHNG = 2.          !Length of inhalation exposure

CONSTANT POINTS = 100.       !Number of points in plot
CINT = TSTOP/POINTS          !Communication interval

!***** Inhalation Exposure Definition *****

AIO = (CONC * MW)/24450      !Initial Chamber Conc (mg/l)
```

```
!***** Oral Exposure Definition *****

CONSTANT      DV = 0.002        !Dosing Volume in L/kg
CONSTANT      SOCO = 100000     !Dosing Soln Conc, mg/L
CONSTANT      KA = 5.0          !First Order GI abs, 1/hr

ODTOL = DV*BW*SOCO              !Bolus gavage dose in mg
ORTOL = (DV*SOCO*BW)/BW         !Bolus dose in mg/kg

!***** Scaled Parameters *****

QC = QCC * (BW**0.74)   !Cardiac Output (l/hr)
QP = QPC * (BW**0.74)   !Alveolar Ventilation Rate (l/hr)
QL = QLC * QC           !Flow Liver Compartment (l/hr)
QF = QFC * QC           !Flow Fat Compartment (l/hr)
QB = QBC * QC           !Flow Brain Compartment (l/hr)
QG = QGC * QC           !Flow GI Compartment (l/hr)
QS = QSC * QC           !Flow Slowly Perf. Tis. Cmpt. (l/hr)
QR = QRC * QC           !Flow Richly Perf. Tis. Cmpt. (l/hr)
VL = VLC * BW           !Volume Liver Compartment, Total
VF = VFC * BW           !Volume Fat Compartment
VB = VBC * BW           !Volume Brain Compartment
VG = VGC * BW           !Volume GI Compartment
VS = VSC * BW           !Volume Slowly Perfused Tis. Cmpt.
VR = VRC * BW           !Volume Richly Perfused Tis. Cmpt.
VMAX= VMAXC * BW**0.74  !VMAX scaled

VVB = VVBC * BW         !Volume Venous Blood Cmpt.
VAB = VABC * BW         !Volume Arterial Blood Cmpt.
VN = VNC * BW           !Volume Lung Cmpt.

END     !**** END OF INITIAL ****

DYNAMIC         !Code executed at end of each commun. interval

ALGORITHM     IALG = 2          !Gear Method for Stiff Systems (LSODE)

DISCRETE DS1            !Discontinuity in Simulation executed
                        !when inhalation exposure ends
CIZONE = 0.0            !Turn inhalation off
CALL LOGD(.TRUE.)       !Forced logging for plots
END

DERIVATIVE

!Gavage oral dose of Toluene in mg
RDSTOM = -KA*STOMD
STOMD = INTEG(RDSTOM, ODTOL)
```

```
!CI - Concentration TOL in inhaled air (mg/l)
RAI = QP * C                !Rate TOL to lung (mg/hr)
AI = INTEG (RAI, 0.)        !Amount TOL entering lung, mg
CI = AIO * CIZONE

!CA - Concentration TOL in arterial blood (mg/l)
! CA1 - Concentration part to lung
!AAB - Amount TOL in arterial blood (mg)
RAAB = QC * CA1 - QC * CA
AAB = INTEG(RAAB, 0.)
CA = AAB/VAB

!AX - Amount TOL exhaled (mg)
RAX = QP * CX               !Rate TOL exhaled (mg/hr)
AX = INTEG (RAX, 0.)
CX = CA1/PB                 !Conc. TOL in exhaled air(mg/l)
CXPPM = ((0.7 * CX) + (0.3 * CI)) * (24450/MW) !ppm
AXKG = AX/BW                !mg exhaled/kg body weight

!AN - Amount TOL in lung (mg)
RAN = QC * CV + QP * CI - QC * CA1 - QP * CX
AN = INTEG (RAN, 0.)
CA1 = AN/(VN * PN)
CN = AN/VN

!AS - Amount TOL in slowly perfused tissues (mg)
RAS = QS * (CA - CVS)       !Rate of change in conc. (mg/hr)
AS = INTEG (RAS, 0.)
CVS = AS / (VS * PS)        !Conc partition to slow per. tis.(mgl)
CS = AS / VS                !Conc in volume slow per. tis.(mg/l)

!AR - Amount TOL in rapidly perfused tissues (mg)
RAR = QR * (CA - CVR)       !Rate of change in conc. (mg/hr)
AR = INTEG (RAR, 0.)
CVR = AR / (VR * PR)        !Conc partition to rap per. tis.(mg/l)
CR = AR / VR                !Conc in volume rap per. tis.(mg/l)

!ABR - Amount TOL in brain (mg)
RABR = QB * (CA - CVBR)         !Rate of change in conc (mg/hr)
ABR = INTEG (RABR, 0.)
CVBR = ABR / (VB * PBR)         !Conc partition to brain(mg/l)
CBR = ABR / VB                  !Conc in volume brain(mg/l)
AUCBR = INTEG(CBR, 0.)          !AUC for TOL in brain

!AF - Amount TOL in fat tissue(mg)
RAF = QF * (CA - CVF)       !Rate of change in conc(mg/hr)
AF = INTEG (RAF, 0.)
CVF = AF / (VF * PF)        !Conc partition to fat(mg/l)
CF = AF / VF                !Conc in fat volume(mg/l)
```

```
!AG - Amount TOL in gut tissue(mg)
!RAG - rate of change TOL in gut conc, mg/hr
RAG = QG * (CA - CVG) - RDSTOM
AG = INTEG (RAG, 0.)
CVG = AG / (VG * PG)      !Conc partition to gut (mg/l)
CG = AG / VG              !Conc in gut volume(mg/l)

!AL - Amount TOL in liver(mg)
!RAL - rate of change in liver conc, mg/hr
RAL = (QL * CA) + (QG * CVG) - ((QL+QG) * CVL) - RAM
AL = INTEG (RAL, 0.)
CVL = AL / (VL * PL)      !Conc partition to liver(mg/l)
CL = AL / VL              !Conc in liver volume(mg/l)

!AUCPO - Amount TOL oxidatively metabolized (mg)
!RAM - Rate of oxidative metabolism of TOL (mg/hr)
RAM = (VMAX * CVL) / (KM + CVL)
AUCPO = INTEG (RAM, 0.)
AUCKG = AUCPO / BW    !Amount TOL metabolized/kg body weight

!CV - TOL mixed venous blood concentration (mg/l)
!RAVB - Rate of change in concentration (mg/hr)
RAVB = (QL+QG)*CVL) + QF*CVF + QS*CVS + QR*CVR + QB*CVBR - QC * CV
AVB = INTEG(RAVB, 0.)
CV = AVB/VVB              !Conc in venous blood volume (mg/l)
AUCV = INTEG(CV,0.)       !AUC for toluene in venous blood

!PMASS - TOL Mass balance(mg)
PMASS = AN + AF + AG + AL + AS + AR + ABR + AUCPO + AX + AVB +
          AAB + STOMD

TERMT (T .GE. TSTOP)    !terminate solution

END      !END OF DERIVATIVE

!**Code to calculate variables used in checking mass balance**

BALPC = (AI + ODTOL) - PMASS
TBALPC = ABS(BALPC)

END      !END OF DYNAMIC

END      !END OF PROGRAM
```

APPENDIX D

TOLUENE SIMULATIONS

Vernon Benignus, Elaina M. Kenyon, William Boyes, and Philip Bushnell
2/22/2013

Acute exposure to toluene vapor impairs neurologic function. The degrees of neurologic impairment produced by exposures to toluene, and dose response-relationships, have been determined using a variety of behavioral procedures. Some of these behavioral procedures, such as choice reaction time tasks, have also been used to evaluate the acute consequences of exposure to another common intoxicant, ethanol. This circumstance allows the potency of toluene and ethanol to be compared relative to a common degree of behavioral impairment. Because the behavioral impairments caused by ethanol intoxication have also been associated with fatal automobile accidents in a dose-effect manner, it is possible to estimate the degree of toluene exposure associated with a level of impairment that might increase the probability of causing a fatal automobile accident if an exposed person were also driving at the same time. In addition to the probability of an automobile accident, this level of impairment would also be expected to put a person who was not driving at risk for other accidents or dangers given their unique circumstances and surroundings. With this approach, it is possible to estimate the potential severity of acute behavioral impairments caused by toluene in terms that are relevant for AEGL value determinations.

Behavioral Consequences of Toluene Exposure

Simulations comparing the behavioral effects of toluene and ethanol were made to provide context for the danger of toluene exposure in terms of the danger associated with comparable levels of intoxication with ethanol. These simulations used a behavioral effect (speed of choice reaction time) as a dependent variable. In these tests, the subject must make a decision about which response is correct as quickly as possible. Table D-1 and Figure D-1 show the severity of a decrement in reaction time (percent of maximum possible effect) as a function of brain toluene concentration, and also the blood ethanol concentrations equivalent to these brain toluene concentrations. Brain toluene concentrations are related quantitatively to blood ethanol concentrations in terms of the magnitude of change in reaction time associated with each chemical (Benignus et al. 2005).

In addition, Table D-1 and Figure D-1 show corresponding increases in fatal automobile crashes as a function of degree of intoxication with either toluene or ethanol. These functions were derived from data relating the increased risk of a fatal car crash to blood ethanol concentration and the quantitative relationship between the effects of toluene and ethanol on reaction time. These relationships allow one to

estimate the number of fatal automobile accidents that would be produced by toluene exposure as a function of the degree of intoxication (Benignus et al. 2011). It should be noted that the increase in fatal automobile accidents is given as the number of fatalities per 1,000 drivers who had the toxicant in their bodies while driving.

From Table D-1 it may be concluded that a concentration of toluene in brain of 119 μM produces a degree of intoxication associated with about 13% reduction in speed of choice reaction time. This degree of impairment is also associated with 0.08 g/dl of venous ethanol, a concentration that defines legal intoxication and is associated with an increase over baseline of 305 fatal automobile accidents per 1,000 drivers. Almost half of drivers with 0.10 g/dl venous ethanol or a brain toluene concentration of 241 μM would be expected to have fatal automobile accidents.

Inhaled Concentrations of Toluene Required to Produce Specific Brain Concentrations

In addition to the duration of exposure, alveolar ventilation, which depends upon physical activity, affects the concentration of toluene in the inhaled air that is required to produce a given brain toluene concentration. Table D-2 and Figure D-2 give approximate concentrations of toluene in inhaled air for a person exercising at four levels of exertion for two brain concentrations and for five exposure durations of interest. This illustrates the large impact of exertion on toluene uptake.

TABLE D-1 The Importance of the Behavioral Effects of Toluene Exposure Estimated via the Alcohol Effects on Fatal Automobile Accidents and Employing the Equivalent Dose of Brain Toluene

Venous Blood Alcohol (g/dL)	Proportion of Fatal Automobile Accidents Greater Than Baseline[a]	Equivalent Brain Toluene (μM)[b]	Effect on Choice Reaction Time Test (% of Maximum)[c]
0.10	0.478	241.0	26.2
0.09	0.386	172.0	19.1
0.08	0.305	119.0	13.1
0.07	0.216	83.1	8.9
0.06	0.132	48.8	4.9

[a]Fatal automobile accident estimates were obtained from Zador (1991) and Zador et al. (2000) as expressed in Figure 2 of Benignus et al. (2011). The proportion of persons who were killed in a single-car crash with a measured post-mortem blood-ethanol concentration, relative to persons driving with that same blood-ethanol concentration who did not crash, is expressed as a proportional increment above baseline (0.00 g/dL).
[b]Toluene/alcohol equivalence was computed using Equation 2 in Benignus et al. (2011).
[c]Behavioral effect magnitudes were computed using Equation 1, with human parameters for the low motivation case, from Table 4 of Benignus et al. (2009).

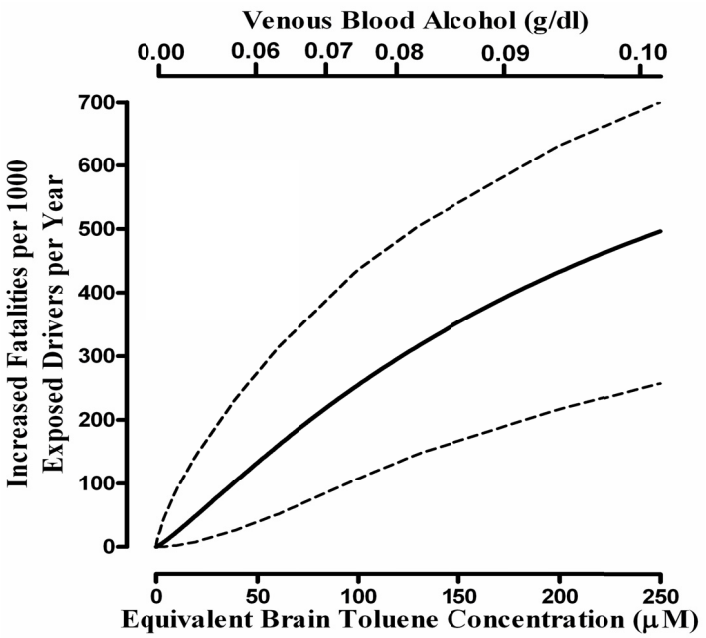


FIGURE D-1 The effect of alcohol intoxication (top horizontal axis) on fatal automobile accidents (per 1,000 drivers per year) compared with the equivalent amount of toluene in the brain (μM). This graph is a modified form of Figure 3 in Benignus et al. (2011). The alcohol axis was constructed from Figrure 1c from the same source. The plotted functions reflect the mean estimate (solid line) and the upper and lower 95% confidence limits (dashed lines).

TABLE D-2 Approximate Exposures Required to Produce Brain Toluene Concentrations Given in Table D-1 as Determined by the GPAT Model

	Concentration Required for 241 μM Brain Toluene (ppm)				Concentration Required for 119 μM Brain Toluene (ppm)			
Time	Lying	Standing	1 mph	2 mph	Lying	Standing	1 mph	2 mph
10 min	2,290	1,860	1,350	1,000	1,150	930	670	500
30 min	1,320	1,000	680	480	700	520	350	240
1 h	1,010	730	460	320	540	390	240	165
4 h	555	390	250	200	325	230	140	110
8 h	445	320	220	190	275	190	130	100

The values in the table were approximated by iteratively applying GPAT (Benignus et al. 2006). The modeled subject was lying down, standing, or walking at 1 or 2 mph.

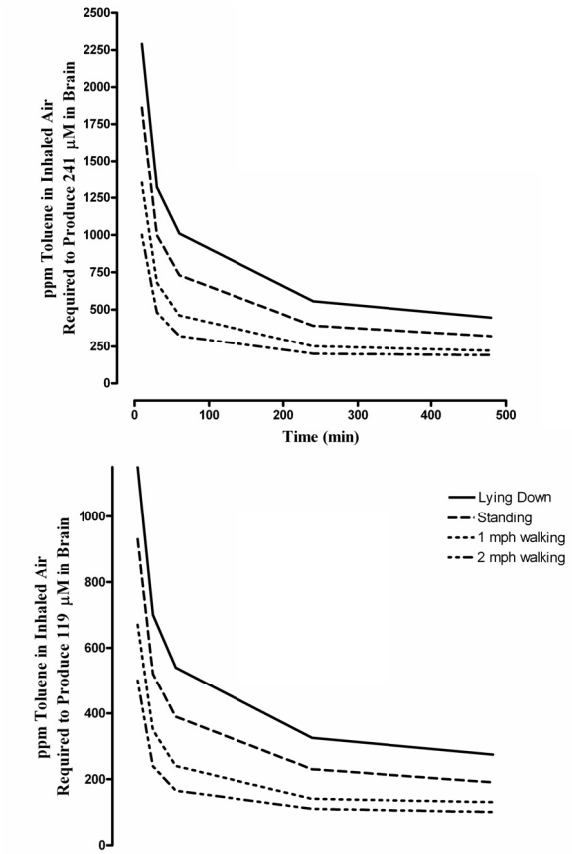


FIGURE D-2 Concentration of inhaled toluene (ppm) required to produce brain toluene concentrations of 241 or 119 µM at four exercise levels. The two brain toluene concentrations are equivalent to venous concentrations of alcohol of 0.1 or 0.08 g/dl. Those concentrations are roughly approximate values of ppm generated by the GPAT model (Benignus et al. 2006).

Inhaled Air Concentrations Required to Produce Toluene Concentrations of 119 or 241 µM in the Brain

All calculations so far were made using the GPAT model, because the Dennison model does not have a brain compartment. In order to make exposure estimates with the accepted Dennison model, (a) a GPAT model was used to estimate the venous concentrations of toluene required to produce brain concentrations of 110 or 241 µM and (b) the Dennison model was used to determine the ppm values necessary to produce these venous concentrations. These venous and inhaled-air concentrations are presented in Table D-3.

TABLE D-3 Inhaled Air and Venous Concentrations of Toluene Required to Produce Either 119 or 241 μM Brain Toluene Concentrations Computed from the Dennison PBPK Model

Time	For 119 μM		For 241 μM	
	Air (ppm)	Venous (mg/L)		
10 min	625	2.07	1,498	5.24
30 min	372	2.75	729	5.87
1 h	312	3.05	597	6.49
4 h	258	3.55	481	7.52
8 h	239	3.66	436	7.73

Behavioral Contingencies

For both rats and humans, sensitivity to a given concentration of a solvent in the brain depends upon the situation under which the exposed individual was tested (Benignus et al. 2007, 2009). When a behavioral decrement has little consequence to the subject, the behavioral disruption by the toxicant will be maximal. If the subject loses a reward for poor performance, the effect of the tested toxicant will be reduced, or more toxicant will be necessary to disrupt the behavior. If painful punishment follows poor performance, the effect of the tested toxicant is greatly reduced. For example, rats working to avoid painful shocks are less susceptible to toluene exposure than are rats working for a food reward. Rats working for a food reward are less susceptible than are some nonmotivated neurophysiologic procedures that are not subject to either reward or punishment. It is important to consider behavioral measurements that are reasonably comparable if sensitivity is to be compared across factors such as different behavioral tasks or across different species.

Quantitative Rat-to-Human Extrapolation

Using ED_{10} values for various situations in rats and humans from Figure 3 in Benignus et al. (2009), a table of extrapolation ratios was created (see Table D-4). Table D-4 shows that if experimental procedures are the same in rats and humans, the same brain solvent concentrations in the two species should produce the same ED_{10}. In contrast, if the contingencies on performance differ, then ED_{10}s will differ accordingly. Thus, modeling studies with rats suggest that the ED_{10} of a subject whose behavior is minimally constrained by contingencies will be lower by a factor of 86 compared to a subject avoiding punishment (Benignus et al. 2009). Thus quantitative rat-human extrapolation requires information about the experimental contingencies applied during the tests; data from animal studies suggest that if the contingencies differ, then the extrapolation must take into account their relative impacts of the behavioral contingencies applied to each species.

TABLE D-4 Extrapolating Factors[a] from Rats to Humans Depending on Experimental Conditions

	None	Minimum	Withhold reward	Painful punishment
None	1.00	7.30	19.40	86.30
Minimum	–	1.00	2.70	11.80
Withhold Reward	–	–	1.00	4.40
Painful punishment	–	–	–	1.00

[a]Divide rat ED_{10} for the appropriate rat experimental condition by the extrapolation factor to calculate the human ED_{10}. Factors calculated from the data to produce Figure 3 in Benignus et al. (2009).

REFERENCES

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2005. Toward cost-benefit analysis of acute behavioral effects of toluene in humans. Risk Anal 25(2):447-456.

Benignus, V.A., T. Coleman, C.R. Eklund, and E.M. Kenyon. 2006. A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol. Mech. Methods 16(1):27-36.

Benignus, V.A., W.K. Boyes, E.M. Kenyon, and P.J. Bushnell. 2007. Quantitative comparison of the acute neurotoxicity of toluene in rats and humans. Toxicol. Sci. 100(1):146-155.

Benignus, V.A., P.J. Bushnell, W.K. Boyes, C. Eklund, and E.M. Kenyon. 2009. Neurobehavioral effects of acute exposure to four solvents: Meta-analyses. Toxicol. Sci. 109(2):296-305.

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2011. Estimated rate of fatal automobile accidents attributable to acute solvent exposure at low inhaled concentrations. Risk Anal. 31(12):1935-1948.

Zador, P.L. 1991. Alcohol-related relative risk of fatal driver injuries in relation to driver age and sex. J. Stud. Alcohol 52(4):302-310.

Zador, P.L., S.A. Krawchuck, and R.B. Voas. 2000. Alcohol-related relative risk of driver fatalities and driver involvement in fatal crashes in relation to driver age and gender: An update using 1996 data. J. Stud. Alcohol 61(3):387-395.

APPENDIX E

ACUTE EXPOSURE GUIDELINE LEVELS FOR TOLUENE

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)

Key references: Multiple clinical studies, including:
(1) Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Scand. Work Environ. Health 9:119-130.
(2) Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3):131-139.
(3) Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72.

Test species/Strain/Number: Humans, (1) 15, both sexes; (2) 12 males; (3) 71 subjects

Exposure route/Concentrations/Durations: Inhalation; (1) 100 or 200 ppm for 60 min, exercise incorporated into protocol; (2) 100, 300, 500, or 700 ppm, successive 20-min exposures for a total of 85 min (one 5-min break), exposure via a mouthpiece; (3) 100 ppm for 7.5 h, varying exposures of 50-300 ppm (TWA of 100 ppm) for 7.5 h.

Effects:
(1) 100 or 200 ppm with exercise: no effect on heart rate, pulmonary ventilation, oxygen consumption, or blood lactate; subjective symptoms not assessed.
(2) One of 12 subjects able to distinguish between control and toluene exposure
100 ppm: no effect on reaction time
300 ppm: increase in simple reaction time
500 ppm: increase in complex reaction time
700 ppm: decrease in perceptual speed at end of exposure
(3) 100 ppm: no ocular irritation, complaints of "poor air quality," irritation of nose and lower airways.
50-300 ppm (TWA of 100 ppm): same symptoms as above.

End point/Concentration/Rationale: Weight of evidence from multiple clinical studies indicated that toluene at 200 ppm for up to 8 h would be without effects that exceed the definition of AEGL-1. Slight irritation reported in some studies, but not others.

Uncertainty factors/Rationale:
Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: Not applied; steady-state at 67 ppm is approached fairly rapidly.

Data adequacy: Twenty clinical studies, many of them recent and well-conducted, addressed sensory irritation and the threshold for CNS effects. Metabolism and monitoring studies also indicate a lack of substantial effects at 200 ppm.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)

Reference: Bushnell, P.J., W.M. Ohiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A Dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.

Test species/Strain/Number: Rat; Long-Evans; 16 male rats exposed in groups of 4.

Exposure route/Concentrations/Durations: Inhalation; 0, 1,200, 1,600, 2,000, or 2,400 ppm for up to 70 min.

Effects: Reaction time doubled compared with air-exposed controls. Concentration-related increase in reaction time. NOAEL for a doubling of reaction time was 1,600 ppm for a 34-min exposure.

End point/Concentration/Rationale: Doubling of reaction time, threshold of 1,600 ppm for 34-min exposure

Uncertainty factors/Rationale:
Interspecies: 1, PBPK modeling eliminated the toxicokinetic component of the uncertainty factor; the pharmacodynamic component was assigned a factor of 1 because similar central-nervous-system effects were observed in rodents and humans.
Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: PBPK modeling performed

Time scaling: PBPK modeling was used to determine the equivalent exposure concentrations that yield the dose metric at each of the AEGL exposure durations.

Data adequacy: The values are supported by a comparison of the AEGL values and corresponding effect levels from ethanol consumption in humans (Benignus et al. 2011).

[a]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
–[a]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6,800 mg/m^3)	1,400 ppm[b] (5,300 mg/m^3)

Reference: Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.

Test species/Strain/Number: Rats, CD, 6 males per group

Exposure route/Concentrations/Durations: Inhalation, 810, 1,660, or 3,100 ppm for 4 h; 6,250 ppm for 2 h

Effects: No deaths after a 2-h exposure at 6,250 ppm

End point/Concentration/Rationale: NOAEL for lethality, 6,250 ppm for 2 h

Uncertainty factors/Rationale: Interspecies: 1, PBPK modeling eliminated the toxicokinetic component of the uncertainty factor; the pharmacodynamic component was assigned a factor of 1 because similar central-nervous-system effects were observed in rodents and humans. Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
Modifying factor: None
Animal-to-human dosimetric adjustment: PBPK modeling performed
Time scaling: PBPK modeling was used to determine the equivalent exposure concentrations that yield the dose metric at each of the AEGL exposure durations.
Data adequacy: There are multiple lethality studies in rats and mice. The AEGL-3 values are supported by the 20-min NOAEL of 12,000 ppm for lethality in the mouse (Bruckner and Peterson 1981a), the 2-h NOAEL of 5,000 ppm for lethality in rats (Kojima and Kobayashi 1973), the 4-h NOAEL of 6,000 ppm for lethality in rats (Wada et al. 1989), the NOAEL of 6,000 ppm in mice repeatedly exposed for 30 min/day (Moser and Balster 1981), and the chronic NOAEL of 1,200 ppm for mice and rats (NTP 1990).

[a]The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

7

Trimethylacetyl Chloride[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Lisa Ingerman (SRC, Inc.), Chemical Manager George Rusch (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Trimethylacetyl chloride is a clear colorless liquid. It is corrosive and is a moisture-sensitive lachrymator. Trimethylacetyl chloride is used as an intermediate in the preparation of trialkylacetic acids, which are used in polymers, pharmaceuticals, agricultural chemicals, cosmetics, and metal-working fluids.

Data were insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

In the absence of appropriate chemical-specific data on trimethylacetyl chloride, the AEGL-3 values were divided by 3 to derive AEGL-2 values. That approach is justified by the steep concentration-response curve. In a mouse irritation study, a 30-min exposure to trimethylacetyl chloride at 115 ppm resulted in 25% mortality, and a 1.6 increase in the concentration resulted in a 3-fold increase in mortality (75% mortality at 180 ppm) (Hardy and Kieran, 1992). Rats or mice exposed to trimethylacetyl chloride at 78, 115, 180, and 249 ppm for 30 min to 6 h experienced 0, 25, 75, and 100% mortality, respectively (Eastman Kodak 1992; Hardy and Kieran 1992).

An exposure to trimethylacetyl chloride causing no death in rats (78 ppm for 6 h) (Eastman Kodak 1992) was used as the point of departure for the AEGL-3 values. Rough coat, labored breathing, and body weight loss were noted at that concentration, and 100% mortality was noted at the next highest concentration tested (249 ppm for 3.5 h). Values were scaled across time using the equation $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter

durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value was adopted as the 10-min value because of the added uncertainty of extrapolating a 6-h point of departure to a 10-min AEGL-3 value. Two uncertainty factors of 10 were applied; one factor to account for interspecies differences and one factor to account for the absence of information available to describe interindividual variability. Although clinical signs and pathology from the available data set suggest contact irritation and corrosion (labored breathing, gasping, and corneal opacity in rats, and decreased respiratory rate, lung necrosis, and increased lung weight in mice) and that type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. In addition, RD_{50} (concentration that reduces the respiratory rate by 50%) data suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-182 ppm from the mouse RD_{50} study [Hardy and Kieran 1992]). A modifying factor of 3 was applied to account for the sparse database. Therefore, the total adjustment is 300. The AEGL values for trimethylacetyl chloride are presented in Table 7-1.

1. INTRODUCTION

Trimethylacetyl chloride is a clear colorless liquid (Hardy and Kieran 1992). It is corrosive and is a moisture-sensitive lachrymator (ChemFinder 2007). Trimethylacetyl chloride is used as an intermediate in the preparation of trialkylacetic acids, which are used in polymers, pharmaceuticals, agricultural chemicals, cosmetics, and metal-working fluids. The chemical and physical properties of trimethylacetyl chloride are presented in Table 7-2.

TABLE 7-2 Chemical and Physical Properties of Trimethylacetyl Chloride

Parameter	Value	References
Synonyms	Pivaloyl chloride; 2,2-dimethyl-propanoyl chloride	ChemFinder 2007
CAS registry no.	3282-30-2	ChemFinder 2007
Chemical formula	C_5H_9ClO	ChemFinder 2007
Molecular weight	120.58	ChemFinder 2007
Physical state	Clear, colorless liquid	Hardy and Kieran 1992
Melting point	-56°C	ChemFinder 2007
Boiling point	105°C	ChemFinder 2007
Flash point	19°C	ChemFinder 2007
Density	0.979	ChemFinder 2007
Solubility in water	Moisture sensitive	ChemFinder 2007
Vapor pressure	27 mm Hg at 20°C	ChemFinder 2007
Conversion factors	1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.20 ppm	

2. HUMAN TOXICITY DATA

No human toxicity data or odor threshold data on trimethylacetyl chloride were found.

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

Groups of three rats were exposed to trimethylacetyl chloride at 78 ppm for 6 h or at 249 ppm for 3.5 h, followed by a 14-day observation period (Eastman Kodak 1992). No further experimental details were provided. Rats in the 249-ppm group exhibited dark eyes, labored breathing, loss of coordination, gasping, and jumping during exposure. All three were prostrate 3 h into exposure and dead within 3.5 h of exposure. Corneal opacity was found at death. No mortality was observed at 78 ppm. However, clinical signs including rough coat and labored breathing, and an average weight loss of 8 g in the 14-day follow-up period were observed.

In an RD_{50} irritancy test, groups of four male albino mice were exposed to trimethylacetyl chloride at 0, 115, 180, or 634 ppm (analytic concentrations) for 30 min, followed by a 24-h observation period (Hardy and Kieran 1992). Flow rate was 13 L/min, and the test atmosphere was analyzed by gas chromatography. The study followed GLP guidelines. An RD_{50} of 290 ppm was calculated. Mortality occurred at all test concentrations; one of four rats died at 115 ppm, three of four at 180 ppm, and three of four at 634 ppm. Absolute lung weight and relative lung-to-body-weight ratios were increased in a concentration-dependent manner in animals surviving 24 h. Microscopic lung pathology in animals surviving 24 h included vascular congestion, alveolar edema, single cell necrosis of bronchiolar epithelium, alveolar duct necrosis, debris in the alveolar ducts, and generalized necrosis of bronchiolar epithelium. Because the RD_{50} was also associated with lethality in the test population, it was not used for the development of AEGL values. An LC_{50} value of 101-182 ppm for 30 min was estimated by the study authors. (The benchmark dose modeling failed because the lower limit included zero.)

3.2. Developmental and Reproductive Toxicity

No data on developmental or reproductive toxicity on trimethylacetyl chloride were found.

3.3. Genotoxicity

No genotoxicity data on trimethylacetyl chloride were found.

3.4. Chronic Toxicity and Carcinogenicity

No data on chronic toxicity or carcinogenicity of trimethylacetyl chloride were found.

3.5. Summary

Animal toxicity data on trimethylacetyl chloride are sparse. Clinical signs and lung pathology in rats and mice are consistent with severe irritation and corrosion. No data on developmental or reproductive toxicity, genotoxicity, or chronic toxicity and carcinogenicity were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information concerning the metabolism and disposition of trimethylacetyl chloride was found.

4.2. Mechanism of Toxicity

Acute inhalation exposure to trimethylacetyl chloride appears to cause irritation (Hardy and Kieran 1992; Eastman Kodak 1992).

4.3. Structure-Activity Relationships

No information was available on structure-activity relationships relevant to trimethylacetyl chloride.

4.4. Other Relevant Information

4.4.1. Species Variability

No information was available on species variability in response to trimethylacetyl chloride.

4.4.2. Susceptible Populations

No information was available on populations sensitive to trimethylacetyl chloride toxicity. However, clinical signs are consistent with irritation. Therefore, effects are not expected to vary widely among individuals.

4.4.3. Time Scaling

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on trimethylacetyl chloride were inadequate to derive an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values for trimethylacetyl chloride were available.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values for trimethylacetyl chloride were available.

5.3. Derivation of AEGL-1 Values

No human or animal data were available for derivation of AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values for trimethylacetyl chloride were available.

6.2. Animal Data Relevant to AEGL-2

No mortality was observed in rats exposed to trimethylacetyl chloride at 78 ppm for 6 h. Rough coat, labored breathing, and body weight loss were noted at that concentration (Eastman Kodak 1992). Mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). No lower concentrations were tested.

6.3. Derivation of AEGL-2 Values

No suitable data that provided a point of departure for deriving AEGL-2 values for trimethylacetyl chloride were available. In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to estimate AEGL-2 values for trimethylacetyl chloride. That approach is justified by the steep concentration-response curve. In the mouse irritation study, a 30-min exposure to trimethylacetyl chloride at 115 ppm resulted in 25% mortality, and 1.6 increase in the concentration resulted in a 3-fold increase in mortality (75% mortality at 180 ppm) (Hardy and Kieran 1992). Rats or mice exposed to trimethylacetyl chloride at 78, 115, 180, and 249 ppm for 30 min to 6 h experienced 0, 25, 75, and 100% mortality, respectively (Eastman Kodak 1992; Hardy and Kieran 1992). AEGL-2 values for trimethylacetyl chloride are presented in Table 7-3.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values for trimethylacetyl chloride were available.

7.2. Animal Data Relevant to AEGL-3

No mortality was observed in rats exposed to trimethylacetyl chloride at 78 ppm for 6 h. Rough coat, labored breathing, and body weight loss were noted at that concentration (Eastman Kodak 1992). Mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). No other concentrations were tested.

7.3. Derivation of AEGL-3 Values

The concentration of trimethylacetyl chloride causing no death in rats (78 ppm for 6 h) (Eastman Kodak 1992) was used as the point of departure for the AEGL-3 values. Rough coat, labored breathing, and body weight loss were found at that concentration, and mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). Two uncertainty factors of 10 were applied; one factor to account for interspecies differences and one factor due to the absence of information available to describe interindividual variability. Although clinical signs and pathology from the sparse data set suggest contact irritation and corrosion (labored breathing, gasping, and corneal opacity in rats, and decreased respiratory rate, lung necrosis, and increased lung weight in mice) and that type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. In addition, the RD_{50} data on trimethylacetyl chloride suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-

182 ppm from the mouse RD_{50} study [Hardy and Kieran 1992]). A modifying factor of 3 was applied to account for the sparse database. Therefore, the total adjustment was 300.

Time scaling was performed using the equation $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value for trimethylacetyl chloride was adopted as the 10-min value because of the added uncertainty of extrapolating a 6-h point of departure to a 10-min AEGL-3 value.

The AEGL-3 values for trimethylacetyl chloride are presented in Table 7-4, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for trimethylacetyl chloride are presented in Table 7-5. AEGL-1 values are not recommended due to insufficient data. AEGL-2 values were derived by taking one-third of the AEGL-3 values, and AEGL-3 values were based on an exposure causing no death in rats exposed to trimethylacetyl chloride for 6 h.

TABLE 7-3 AEGL-2 Values for Trimethylacetyl Chloride

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)

TABLE 7-4 AEGL-3 Values for Trimethylacetyl Chloride

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

TABLE 7-5 AEGL Values for Trimethylacetyl Chloride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)
AEGL-3 (lethal)	0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposures below the AEGL-2 value are without adverse effect.

8.2. Other Standards and Guidelines

There are no other exposure standards or guidelines for trimethylacetyl chloride.

8.3. Data Adequacy and Research Needs

There are no human data on trimethylacetyl chloride, and there are no animal data relevant to AEGL-1 or AEGL-2 end points. Available toxicity data on trimethylacetyl chloride are limited to unpublished lethality data in groups of three rats exposed to two concentrations for 3.5 or 6 h (Eastman Kodak 1992) and a 30-min RD_{50} test in mice, in which mortality occurred at all exposure concentrations (Hardy and Kieran 1992). There are no data on nonlethal toxicity in animals, metabolism, or disposition of trimethylacetyl chloride in humans or animals, or on the mechanism of action of the chemical. Additional research on workplace exposures (if applicable), acute inhalation toxicity in animals, toxicokinetics, and mechanism of action would enhance confidence in the AEGL values.

9. REFERENCES

ChemFinder. 2007. Pivaloyl Chloride (CAS Reg. No. 3282-30-2) [online]. Available: http://www.cambridgesoft.com/ [accessed July 2007].

Eastman Kodak Co. 1992. Initial Submission: Acute Inhalation Toxicity Study with Pivaloyl Chloride in Rats. Submitted to EPA, Washington, DC, by Eastman Kodak Co, Rochester, NY with Cover Letter Dated August 10, 1992. EPA Document No. 88-920005125. Microfiche No. OTS0544099.

Hardy, C.J., and P.C. Kieran. 1992. Assessment of the Respiratory Tract Irritancy of Trimethyl Acetyl Chloride in the Mouse. Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England. SLL 206/911521. July 16, 1992. Submitted to EPA, Washington, DC, by Shell Oil Company, Houston, TX with Cover Letter Dated November 12, 1992. EPA Document No. 88-930000053. Microfiche No. OTS0538315.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Acute Exposure Guideline Levels for Selected Airborne Chemicals. Washington, DC: The National Academies Press

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

APPENDIX A

DERIVATION OF AEGL VALUES FOR TRIMETHYLACETYL CHLORIDE

Derivation of AEGL-1 Values

Data are insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

Derivation of AEGL-2 Values

Data are insufficient to derive AEGL-2 values for trimethylacetyl chloride. Therefore, AEGL-2 values were derived by taking one-third of the respective AEGL-3 values. That approach is justified by the steep concentration-response for the chemical.

10-min AEGL-2:	0.60 ppm ÷ 3 = 0.20 ppm
30-min AEGL-2:	0.60 ppm ÷ 3 = 0.20 ppm
1-h AEGL-2:	0.47 ppm ÷ 3 = 0.16 ppm
4-h AEGL-2:	0.30 ppm ÷ 3 = 0.10 ppm
8-h AEGL-2:	0.20 ppm ÷ 3 = 0.07 ppm

Derivation of AEGL-3 Values

Key study:	Eastman Kodak Co. 1992. Initial Submission: Acute Inhalation Toxicity Study with Pivaloyl Chloride in Rats. Submitted to EPA, Washington, DC, by Eastman Kodak Co, Rochester, NY with Cover Letter Dated August 10, 1992. EPA Document No. 88-920005125. Microfiche No. OTS0544099.
Toxicity end point:	No death in rats (78 ppm for 6 h)
Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986), with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). $(78 \text{ ppm})^3 \times 6 \text{ h} = 2{,}847{,}312 \text{ ppm-h}$ $(78 \text{ ppm})^1 \times 6 \text{ h} = 468 \text{ ppm-h}$

Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability
Modifying factor:	3 for sparse database
10-min AEGL-3:	0.60 ppm (set equal to the 30-min AEGL-3 value)
30-min AEGL-3:	$C^3 \times 0.5$ h = 2,847,312 ppm-h C^3 = 5,694,624 ppm C = 179 ppm 179 ppm ÷ 300 = 0.60 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 2,847,312 ppm-h C^3 = 2,847,312 ppm C = 142 ppm 142 ppm ÷ 300 = 0.47 ppm
4-h AEGL-3:	$C^3 \times 4$ h = 2,847,312 ppm-h C^3 = 718,578 ppm C = 89.3 ppm 89.3 ppm ÷ 300 = 0.30 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 468 ppm-h C = 58.5 ppm 58.5 ppm ÷ 300 = 0.20 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR TRIMETHYLACETYL CHLORIDE

Derivation Summary

AEGL-1 VALUES

Data were insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended for trimethylacetyl chloride.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)

Data adequacy: Data on trimethylacetyl chloride are sparse. AEGL-2 values were derived by dividing the AEGL-3 values for trimethylacetyl chloride by 3. That approach is supported by the steep concentration-response curve (0% mortality in rats exposed at 78 ppm for 6 h and 100% mortality at 249 ppm for 3.5 h (Eastman Kodak 1992); 25% mortality in mice exposed at 115 ppm and 75% mortality at 180 ppm for 30 min (Hardy and Kieran 1992).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

Key reference: Eastman Kodak Co. 1992. Initial Submission: Acute Inhalation Toxicity Study with Pivaloyl Chloride in Rats. Submitted to EPA, Washington, DC, by Eastman Kodak Co, Rochester, NY with Cover Letter Dated August 10, 1992. EPA Document No. 88-920005125. Microfiche No. OTS0544099.

Test species/Strain/Number: Rat; strain and sex not specified; 3/group

Exposure route/Concentrations/Durations: Inhalation; various concentrations for up to 6 h

Effects:
249 ppm for 3.5 h: 3/3 rats died; clinical signs included labored breathing, loss of coordination, gasping, and corneal opacity.
78 ppm for 6 h: No mortality; rough coat, labored breathing, and body weight loss.

End point/Concentration/Rationale: No mortality in rats exposed at 78 ppm for 6 h; considered a threshold for lethality.

Uncertainty factors/Rationale: Total uncertainty factor of 100.
Interspecies: 10, RD_{50} data suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-182 ppm from the mouse RD_{50} study) (Hardy and Kieran 1992)

Intraspecies: 10
Modifying factor: 3, because of the sparse database.
Animal-to-human dosimetric adjustment: None
Time scaling: $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value was adopted as the 10-min value because of the added uncertainty of extrapolating the 6-h point of departure to the 10-min AEGL-3 value.
Data adequacy: Sparse data set. Values are considered protective. The 30-min AEGL-3 value is approximately 75-fold lower than the estimated 30-min LC_{50} of 101-182 ppm from the mouse RD_{50} study (Hardy and Kieran 1992), and the 4-h AEGL-3 value is approximately 250-fold lower than the 249 ppm that caused 100% mortality in rats exposed to trimethylacetyl chloride for 3.5 h (Eastman Kodak 1992).

APPENDIX C

CATEGORY PLOT FOR TRIMETHYLACETYL CHLORIDE

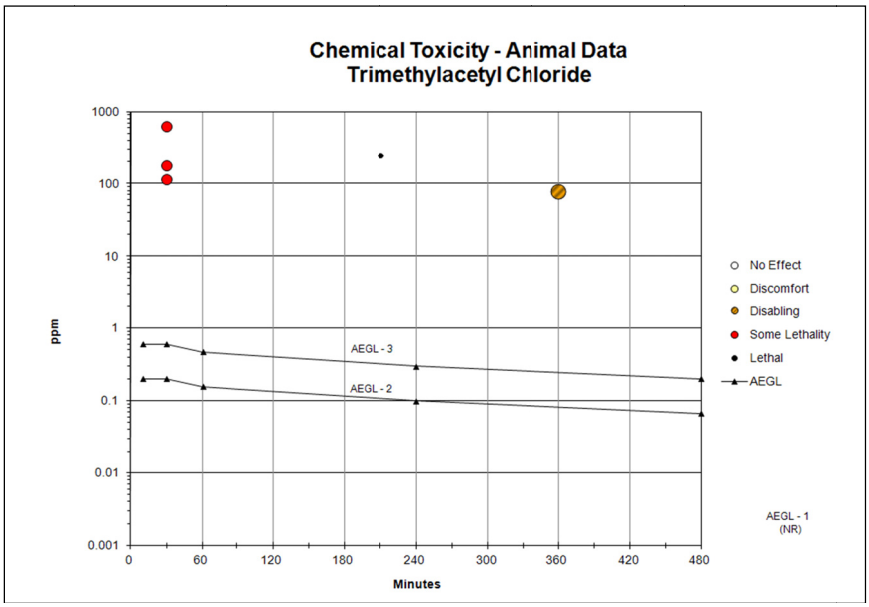


FIGURE C-1 Category plot of toxicity data and AEGL values for trimethylacetyl chloride.

TABLE C-1 Data Used in the Category Plot for Trimethylacetyl Chloride

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
AEGL-2				0.20	10	AEGL	
AEGL-2				0.20	30	AEGL	
AEGL-2				0.16	60	AEGL	
AEGL-2				0.10	240	AEGL	
AEGL-2				0.07	480	AEGL	
AEGL-3				0.60	10	AEGL	
AEGL-3				0.60	30	AEGL	
AEGL-3				0.47	60	AEGL	
AEGL-3				0.30	240	AEGL	
AEGL-3				0.20	480	AEGL	
Eastman Kodak 1992	Rat		1	78	360	2	Rough coat, labored breathing, body weight loss.
Eastman Kodak 1992	Rat		1	249	210	3	Mortality 3/3
Hardy and Kieran 1992	Mouse		1	115	30	SL	Mortality 1/4
Hardy and Kieran 1992	Mouse		1	180	30	SL	Mortality 3/4
Hardy and Kieran 1992	Mouse		1	634	30	SL	Mortality 3/4

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

8

Hydrogen Bromide[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Susan Ripple (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Hydrogen bromide (HBr) is a colorless, corrosive, and non-flammable gas. HBr fumes strongly in moist air. It is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl). It is extremely soluble in water, forming a strong acid that is available as 48% or 68% solutions. HBr is used both as a reagent and as a catalyst in a variety of organic reactions; it is also used in the preparation of numerous bromide compounds. Anhydrous HBr is shipped in high-pressure steel cylinders.

HBr is a severe irritant to the eyes, skin, and nasal passages; high concentrations may penetrate to the lungs resulting in edema and hemorrhage. Data on irritant effects in humans and lethal and sublethal effects in rats and mice were available for developing AEGL values. Although the database for HBr is sparse, data on the toxicity of HBr relative to that of hydrogen fluoride (HF) and HCl were available for comparison purposes. The databases for HCl and HF are robust. On the basis of lethality data from studies of rats and mice, HF is more potent than HCl and HBr; HCl and HBr have similar potencies (MacEwen and Vernot 1972). At sublethal concentrations, the severity and extent of lesions to the upper respiratory tract were greatest for HF, followed by HCl and then HBr, although the severity and extent of lesions in the anterior most region of the respiratory tract were similar among the three chemicals (Kusewitt et al. 1989; Stavert et al. 1991). The data also show that all three chemicals are well scrubbed in the upper respiratory passages.

The AEGL-1 values for HBr are based on a study of six human volunteers exposed at 2, 3, 4, 5, or 6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). No nasal, throat, or ocular irritation was reported at 2 ppm. One subject reported nasal and throat irritation (severity not defined) but no ocular irritation at 3 ppm. Nasal irritation was reported by all six subjects at 5 and 6 ppm, but only one reported throat irritation and none reported ocular irritation. The concentration of 3 ppm was considered a no-observed-adverse-effect level (NOAEL) for notable discomfort. This point of departure was divided by an uncertainty factor of 3 to protect sensitive individuals; time-scaling was not performed, because irritation is concentration related and humans adapt to the slight sensory irritation that defines the AEGL-1. A concentration of 1.0 ppm across the AEGL exposure durations is supported by the AEGL-1 values for HF and HCl of 1.0 and 1.8 ppm, respectively (NRC 2004). The AEGL-1 value might be conservative, as only one of six subjects reported any sensory irritation and the value is the same as that of HF, a slightly more toxic chemical. It is also below the AEGL-1 value of 1.8 ppm for HCl, which was based on a no-effect concentration in exercising asthmatics.

There are limited data on AEGL-2 effects from exposure to HBr. Stavert et al. (1991) reported severe necrohemorrhagic rhinitis in rats exposed to HBr at 1,300 ppm for 30 min; however, 8% mortality was also reported at that concentration. In the absence of suitable data, the AEGL-3 values for HBr were divided by 3 to derive AEGL-2 values.

A $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 1,239 ppm was calculated from 1-h lethality data from studies of Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972). The $BMCL_{05}$ is an estimate of the threshold for lethality, and was used as the point of departure for calculating AEGL-3 values for HBr. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for human variability. Those individual factors are considered sufficient because the action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001). The 60-min point of departure was time-scaled to the other AEGL durations using the equation $C^n \times t = k$. The value of n was 1, on the basis of data for the related compound HCl, for which regression analysis of combined rat and mouse LC_{50} (lethal concentration, 50% lethality) data resulted in a value of 1 for n (see NRC 2004).

The AEGL values for HBr are presented in Table 8-1.

1. INTRODUCTION

Hydrogen bromide (HBr) is a colorless nonflammable gas that fumes strongly in moist air. It is highly water soluble. HBr is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl) (Jackisch 1992). Chemical and physical properties for HBr are presented in Table 8-2.

TABLE 8-1 AEGL Values for Hydrogen Bromide

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	Threshold for nasal irritation in humans (CT Department of Health, unpublished data 1955).
AEGL-2 (disabling)	250 ppm (830 mg/m^3)	83 ppm (270 mg/m^3)	40 ppm (130 mg/m^3)	10 ppm (33 mg/m^3)	5 ppm (17 mg/m^3)	One-third of AEGL-3 values.
AEGL-3 (lethal)	740 ppm (2400 mg/m^3)	250 ppm (830 mg/m^3)	120 ppm (400 mg/m^3)	31 ppm (100 mg/m^3)	15 ppm (50 mg/m^3)	Threshold for lethality in rats (MacEwen and Vernot 1972)

TABLE 8-2 Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Anhydrous bromic acid, hydrobromic acid	HSDB 2008
Chemical formula	HBr	HSDB 2008
Molecular weight	80.91	HSDB 2008
CAS registry no.	10035-10-6	HSDB 2008
Physical state	Colorless gas	HSDB 2008
Boiling point	-67°C	HSDB 2008
Melting point	-87°C	HSDB 2008
Density	3.307 g/L	Jackisch 1992; HSDB 2008
Solubility in water	Freely soluble 600:1 v:v, HBr to water	HSDB 2008
Vapor density (air = 1)	2.71	HSDB 2008
Vapor pressure	>760 torr at 20°C 335 psia at 21°C	ACGIH 2004; Braker and Mossman 1980
Flammability limits	Nonflammable	Jackisch 1992; HSDB 2008
Conversion factors	1 ppm = 3.3 mg/m^3 1 mg/m^3 = 0.30 ppm	NIOSH 2011

HBr is produced by burning a mixture of hydrogen and bromine vapor. Platinized asbestos or silica gel may be used as catalysts. The vapor is passed through hot, activated charcoal or iron to remove the free bromine. The vapor is then either liquefied by cooling for shipment in cylinders or is absorbed in water. Technical HBr, a colorless to light-yellow liquid, is available as 48% or 62% acids in drums, 15,140-L tank trailers, and 37,850-L tank cars. Anhydrous HBr is available in high-pressure steel cylinders (Braker and Mossman 1980; Jack-

isch 1992). HBr is used in the manufacture of organic and inorganic bromides, hydrobromic acid, as a reducing agent, as a catalyst in controlled oxidation reactions, in the alkylation of aromatic compounds, and in the isomerization of conjugated diolefins (O'Neil et al. 2006).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on concentrations of HBr lethal to humans were found.

2.2. Nonlethal Toxicity

Amoore and Hautala (1983) reported an odor threshold of 2 ppm for HBr. HBr liquid and vapor are highly corrosive to tissues. Symptoms of over exposure include coughing, choking, burning in the throat, wheezing, and asphyxia. Skin contact may cause severe burns, and contact of the eyes with the liquid or vapor may result in permanent damage (Jackisch 1992).

One report by the Connecticut State Department of Health (unpublished data, 1955, as cited in ACGIH 2002[2]) addressed responses of human subjects to HBr vapor. Six volunteers inhaled HBr at concentrations of 2-6 ppm for several minutes (Table 8-3). The odor was detected by all subjects at all concentrations. None of the subjects experienced ocular irritation. Only one subject experienced nasal and throat irritation at 3 ppm. One subject (presumably the same one) experienced throat irritation at all of the higher concentrations, and all subjects experienced nasal irritation at 5 and 6 ppm. Responses ranged from slight, stinging sensations to a definite feeling of irritation. Although exposure at 5 ppm caused nasal irritation in all of the subjects, the authors stated that "it was considered unlikely that noticeable disturbances will occur if peak concentrations do not exceed this value for brief periods."

According to Braker and Mossman (1980), hydrogen halides at concentrations of approximately 35 ppm cause irritation of the throat after short exposures. Concentrations of 1,000-2,000 ppm are lethal to humans from brief exposures and concentrations of 1,000-1,300 ppm are dangerous if breathed for 30-60 min. Those data appear to be from the study by Henderson and Haggard (1943) and apply to HCl.

[2]A detailed description of this study was provided in ACGIH's 2002 documentation of threshold limit values and biological exposure indices for HBr. In its update of the documentation in 2004, ACGIH omitted the study description and did not consider the data in its recommendations. The information from the study by the Connecticut Department of Health is retained here because it provides the only quantitative information on human exposure to HBr.

TABLE 8-3 Human Responses to Hydrogen Bromide Vapor

	Number of Subjects (n = 6) Reporting Responses				
Response	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Detectable odor	6	6	6	6	6
Nasal irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Ocular irritation	0	0	0	0	0

Source: Adapted from ACGIH 2002.

2.3. Neurotoxicity

No information on the neurotoxicity of HBr in humans was found.

2.4. Developmental and Reproductive Toxicity

No data on the developmental or reproductive effects of HBr in humans was found.

2.5. Genotoxicity

No data on the genotoxicity on HBr in humans was found.

2.6. Carcinogenicity

No data on the carcinogenicity of HBr in humans was found.

2.7. Summary

The only human data on HBr involved six volunteers exposed at 2-6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). All six volunteers detected HBr at 2 ppm, and one individual experienced subjective irritation involving the nose and throat at 3 ppm. At higher concentrations, at least half of subjects experienced nasal and throat irritation. No information on neurotoxicity, developmental or reproductive effects, genotoxicity, or carcinogenicity of HBr was found.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

As part of a series of inhalation toxicity studies performed at Wright-Patterson Air Force Base, MacEwen and Vernot (1972; also reported in Back et al. 1972 and Vernot et al. 1977) subjected groups of 10 male Sprague-Dawley-

derived rats to HBr at 2,205-3,822 ppm for 1 h (Table 8-4). Exposures took place in a modified Rochester chamber and concentrations were monitored with a bromide ion-specific electrode. The rats were monitored for mortality for 14 days. The 1-h LC_{50} was 2,858 ppm (95% confidence limits of 2,581-3,164 ppm) (Table 8-5). Responses of the animals during the exposures were dose-related and had the following a sequence: nasal and ocular irritation, labored breathing, gasping, and convulsions. The fur turned orange-brown during the exposures, and the color intensity was related to the concentration. The authors attributed a smoky haze around the animals during exposure to the reaction of HBr with the fur or moisture on the fur. During the 14-day postexposure period, the surviving animals were prostrate and most lost weight. Delayed deaths were observed. Burns accompanied by autolysis were observed on exposed areas of the skin. Rats exposed at the lowest concentration (2,205 ppm) returned to a normal weight gain by the end of the postexposure period. Gross examination at necropsy showed severe pulmonary and hepatic congestion and pulmonary edema in rats exposed at 3,822 ppm. The investigators noted that rats exposed at the lower concentration (not specified) had necrotic lesions on their feet and tails for up to 14 days. Opacity of the cornea, observed immediately following exposure, disappeared within 24 h.

Groups of 5-8 male Fischer 344 rats were exposed to HBr at approximately 1,300 ppm for 30 min (Stavert et al. 1991). Rats were placed into whole body flow plethysmographs to measure ventilatory rates. Body weight and respiratory-tract histology were investigated 24 h later. The mortality rate was 8% (Table 8-5). Rats exposed to HBr experienced an immediate and persistent drop in minute ventilatory rate of 25%. The effect on ventilatory rate was similar with HF exposure, whereas exposure to HCl caused a much smaller decrease in ventilation. A small (<10%) reduction in body weight compared to nonexposed rats occurred by 24 h postexposure.

TABLE 8-4 Results of One-Hour Inhalation Studies of Hydrogen Bromide in Rats and Mice

Species	Concentration (ppm)	Mortality Ratio
Rat	2,205	1/10
	2,328	4/10
	2,759	4/10
	3,253	6/10
	3,711	7/10
	3,822	10/10
Mouse	507	0/10
	875	7/10
	1,036	9/10
	1,163	10/10

Source: Adapted from MacEwen and Vernot 1972.

TABLE 8-5 Summary of Acute Lethality Data on Hydrogen Bromide in Rats and Mice

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1,300	30 min	8% mortality	Stavert et al. 1991
	2,858	1 h	LC_{50}	MacEwen and Vernot 1972
Mouse	507	1 h	No deaths	MacEwen and Vernot 1972
	814	1 h	LC_{50}	

As part of the same study, Stavert et al. (1991) compared the toxicities of three hydrogen halides (HF, HCl, and HBr) in rats exposed at 1,300 ppm for 30 min. Mortalities were 0% for HF, 6% for HCl, and 8% for HBr. Damage to the respiratory tract was assessed 24 h after the exposure. For all three hydrogen halides, tissue injury was confined to the nasal cavity. Tissue injury in the anterior nasal cavity was similar for all three compounds and involved moderate to severe fibrinonecrotic rhinitis. The mucosa and submucosa were necrotic, with necrosis extending to the turbinate bone. Blood clots were observed in nasal blood vessels; hemorrhage, fibrin, and fluid were observed in the nasal passages; and polymorphonuclear cells were observed in the submucosa and in the lumen. The severity of these lesions is summarized in Table 8-6. Exposure to HBr resulted in bilateral or unilateral severe necrohemorrhagic rhinitis in the anterior quarter of the nasal cavity, and necrosis of the mucosa and submucosa that extended to the nasal turbinate bone. For HF and HCl, but not HBr, the lesions were also observed in the second anterior quarter of the nasal cavity. After exposure to all three halogen halides, the posterior half of the nasal cavity (including the ethmoid region) was essentially normal in appearance, showing that all three chemicals were well scrubbed. No pulmonary or tracheal injury was evident for any of the chemicals. The authors concluded that respiratory-tract injury caused by exposure to the three hydrogen halides was quantitatively similar. There was no change in pulmonary weight.

In the same study (Stavert et al. 1991), groups of male Fischer 344 rats were exposed to HBr at 1,300 ppm for 30 min via a tracheal cannula (to simulate mouth breathing). This procedure bypasses the scrubbing of the nasal passages. Within 24 h after exposure, 19% of the rats died. Mean pulmonary weight was not significantly different from that of noncannulated rats or of rats exposed to air. Pulmonary lesions observed in treated animals were not significantly different from those of the cannulated control group.

3.1.2. Mice

MacEwen and Vernot (1972) (see also Back et al. 1972) exposed groups of 10 CF1 (ICR-derived) mice (20-30 g) to HBr at concentrations ranging from 507 to 1,163 ppm for 1 h (Table 8-4). The LC_{50} was 814 ppm (95% confidence

limits of 701-947 ppm) (Table 8-5). Responses during exposure were the same as those described for rats (see Section 3.1.1). No deaths occurred in mice exposed at 507 ppm, and the mice had a normal weight gain during the 14-day recovery period. Mice surviving the 14-day postexposure period had necrotic lesions of their tails. No other gross pathologic changes were apparent in surviving mice.

3.2. Nonlethal Toxicity

As part of the Stavert et al. (1991) study, Kusewitt et al. (1989) reported on exposures to three hydrogen halides at lower concentrations. Fischer 344 rats (number not specified) were exposed to HF, HCl, or HBr at concentrations of 100-1,000 ppm for 30 min and were killed 8 and 24 h later. Tissue damage was restricted to the nasal region and consisted of necrosis and inflammation; the severity of the damage increased with concentration. HF was the most toxic, and that the toxicities of HCl and HBr were similar. Histopathologic examinations and gravimetric measurements revealed no damage to the lungs. No further details were reported in the available abstract.

Toxicity data on the related chemical, HCl, are relevant to evaluating the toxicity of HBr. In a study in which the ventilatory rate of rats exposed to HCl at 1,000 ppm for 30 min was increased by the addition of CO_2 to the exposure chamber, no deaths occurred and histopathologic lesions were confined to the upper respiratory tract and (Lehnert and Stavert 1991). Barrow et al. (1977) exposed groups of four male Swiss-Webster mice to HCl at concentrations of 40, 99, 245, 440, or 943 ppm for 10 min. An RD_{50} (a 50% decrease in the respiratory rate) of 309 ppm was calculated. At 99 ppm, approximately one-third of the RD_{50}, the decrease in respiratory rate was 25-30%. Additional studies summarized in NRC (2004) showed that primates were less sensitive to the toxic effects of HCl than rodents.

TABLE 8-6 Severity of Lesions in the Anterior Region of the Nasal Cavity of Rats Following Exposure to Hydrogen Fluoride, Hydrogen Chloride, or Hydrogen Bromide at 1,300 ppm for 30 Minutes

Necrotic Lesion	HF	HCl	HBr
Epithelial	3.3[a]	3.8[a]	3.3[a]
Submucosal	2.6[a]	3.0[a]	2.6[a]
Bone	0.3	2.4[a]	1.6[a]
Gland	1.8[a]	2.4[a]	1.4[a]

Severity index: 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe (n = 8).
[a]Statistically significant compared to air-exposed controls, $p < 0.05$.
Source: Adapted from Stavert et al. 1991.

3.3. Neurotoxicity

No information on the neurotoxicity of HBr in animals was found.

3.4. Developmental and Reproductive Toxicity

No information on the developmental or reproductive effects of HBr in animals was found.

3.5. Genotoxicity

No information on the genotoxicity of HBr in animals was found.

3.6. Chronic Toxicity and Carcinogenicity

No information on the chronic toxicity or carcinogenicity of HBr in animals was found.

3.7. Summary

Two studies of HBr in animals were available. In the first study (MacEwen and Vernot 1972), groups of rats and mice were exposed by inhalation to a range of concentrations for 1 h. The 1-h LC_{50} value was 2,858 in rats and 814 ppm in mice. All tested concentrations resulted in lethality in rats during the 14-day postexposure period. No deaths occurred in mice exposed at 507 ppm for 1 h. In rats exposed at 1,300 ppm for 30 min, mortality was 8% (presumably one of 12 rats) and lesions were confined to the anterior nasal passages (Stavert et al. 1991). Nasal lesions were also observed in rats exposed at up to 1,000 ppm for 30 min (Kusewitt et al. 1989). Animals in the Kusewitt et al. (1989) and Stavert et al. (1991) studies were killed 24 h after exposure. Only one of 10 rats exposed at 2,205 ppm died in the MacEwen and Vernot (1972) study.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the metabolism and deposition of HBr were found. Data on soluble bromides are available from their medical use as oral sedatives, diuretics, and antiepileptics. An oral dose of 3 g (30-60 mg/kg for an adult) is considered a “no-ill effect” dose (Teitelbaum 2001).

4.2. Mechanism of Toxicity

The available studies indicate that the hydrogen halides are severe irritants to the skin, eyes, and respiratory tract, particularly the anterior nasal passages where, depending on concentration, they appear to be effectively scrubbed from the inhaled air. For HBr, deposition in the anterior nasal passages may be attributed to its high solubility and reactivity. At high concentrations (e.g., 3,822 ppm for 1 h), penetration into the lungs occurs as evidenced by pulmonary hemorrhage, edema, and death. Although HBr is absorbed, serious systemic effects are unlikely to occur at concentrations below those that would cause serious respiratory effects. In the studies summarized in Tables 8-4 and 8-5, the tissues of the respiratory tract and exposed dermal surfaces sustained the impact of an acute exposure. Therefore, the concentration of HBr in the inhaled air and not the absorbed dose is the primary determinant of the effects from acute exposures.

4.3. Structure-Activity Relationships

Differences in size and electron configuration of the various halogen atoms result in substantial differences with respect to their chemical and physical properties, which in turn affect their toxicologic properties. The atomic weights of fluorine, chlorine, bromine, and iodine are 19, 35.5, 80, and 127, respectively.

Data on the relative toxicities of HF, HCl, and HBr on the basis of lethality are available. As can be seen from the data in Table 8-7, three rodent studies using different exposure durations show that HF is more lethal than HCl (Rosenholtz et al. 1963; Higgins et al. 1972; MacEwen and Vernot 1972; Wohlslagel et al. 1976). For both the rat and mouse, HF is also more lethal than HBr (MacEwen and Vernot 1972). Data from the same laboratory (Wohlslagel et al. 1976; MacEwen and Vernot 1972) show that HCl and HBr have similar 1-h LC_{50} values of 3,124 and 2,858 ppm, respectively. Data on the nonlethal toxicity of the three hydrogen halides (Stavert et al. 1991) suggest that HF, HCl, and HBr are similarly toxic to the nasal cavity following acute exposure. HBr and HF exposure resulted in similar decreases (by about 25%) in the ventilation rate of cannulated rats (simulation of mouth breathing), whereas the decrease associated with HCl exposure was smaller (Stavert et al. 1991).

4.4. Other Relevant Information

4.4.1. Species Variability

HBr toxicity data, available for only the rat and mouse, showed that mice are more susceptible than rats. However, when considering lethal concentrations of respiratory irritants (such as HCl), the mouse "may not be an appropriate model for extrapolation to humans," because "mice appear to be much more

TABLE 8-7 Relative Toxicities of Hydrogen Fluoride, Hydrogen Chloride, and Hydrogen Bromide

Species	Exposure Duration	LC_{50} Values (ppm) HF	HCl	HBr	Reference
Rat	5 min	18,200	41,000	–	Higgins et al. 1972
Mouse	5 min	6,247	13,750	–	
Rat	30 min	2,042	4,700		Rosenholtz et al. 1963; MacEwen and Vernot 1972
Mouse	30 min	–	2,644	–	MacEwen and Vernot 1972
Rat	1 h	1,395	3,124	–	Wohlslagel et al. 1976
Mouse	1 h	342	1,108	–	
Monkey	1 h	1,774	–	–	MacEwen and Vernot 1970
Rat	1 h	1,278	–	2,858	MacEwen and Vernot 1972
Mouse	1 h	501	–	814	MacEwen and Vernot 1972

The data of Wohlslagel et al. (1976) and MacEwen and Vernot (1972) were generated in the same laboratory. Therefore, the values for HCl (Wohlslagel et al. 1976) can be compared with those for HF and HBr (MacEwen and Vernot 1972).

susceptible to the lethal effects of HCl than other rodents or baboons. To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract" (NRC 1991). The same principle reasonably holds true for HF and HBr. The respiratory rate of mice is also higher than that of rats. The data in Table 8-7 show species that mice are the most susceptibile to HF, followed by the rat and nonhuman primate (rhesus monkey).

4.4.2. Susceptible Populations

Individuals with asthma may respond to exposure to respiratory irritants, such as HBr, with increased bronchial responsiveness. No information on the relative susceptibility of asthmatic and normal individuals to HBr was found. In a study with HCl, exposure at1.8 ppm for 45 min was a no-effect level for exercising asthmatics (Stevens et al. 1992).

Individuals under stress, such as those involved in emergency situations and individuals engaged in physical activity, will likely experience increased penetration of HBr into the lower respiratory tract due to increased minute volumes, with the potential for increased irritant response, as compared to individuals at rest.

4.4.3. Concentration-Exposure Duration Relationship

No information on the relationship between concentration and exposure for a single end point was found. When no data are available, time scaling is

based on the equation $C^n \times t = k$, with default values of n = 3 for extrapolation to shorter exposure durations and n = 1 for extrapolation to longer exposure durations (NRC 2001). However, information on relevant chemicals HF and HCl are available. On the basis of lethality data, the n values for time scaling was 2 for HF and 1 for HCl (NRC 2004). HBr is more similar chemically to HCl than HF.

4.4.4. Concurrent Exposure Issues

No information on concurrent exposure issues for HBr was found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Reliable human data on HBr are available from a study of six volunteers exposed at 2-6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). Nasal irritation was reported by 0, 1, 3, 6, and 6 individuals at 2, 3, 4, 5, and 6 ppm, respectively. Throat irritation did not appear to be concentration dependent and no ocular irritation was reported. Therefore, the threshold for subjective nasal irritation is 3 ppm.

5.2. Animal Data Relevant to AEGL-1

No data on HBr relevant to notable discomfort in animals was found.

5.3. Derivation of AEGL-1 Values

The threshold for nasal irritation of 3ppm in human subjects exposed to HBr for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002) was selected as the basis for the AEGL-1 values. That concentration was considered to be a threshold for notable discomfort, as only one individual was affected at that concentration. The 3 ppm point-of-departure was divided by an intraspecies uncertainty factor of 3, because response to sensory irritation is not expected to vary greatly among individuals (NRC 2001). A factor of 3 was considered sufficient because the effect of slight irritation is below the definition of AEGL-1. In addition, an intraspecies uncertainty factor of 3 was used to derive AEGL values for the related compounds HCl and HF, which have the same mode of action as HBr (NRC 2004). It is reasonable to use the same uncertainty factors for a class of chemicals whose mode of action is the same. Finally, the uncertainty factor used to derive the AEGL-1 values for HBr is believed to be protective of asthmatic individuals on the basis of comparison of the AEGL-1 value for HBr (1.0 ppm) with the AEGL-1 value for HCl (1.8

ppm); the latter is based on a no-effect level for irritation in exercising asthmatics. There is evidence that HBr is of similar toxicity to HCl; thus, the lower AEGL-1 values for HBr are considered to be protective of asthmatics on the basis of data on HCl.

Because irritation depends on concentration rather than time, and adaptation to slight irritation occurs (Dalton 2001), 1.0 ppm was used for all of the AEGL-1 exposure durations (see Table 8-8). Derivation of the AEGL-1 values for HBr are presented in Appendixes A and D, and a category plot of the toxicity data for HBr in relation to AEGL values is presented in Appendix B.

Although the AEGL-1 values for HBr are based on data presented in a secondary source, the values obtained from the data are supported by comparison with the related compounds HF and HCl. The AEGL-1 values for HF (1.0 ppm) and HCl (1.8 ppm) are equal to or higher than the values obtained for HBr using data from Connecticut State Department of Health (unpublished data, 1955, as cited in ACGIH 2002). Thus, if AEGL-1 values for HBr were obtained by analogy to these related compounds, the same or higher AEGL-1 values would be derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on HBr relevant to development of AEGL-2 values were found.

6.2. Animal Data Relevant to AEGL-2

The only study of HBr that addresses effects that meet the definition of an AEGL-2 was a study on hydrogen halides by Stavert et al. (1991). Following inhalation of HBr, HCl, or HF at 1,300 ppm for 30 min, male F-344 rats exhibited severe necrotic lesions of the anterior nasal passages and 8% of the rats died (Stavert et al. 1991). Lesions consisting of necrosis and inflammation were restricted to the nasal region; the lungs appeared unaffected. Rats were killed 24 h after exposure and no judgment could be made about whether the lesions were reversible. The authors noted that the nasal lesions were similar in severity and location for all three hydrogen halides when tested at the same concentration.

6.3. Derivation of AEGL-2 Values

The Stavert et al. (1991) study was not considered a suitable basis for derivation of AEGL-2 values because 8% of the animals died after exposure to HBr at 1,300 ppm. Additionally, the study only tested a single concentration and the number of animals tested was not specified. In the absence of suitable data, the

TABLE 8-8 AEGL-1 Values for Hydrogen Bromide

10 min	30 min	1 h	4 h	8 h
1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)

AEGL-3 values for HBr were divided by 3 to estimate AEGL-2 values. This approach is supported by the steep concentration-response curve demonstrated in the MacEwen and Vernot (1972) lethality studies. The AEGL-2 values for HBr are presented in Table 8-9, and the calculations are presented in Appendixes A and D. A category plot of the toxicity data on HBr in relation to AEGL values is presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on HBr relevant to development of AEGL-3 values were found.

7.2. Animal Data Relevant to AEGL-3

Lethality data on HBr were available for the rat and mouse. One-hour LC_{50} values for the rat and mouse were 2,858 and 814 ppm, respectively (MacEwen and Vernot 1972). The data are summarized in Table 8-4. A 30-min exposure to HBr at 1,300 ppm resulted in 8% mortality in rats (Stavert et al. 1991). From the MacEwen and Vernot study in the rat, a 1-h LC_{01} of 1,350 ppm was calculated by probit analysis. The $BMCL_{05}$ was 1,239 ppm (see Appendix C) and the BMC_{01} was 1,456 ppm (data not shown). No deaths occurred in rats exposed at 1,000 ppm for 30 min (Kusewitt et al. 1989) or in mice exposed at 507 ppm for 1 h (MacEwen and Vernot 1972). As noted in Section 4.4.1 (Species Variability), mice are not considered an appropriate species for setting lethality values for hydrogen halides, because mice are more susceptible to the lethal effects of HCl than rats or non-human primates (NRC 1991).

7.3. Derivation of AEGL-3 Values

The $BMCL_{05}$ of 1,239 ppm, calculated from 1-h lethality data from studies in Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972), is an estimate of the threshold for lethality and was selected as the point of departure to develop AEGL-3 values for HBr. This value was more conservative than the BMC_{01} of 1,456 ppm calculated from the same data. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability.

TABLE 8-9 AEGL-2 Values for Hydrogen Bromide

10 min	30 min	1 h	4 h	8 h
250 ppm (830 mg/m^3)	83 ppm (270 mg/m^3)	40 ppm (130 mg/m^3)	10 ppm (33 mg/m^3)	5 ppm (17 mg/m^3)

The individual factors are considered to be sufficient because the action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001).

The 60-min point of departure was time-scaled to the other AEGL-3 durations using the equation $C^n \times t = k$. The value of n was 1, on the basis of data on the related compound HCl, for which regression analysis of combined LC_{50} data from rats and mice resulted in an estimate of n = 1 (see NRC 2004). The AEGL-3 values for HBr are presented in Table 8-10. The use of the $BMCL_{05}$ as the point-of-departure for the AEGL-3 values is supported by the finding that the point-of-departure for the 30-min AEGL-3 is an estimate of the threshold for lethality of 155 ppm and is approximately 10-fold lower than the concentration which resulted in 8% mortality (1,300 ppm) (Stavert et al. 1991). The AEGL-3 calculations are presented in Appendices A and D, and a category plot of the toxicity data on HBr in relation to the AEGL values is presented in Appendix B.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for HBr are presented in Table 8-11. The AEGL-1 values were based on the concentration that did not result in nasal irritation in subjects exposed to HBr for several minutes. AEGL-2 values were derived by taking one-third the AEGL-3 values, and the AEGL-3 values were based on the $BMCL_{05}$ estimated from rat lethality data.

A comparison of the AEGL values for HBr, HCl, and HF is presented in Table 8-12. The AEGL-1 values for the three hydrogen halides are similar, as are the longer-term AEGL-2 values. The AEGL-3 values for HBr and HCl are similar and the HF values are generally lower; this is consistent with the findings presented in Table 8-7, which showed that lethality was observed at lower concentrations of HF, as compared to HBr and HCl.

8.2. Comparison with Other Standards and Guidelines

Other standards and guidelines for HBr are presented in Table 8-13. Except for the Occupational Safety and Health Administration's permissible exposure limit, ceiling or peak limits rather than 8-h time-weighted averages (TWA) have been derived for the workplace. The AEGL-1 for HBr is below the workplace guidelines. The immediately dangerous to life or health (ILDH) value is

based on analogy with HCl (NIOSH 1994). The IDLH for HCl is 50 ppm which is 10 times the recommended exposure limit (REL) of the National Institute for Occupational Safety and Health (NIOSH). Therefore, the IDLH for HBr was set at 10 times the NIOSH REL of 3 ppm. The 30-min AEGL-2 is similar to the IDLH.

TABLE 8-10 AEGL-3 Values for Hydrogen Bromide

10 min	30 min	1 h	4 h	8 h
740 ppm (2,400 mg/m^3)	250 ppm (830 mg/m^3)	120 ppm (400 mg/m^3)	31 ppm (100 mg/m^3)	15 ppm (50 mg/m^3)

TABLE 8-11 AEGL Values for Hydrogen Bromide

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 (disabling)	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
AEGL-3 (lethal)	740 ppm	250 ppm	120 ppm	31 ppm	15 ppm

TABLE 8-12 AEGL Values for Hydrogen Bromide, Hydrogen Chloride, and Hydrogen Fluoride (ppm)

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1					
HBr	1.0	1.0	1.0	1.0	1.0
HCl	1.8	1.8	1.8	1.8	1.8
HF	1.0	1.0	1.0	1.0	1.0
AEG-2					
HBr	250	83	40	10	5
HCl	100	43	22	11	11
HF	95	34	24	12	12
AEGL-3					
HBr	740	250	120	31	15
HCl	620	210	100	26	26
HF	170	62	44	22	22

Source of the HCl and HF values: NRC 2004.

TABLE 8-13 Standards and Guidelines for Hydrogen Bromide

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	15 ppm
IDLH (NIOSH)[b]	–	30 ppm	–	–	–
PEL-TWA (OSHA)[b]	–	–	–	–	3 ppm
TLV-C (ACGIH)[c]	2 ppm	2 ppm	2 ppm	2 ppm	2 ppm
REL-C (NIOSH)[d]	3 ppm	3 ppm	3 ppm	3 ppm	3 ppm
MAK peak limit (Germany)[e]	2 ppm (15 min, 4 times/shift)		–	–	–

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects.
[b]PEL-TWA (permissible exposure limits – time-weighted average, Occupational Health and Safety Administration) (29CFR 1910.1045 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/wk.
[c]TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is a limit that should not be exceeded during the working day.
[d]REL-C(recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-ceiling.
[e]MAK Spitzenbegrenzung (peak limit) (German Research Association (DFG 1999) constitutes the maximum average concentration to which workers can be exposed for a period of 15 min with no more than four excursions per work shift and with an interval of 1 h between excursions.

8.3. Data Adequacy and Research Needs

Only one study of human subjects was available for development of AEGL-1 values (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). The study was unpublished and available only in a secondary source. Although the study used short exposure durations, an adequate number of subjects was used, a range of concentrations was tested, and irritant levels were clearly described. Animal data on HBr were available from studies of two species, the rat and mouse. The well-conducted studies with rats from two different laboratories (MacEwen and Vernot 1972; Stavert et al. 1991) had reasonable agreement in results. Those studies also addressed the relative toxicities of HBr, HF, and HCl in the rat. Although the data on HBr were sparse, supporting information on related hydrogen halides and information on relative toxicity are

available; thus, the data were considered adequate to derive AEGL-1 and 3 values for HBr. The database was not considered suitable for AEGL-2 values; the AEGL-3 values were divided by 3 to derive AEGL-2 values for HBr.

9. REFERENCES

ACGIH (American Conference of Government and Industrial Hygienists). 2002. Documentation of the Threshold Limit Values (TLVs) for Chemical and Physical Agents and Biological Exposure Indices (BEIs): Hydrogen Bromide. American Conference of Government and Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Government and Industrial Hygienists). 2004. Documentation of the Threshold Limit Values for Chemical and Physical Agents and Biological Exposure Indices (BEIs): Hydrogen Bromide. American Conference of Government and Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Government and Industrial Hygienists). 2012. Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) Based on the Documentation of the Threshold Limit Values for Chemical and Physical Agents and Biological Exposure Indices. American Conference of Government and Industrial Hygienists, Cincinnati, OH.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-289.

Back, K.C., A.A. Thomas, and J.D. MacEwen. 1972. Reclassification of Materials Listed as Transportation Health Hazards. Report No. TSA-20-72-3. Aerospace Medical Research Laboratory, Wright Patterson Air Force Base, OH.

Barrow, C.S., Y. Alarie, M. Warrick, and M.F. Stock. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health. 32(2):68-76.

Braker, W., and A.L. Mossman. 1980. Matheson Gas Data Book, 6th Ed. Lyndhurst, NJ: Matheson.

Dalton, P. 2001. Evaluating the human response to sensory irritation: Implications for setting occupational exposure limits. Am. Ind. Hyg. Assoc. J. 62(6):723-729.

DFG (Deutsche Forschungsgemeinschaft). 1999. List of MAK and BAT Values, 1999. Maximum Concentrations and Biological Tolerance Value at the Workplace Report No. 35. Weinheim, Federal Republic of Germany: Wiley-VCH.

Henderson, Y., and H.W. Haggard. 1943. Hydrochloric acid (Hydrogen chloride). P. 126-127 in Noxious Gases and the Principles of Respiration Influencing Their Action, 2nd Rev. Ed. New York: Reinhold Publishing.

Higgins, E.A., V. Fiorca, A.A. Thomas, and H.V. Davis. 1972. Acute toxicity of brief exposures to HF, HCl, NO2 and HCN with and without CO. Fire Technol. 8(2):120-130.

HSDB (Hazardous Substances Data Base). 2008. Hydrogen bromide. TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov [accessed Jan. 10, 2013].

Jackisch, P.F. 1992. Bromine compounds. Pp. 536-560 in Kirk-Othmer Encyclopedia of Chemical Technology, 4th Ed., Vol. 4. New York: John Wiley & Sons.

Kusewitt, D.F., D.M. Stavert, G. Ripple, T. Mundie, and B.E. Lehnert. 1989. Relative acute toxicities in the respiratory tract of inhaled hydrogen fluoride, hydrogen bromide, and hydrogen chloride. Toxicologist 9:36 [Abstract No. 144].

Lehnert, B.E., and D.M. Stavert. 1991. The Acute Inhalation Toxicity of Pyrolysis Products of Halon 1301. Annual Report. AD-A246 031. Los Alamos National Laboratory, Los Alamos, NM.

MacEwen, J.D., and E.H. Vernot. 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. AMRL-TR-70-77, AD 714694. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH [online]. Available: http://www.dtic.mil/dtic/tr/fulltext/u2/714694.pdf online]. [accessed Apr. 5, 2014].

MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72-62, AD 755 358. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH [online]. Available: http://www.dtic.mil/dtic/tr/fulltext/u2/755358.pdf [accessed Apr.5, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs): Hydrogen bromide. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/10035106.html [accessed Apr. 5, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Hydrogen bromide. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0331.html [accessed Apr. 5, 2014].

NRC (National Research Council). 1991. Hydrogen chloride. Pp. 37-52 in Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2006. Hydrogen bromide. P. 829 in The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th ed. Whitehouse Station, NJ: Merck.

Rosenholtz, M.J., T.R. Carson, M.H. Weeks, F. Wilinski, D.F. Ford, and F.W. Oberst. 1963. A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. Am. Ind. Hyg. Assoc. J. 24(3):253-261.

Stavert, D.M., D.C. Archuleta, M.J. Behr, and B.E. Lehnert. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudomouth-breathing rats. Fundam. Appl. Toxicol. 16(4):636-655.

Stevens, B. J.Q. Koenig, V. Rebolledo, Q.S. Hanley, and D.S. Covert. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. J. Occup. Med. 34(9):923-929.

Teitelbaum, D.T. 2001. The halogens. Pp. 731-825 in Patty's Industrial Hygiene and Toxicology, 5th Ed., Vol. 3. New York: John Wiley & Sons.

Vernot, E.H., J.D. MacEwen, C.C. Haun and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.

Wohlslagel, J., L.C. DiPasquale and E.H. Vernot. 1976. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J. Combust. Toxicol. 3:61-69.

APPENDIX A

DERIVATION OF AEGL VALUES FOR HYDROGEN BROMIDE

Derivation of AEGL-1 Values

Key study:	CT Department of Health, unpublished data (1955, as cited in ACGIH 2002)
Toxicity end point:	Nasal and throat irritation in one of six subjects to HBr at 3 ppm for several minutes
Time scaling:	No time scaling, because there is adaptation to slight irritation.
Uncertainty factors:	3 for intraspecies variability; irritation from a direct-contact irritant should not vary greatly among individuals (NRC 2001).
Calculation:	3 ppm ÷ 3 = 1.0 ppm (applied to all AEGL durations)

Derivation of AEGL-2 Values

Because data on HBr were inadequate, AEGL-2 values were derived by taking one-third of the respective AEGL-3 values.

Calculations:

10-min AEGL-2:	740 ppm ÷ 3 = 250 ppm
30-min AEGL-2:	250 ppm ÷ 3 = 83 ppm
1-h AEGL-2:	110 ppm ÷ 3 = 40 ppm
4-h AEGL-2:	31 ppm ÷ 3 = 10 ppm
8-h AEGL-2:	15 ppm ÷ 3 = 5 ppm

Derivation of AEGL-3 Values

Key study:	MacEwen and Vernot (1972)
Toxicity end point:	Lethality in rats exposed for 1 h, $BMCL_{05}$ of 1,238.95 ppm.

Time scaling:	$C^n \times t = k$; n = 1 on the basis of lethality data on HCl in rats (1,238.95 ppm ÷ 10) × 60 min = 7,433.7 ppm-min
Uncertainty factors:	3 for interspecies differences; a direct-contact irritant is not expected to vary greatly between species (NRC 2001) 3 for intraspecies variability; response to a direct-contact irritant is not expected to vary greatly among humans (NRC 2001)
Calculations:	
10-min AEGL-3:	7,433.7 ppm-min ÷ 10 min = 740 ppm
30-min AEGL-3:	7,433.7 ppm-min ÷ 30 min = 250 ppm
1-h AEGL-3:	7,433.7 ppm-min ÷ 60 min = 120 ppm
4-h AEGL-3:	7,433.7 ppm-min ÷ 240 min = 31 ppm
8-hAEGL-3:	7,433.7 ppm-min ÷ 480 min = 15 ppm

APPENDIX B

CATEGORY PLOT FOR HYDROGEN BROMIDE

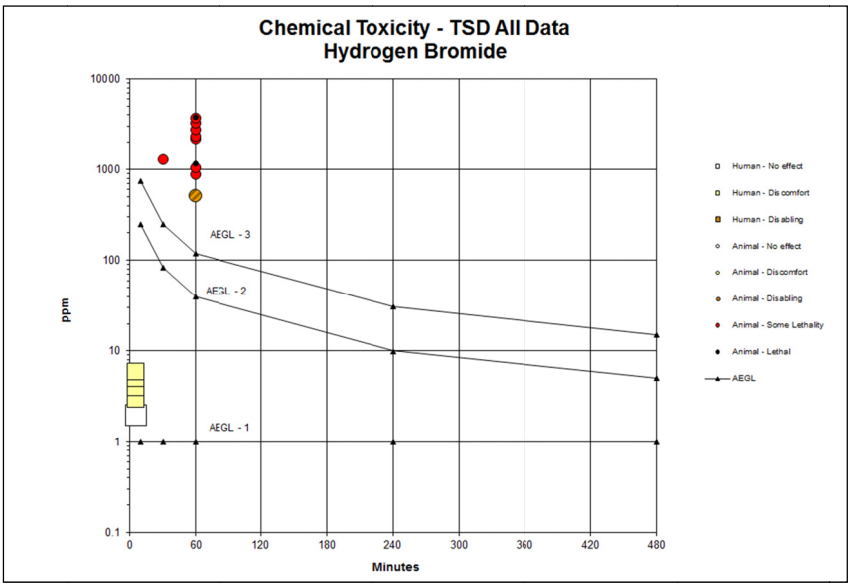


FIGURE B-1 Category plot of toxicity data and AEGL values for hydrogen bromide.

TABLE B-1 Data Used in the Category Plot for Hydrogen Bromide

Source	Species	ppm	Minutes	Category
AEGL-1		1.0	10	AEGL
AEGL-1		1.0	30	AEGL
AEGL-1		1.0	60	AEGL
AEGL-1		1.0	240	AEGL
AEGL-1		1.0	480	AEGL
AEGL-2		250	10	AEGL
AEGL-2		83	30	AEGL
AEGL-2		40	60	AEGL
AEGL-2		10	240	AEGL
AEGL-2		5	480	AEGL
AEGL-3		740	10	AEGL
AEGL-3		250	30	AEGL
AEGL-3		120	60	AEGL
AEGL-3		31	240	AEGL
AEGL-3		15	480	AEGL
CT State Dept. Health 1955	Human	2	5	0, no irritation
CT State Dept. Health 1955	Human	3	5	1, nasal and throat irritation, 1 subject
CT State Dept. Health 1955	Human	4	5	1, nasal and throat irritation, 3 subjects

CT State Dept. Health 1955	Human	5	5	1, nasal and throat irritation, 6 subjects
CT State Dept. Health 1955	Human	6	5	1, nasal and throat irritation, 6 subjects
MacEwen and Vernot 1972	Rat	2,205	60	SL, 10% mortality
MacEwen and Vernot 1972	Rat	2,328	60	SL, 40% mortality
MacEwen and Vernot 1972	Rat	2,759	60	SL, 40% mortality
MacEwen and Vernot 1972	Rat	3,253	60	SL, 60% mortality
MacEwen and Vernot 1972	Rat	3,711	60	SL, 70% mortality
MacEwen and Vernot 1972	Rat	3,822	60	3, 100% mortality
MacEwen and Vernot 1972	Mouse	507	60	2, no mortality
MacEwen and Vernot 1972	Mouse	875	60	SL, 70% mortality
MacEwen and Vernot 1972	Mouse	1,036	60	SL, 90% mortality
MacEwen and Vernot 1972	Mouse	1,163	60	3, 100% mortality
Stavert et al. 1991	Rat	1,300	30	SL, 8% mortality

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal.

APPENDIX C

BENCHMARK CONCENTRATION CALCULATION

Hydrogen bromide $BMCL_{05}$

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\HBR05.(d)
Gnuplot Plotting File: C:\BMDS\HBR05.plt
Mon Dec 17 11:29:37 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept + Slope*Log (Dose), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -29.967
slope = 3.76563

Asymptotic Correlation Matrix of Parameter Estimates

(***The model parameter(s) - background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix.)

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance Test	Test d.f.	P-value
Full model	-29.5498	7			
Fitted model	-32.7425	2	6.38533	5	0.2705
Reduced model	-48.2628	1	37.426	6	<.0001

AIC: 69.485

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-27.4619	7.00164	-41.1848	-13.7389
Slope	3.45097	0.877253	1.73158	5.17035

NA: Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Goodness of Fit

		Scaled			
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
2205.0000	0.1855	1.855	1	10	-0.696
2328.0000	0.2397	2.397	4	10	1.188
2759.0000	0.4518	4.518	4	10	-0.329
3253.0000	0.6727	6.727	6	10	-0.490
3711.0000	0.8164	8.164	7	10	-0.951
3822.0000	0.8422	8.422	10	10	1.369

Chi Sq. = 5.02; DF = 5; P-value = 0.4134

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 1774.18
$BMCL_{05}$ = 1238.95

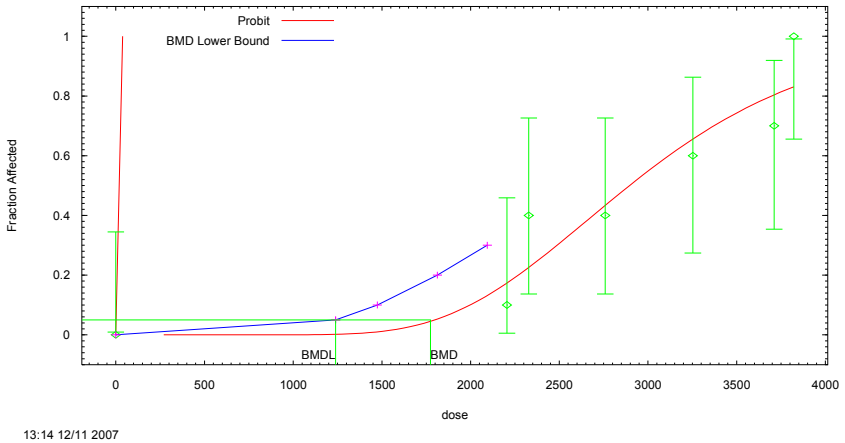


FIGURE C-1 Probit model with 0.95 confidence level.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR HYDROGEN BROMIDE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm

Key reference: Connecticut State Department of Health. 1955. Unpublished data. Occupational Health Section, CT Department of Health, Hartford, CT (as cited in ACGIH 2002)

Test species/Strain/Number: Humans, six subjects

Exposure route/Concentrations/Durations: Inhalation; 2, 3, 4, 5, or 6 ppm for several minutes

Effects: Odor detectable for all six subjects at all concentrations
2 ppm: No nasal, throat, or ocular irritation.
3 ppm: Nasal and throat irritation in one of six subjects; no ocular irritation.
4 ppm: Nasal irritation in three of six subjects; throat irritation in one of six subjects; no ocular irritation.
5 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation.
6 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation.6 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation.

End point/Concentration/Rationale: 3 ppm is considered a threshold for notable discomfort

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because key study is in human subjects
Intraspecies: 3; the response to a direct irritant is not expected to differ greatly among humans (NRC 2001), and the resulting AEGL-1 value appears protective for asthmatics on the basis of data on HCl (NRC 2004).

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applied; humans adapt to the slight sensory irritation.

Data adequacy: Old but well-conducted study with human subjects. AEGL-1 value is supported by similar AEGL values for other chemicals in this class, HF and HCl. The databases on HF and HCl are robust.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
250 ppm	83 ppm	40 ppm	10 ppm	5 ppm

Data adequacy: The database on HBr is inadequate, so AEGL-2 values were derived by dividing the AEGL-3 values by 3. This is supported by the steep concentration-response curve observed in the lethality studies by MacEwen and Vernot (1972).

AEGL-3 VALUES

10-min	30-min	1-hr	4-hr	8-hr
740 ppm	250 ppm	120 ppm	31 ppm	15 ppm

Key reference: MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR- 72-62. AD 755-358. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Test species/Strain/Number: Rat, Sprague-Dawley, 10 per group

Exposure route/Concentrations/Durations: Inhalation; 2,205-3,822 ppm for 1 h

Effects:
Lethality:
2,205 ppm: 1/10
2.328 ppm: 4/10
2,759 ppm: 4/10
3,253 ppm: 6/10
3,711 ppm: 7/10
3,822 ppm: 10/10

End point/Concentration/Rationale: 1-h $BMCL_{05}$ of 1,239 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, a direct-contact irritant is not expected to vary greatly between species (NRC 2001)
Intraspecies: 3, response to a direct-contact irritant is not expected to vary greatly among humans (NRC 2001)

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; n = 1 on the basis of rat and mouse lethality data on HCl.

Data adequacy: Although there were only two well-conducted studies of HBr in the rat and mouse, the values are consistent with those for the related chemicals, HF and HCl. The databases for HF and HCl are robust.

9

Boron Tribromide[1]

Acute Exposure Guideline Levels

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 (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Robert Benson (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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/m^3) 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/m^3) 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 concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Boron tribromide is a colorless, fuming liquid with a sharp or acrid, irritating odor. It hydrolyzes or decomposes violently in the presence of water or moist air, producing heat, hydrogen bromide, and boric acid. In the presence of water, conversion to hydrogen bromide is complete. Boron tribromide is used as a catalyst in the manufacture of diborane, ultrahigh purity boron, and semiconductors. It is an excellent demethylating or dealkylating agent for ethers, particularly in the production of pharmaceuticals. As a Lewis acid catalyst it finds applications in olefin polymerization and in Friedel-Crafts chemistry. Theoretically, one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide.

No human or animal data were available to derive AEGL values for boron tribromide, as the reactive nature of boron tribromide precludes toxicity testing. Hydrogen bromide is considered the irritant hydrolysis product as boric acid has been used in topical antiseptic powders and ointments, and dilute solutions are used in eye and mouthwash solutions. On the basis that boron tribromide hydrolyzes into hydrogen bromide, the AEGL values for boron tribromide were based on the AEGL values for hydrogen bromide. The boron tribromide values were derived by dividing the hydrogen bromide AEGL values by 3. See Chapter 8 for the technical support document on hydrogen bromide. The AEGL values for boron tribromide are presented in Table 9-1.

TABLE 9-1 AEGL Values for Boron Tribromide

Classification	10 min	30 min	1 h	4 h	8 h	End Point[a]
AEGL-1 (nondisabling)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	Analogy with hydrogen bromide
AEGL-2 (disabling)	83 ppm (850 mg/m^3)	28 ppm (290 mg/m^3)	13 ppm (130 mg/m^3)	3.3 ppm (34 mg/m^3)	1.7 ppm (17 mg/m^3)	Analogy with hydrogen bromide
AEGL-3 (lethal)	250 ppm (2,600 mg/m^3)	83 ppm (850 mg/m^3)	40 ppm (410 mg/m^3)	10 ppm (100 mg/m^3)	5 ppm (51 mg/m^3)	Analogy with hydrogen bromide

[a]On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the AEGL values for hydrogen bromide were divided by three.

1. INTRODUCTION

Boron tribromide is a colorless, fuming liquid with a sharp or acrid, irritating odor. It hydrolyzes or decomposes in the presence of water or moist air, producing heat, hydrogen bromide, and boric acid (ACGIH 2001; O'Neil et al. 2006; Krzystowczyk 2007; Ball et al. 2012). Boron tribromide is nonflammable (BOC 1996). However, as a result of the strong Lewis acid properties of bromide, the reaction with water is violent and results in risk of explosion. This reactivity, resulting in caustic action at the site of exposure, makes it impossible to determine systemic toxicity. Breakdown to hydrogen bromide in water is complete (Krzystowczyk 2007). Theoretically, three moles of hydrogen bromide are produced from one mole of boron tribromide. Additional chemical and physical properties are listed in Table 9-2.

The boron trihalides are important industrial chemicals that are used as Lewis acid catalysts and in chemical vapor deposition processes. As a Lewis acid catalyst, boron tribromide finds applications in olefin polymerization and in Friedel-Crafts chemistry. Boron tribromide is used as a catalyst in the manufacture of diborane and ultrahigh purity boron. Boron tribromide is an excellent demethylating or dealkylating agent for ethers in the production of pharmaceuticals. The electronics industry uses boron tribromide as a source of boron in predeposition processes for doping in the manufacture of semi-conductors (Albemarle Corporation 2004; HSDB 2013). Boron tribromide is produced on a large scale by the reaction of bromine and granulated boron carbide (Alam et al. 2003). It is commercially available neat or in solution with dichloromethane or hexanes (Doyaguez 2005). Boron tribromide is shipped in 70-kg stainless-steel drums (Albemarle Corporation 2004).

2. HUMAN TOXICITY DATA

By analogy with hydrogen bromide, the acrid odor of boron tribromide should be detectable at 2 ppm (Ball et al. 2012). Data were insufficient to set a

level of odor awareness. Boron tribromide is considered irritating to the skin and mucus membranes and corrosive to the eyes (HSDB 2013). No inhalation data on lethal concentrations, developmental or reproductive toxicity, genotoxicity, or carcinogenicity of boron tribromide in humans were found. Data on the breakdown products, hydrogen bromide and boric acid, were available.

The Connecticut State Department of Health (unpublished data, 1955) evaluated responses of human subjects to hydrogen bromide vapors. Six volunteers inhaled hydrogen bromide at 2-6 ppm for durations of several minutes (see Table 9-3). The odor was detectable by all subjects at all concentrations. None of the subjects experienced ocular irritation. Only one subject experienced nasal and throat irritation at 3 ppm. One subject experienced throat irritation at the higher concentrations, and all subjects experienced nasal irritation at 5 and 6 ppm. Although exposure at 5 ppm caused nasal and throat irritation in a majority of the volunteers, the report stated that "it was considered unlikely that noticeable disturbances will occur if peak concentrations do not exceed this value for brief periods."

TABLE 9-2 Chemical and Physical Properties of Boron Tribromide

Parameter	Value	References
Synonyms	Boron bromide; tribromoborane	HSDB 2013
CAS registry no.	10294-33-4	HSDB 2013
Chemical formula	BBr_3	HSDB 2013
Molecular weight	250.57	HSDB 2013
Physical state	Liquid	HSDB 2013
Boiling point	91.3ºC	HSDB 2013
Melting point	–46ºC	HSDB 2013
Density (water =1)	2.60 g/mL	HSDB 2013
Solubility in water	Hydrolyzes violently	HSDB 2013
Vapor pressure	69 mm Hg at 25ºC	Barber et al. 1964; ACGIH 2001
Flammability limits	Non-flammable	BOC Gases 1996
Conversion factors	1 ppm = 10.25 mg/m^3 1 mg/m^3 = 0.097 ppm	ACGIH 2001

TABLE 9-3 Human Responses to Hydrogen Bromide Vapor

	Number of Subjects with Response (n = 6)				
Response	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Detectable odor	6	6	6	6	6
Nasal irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Ocular irritation	0	0	0	0	0

Source: Connecticut State Department of Health, unpublished data, 1955.

Although the inhalation toxicity of boron oxide and borates is well established (ATSDR 2010), no information on the inhalation toxicity of boric acid in humans was found. Boric acid is used as an astringent and antiseptic. Borates in general are considered either nonirritating or mild dermal and ocular irritants (Hubbard 1998). Oral exposure to boric acid has low acute toxicity in adults (Hubbard 1998), but there are some reports of fatalities (Jordan and Crissey 1957). Death has occurred from intake of less than 5 g in infants and from 5-20 g in adults (O'Neil et al. 2006). Wong et al. (1964) reported that five of 14 infants were killed within 2-3 day after ingesting boric acid; the infants that died consumed 4.6-14 g of the chemical, whereas those that survived consumed 2-4.5 g. Mortality was 70% among infants who were accidentally poisoned with boric acid (Goldbloom and Goldbloom 1953).

Boric acid has been held responsible for systemic intoxication after ingestion, injection, application to damaged skin, or enema (McIntyre and Burke 1937; Brooke and Boggs 1951; Ducey and Williams 1953; Johnstone et al. 1955; Rosen and Haggerty 1956; Jordan and Crissey 1957). There is no evidence that boric acid or borates are absorbed through intact skin (Sciarra 1958). Whether the apparent increased susceptibility of infants and children is due to immaturity of the kidneys (which accounts for the primary route of elimination) (Locksley and Sweet 1954) or is related to the relatively high dose on a body weight basis (Young et al. 1949) is not clear. Autopsy is generally unremarkable with deaths occurring several days after exposure, but pancreatic lesions and those in kidneys and brain have been described (McNally and Rust 1928; Valdes-Dapena and Arey 1962). Although seizures can precede death, the hyperchloremic metabolic acidosis is a characteristic feature (Wong et al. 1964).

3. ANIMAL TOXICITY DATA

No data on the lethality, developmental or reproductive effects, genotoxicity, or chronic toxicity or carcinogenicity of boron tribromide were available. Data on the breakdown products, boric acid and hydrogen bromide were available. Toxicity data on other hydrogen halides, such as hydrogen chloride and hydrogen fluoride, are also relevant.

Inhalation exposure of male Swiss-Webster mice to boric acid aerosol at 300 mg/m^3 (approximately 120 ppm), the highest achievable concentration, resulted in a decrease in respiratory rate by less than 20%. The effect was attributed to sensory irritation, as there was no indication of pulmonary effects (Krystofiak and Schaper 1996). The oral LD_{50} (lethal dose, 50% lethality) for boric acid in rats is 5 g/kg (O'Neil et al. 2006).

Groups of five to eight Fisher 344 rats were exposed by inhalation to hydrogen chloride or hydrogen bromide at approximately 1,300 ppm for 30 min (Stavert et al. 1991). Animals were placed in body plethysmographs for nose-only exposure. Mortality rates were 6% in the hydrogen-chloride group and 8% in the hydrogen-bromide group. Lesions were confined to the nasal passages.

Moderate to severe fibrinonecrotic rhinitis was observed only in the anterior most region of the nasal passages. The same authors (Kusewitt et al. 1989) exposed rats to hydrogen chloride or hydrogen bromide at concentrations of 100-1,000 ppm for 30 min. No deaths occurred at 1,000 ppm before the animals were killed after 24 h. Lesions were confined to the nasal passages with no damage to the lungs. No further details were reported in the abstract.

MacEwen and Vernot (1972) exposed groups of 10 male Sprague-Dawley rats to hydrogen bromide at 2,205-3,822 ppm for 1 h. Groups of 10 ICR-derived mice were exposed at 507-1,163 ppm for 1 h. Mortalities from these exposures are summarized in Table 9-4. The 1-h LC_{50} for hydrogen bromide in rats was 2,858 ppm (95% confidence limits: 2,481-3,164 ppm), and the 1-h LC_{50} in mice was 814 ppm (95% confidence limits: 701-947 ppm). Responses in the animals were dose-related, and followed a sequence of nasal and ocular irritation, labored breathing, gasping, and convulsions. The fur turned orange-brown during the exposures, and burns were observed on the exposed skin of both species.

Barrow et al. (1977) exposed groups of four male Swiss-Webster mice to hydrogen chloride at concentrations of 40, 99, 245, 440, or 943 ppm for 10 min. An RD_{50} (concentration that reduces the respiratory rate by 50%) of 309 ppm was calculated. At 99 ppm, approximately one-third of the RD_{50}, the decrease in respiratory rate was 25-30%.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Boron tribromide undergoes rapid hydrolysis in the presence of water or moist air, producing heat, hydrogen bromide, and boric acid (ACGIH 2001). No information on the hydrolysis half-life was found, but reaction with water or moisture in the air is rapid and complete (Krzystowczyk 2007).

4.2. Mechanism of Toxicity

The mechanism of toxicity of boron tribromide appears to be related to the formation of hydrobromic acid. Hydrogen bromide is a severe irritant to the eyes, skin, and nasal passages; high concentration may penetrate to the lungs resulting in edema and hemorrhage (Kusewitt et al. 1989; Stavert et al. 1991; see Chapter 8).

Boric acid is used as an astringent and antiseptic. Orally, it is of low acute toxicity to adult humans. Effects include nausea, vomiting, abdominal pain, diarrhea, depression of the central nervous system, and convulsions. Death has occurred from intakes of less than 5 g in infants and from 5-20 g in adults (ACGIH 2005). In the occupational setting, exposure to airborne boric acid and borax dusts is associated with respiratory and ocular irritation without measurable changes in pulmonary function (ATSDR 2010). No studies were available that describe the mechanism of toxicity of systemic effects.

TABLE 9-4 One-Hour Inhalation Studies of Hydrogen Bromide

Species	Concentration (ppm)	Mortality Ratio
Rat	2,205	1/10
	2,328	4/10
	2,759	4/10
	3,253	6/10
	3,711	7/10
	3,822	10/10
Mouse	507	0/10
	875	7/10
	1,036	9/10
	1,163	10/10

Source: Adapted from McEwen and Vernot 1972.

4.3. Structure-Activity Relationships

Because one mole of boron tribromide breaks down into three moles of hydrogen bromide, the toxicity of hydrogen bromide and related hydrogen halides are relevant. On the basis of lethality, hydrogen fluoride is the most toxic, followed by hydrogen bromide and then hydrogen chloride, although the values for hydrogen bromide and hydrogen chloride were similar (MacEwen and Vernot 1972). At sublethal concentrations, the severity and extent of lesions in the upper respiratory tract of rats exposed to hydrogen halides by inhalation were greatest for hydrogen fluoride, followed by hydrogen chloride and then hydrogen bromide. However, the severity and extent of lesions were similar among the three chemicals (Kusewitt et al. 1989; Stavert et al. 1991).

The halides chlorine, bromine, and iodine, are exceptionally good leaving groups, readily hydrolyzing to their acid forms in the aqueous environment. The exception is boron trifluoride. The lack of outer orbitals on the fluoride atom results in a shorter and, thus, stronger bond than what is present with the other halides (Krzystowczyk 2007). Toxicity comparisons of the boron trihalides with their breakdown products are summarized in Table 9-5. The 4-h LC_{50} for boron trifluoride in rats is 1.21 mg/L (approximately 436 ppm) (Rusch et al. 1986). The 1-h LC_{50} for hydrogen fluoride ranges from 966 ppm to 1,395 ppm (Vernot et al. 1977; NRC 2004). The 1-h LC_{50} for boron trichloride in rats is 2,541 ppm (Vernot et al. 1977). The 1-h LC_{50} for hydrogen chloride in rats is 3,124 ppm (Vernot et al. 1977). The similarity in toxicity values for boron trifluoride and boron trichloride with the hydrolysis products tends to support limited hydrolysis.

4.4. Other Relevant Information

No information on species variability, susceptible populations, or concentration-exposure duration relationships for boron tribromide was available. For

hydrogen halides, such as hydrogen fluoride and hydrogen chloride, the mouse is more susceptible than the rat to the lethal effects (NRC 1991).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data on boron tribromide relevant to AEGL-1 end points were available.

5.2. Animal Data Relevant to AEGL-1

No animal data on boron tribromide relevant to AEGL-1 end points were available.

5.3. Derivation of AEGL-1 Values

No human or animal data on boron tribromide were available to derive AEGL-1 values. On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide in moist air, the AEGL-1 values for boron tribromide were derived by dividing the hydrogen bromide AEGL-1 values by 3. See Chapter 8 of this report for how AEGL-1 values were derived for hydrogen bromide. The AEGL-1 values for boron tribromide are presented in Table 9-6, and the calculations are in Appendix A.

TABLE 9-5 Comparison of LC_{50} Values for Boron Trihalides and Acid Halides in Rats

Chemical	LC_{50} Value	Reference
Boron trifluoride	436 ppm (4 h)	Rusch et al. 1986
Hydrogen fluoride	500 ppm (4 h)[a]	Vernot et al. 1977
Boron trichloride	2,541 ppm (1 h)	Vernot et al. 1977
Hydrogen chloride	3,124 ppm (1 h)	Vernot et al. 1977
Boron tribromide	No data	—
Hydrogen bromide	2,858 ppm (1 h)	MacEwen and Vernot 1972

[a]Value was time scaled from 1 h to 4 h using the equation $C^2 \times t = k$ (NRC 2004).

TABLE 9-6 AEGL-1 Values for Boron Tribromide

10 min	30 min	1 h	4 h	8 h
0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on boron tribromide relevant to AEGL-2 end points were available.

6.2. Animal Data Relevant to AEGL-2

No animal data on boron tribromide relevant to AEGL-2 end points were available.

6.3. Derivation of AEGL-2 Values

No human or animal data on boron tribromide were available to derive AEGL-2 values. On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide in moist air, the AEGL-2 values for boron tribromide were derived by dividing the hydrogen bromide AEGL-2 values by 3. See Chapter 8 of this report for how AEGL-2 values were derived for hydrogen bromide. The AEGL-2 values for boron tribromide are presented in Table 9-7.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on boron tribromide relevant to AEGL-3 end points were available.

7.2. Animal Data Relevant to AEGL-3

No animal data on boron tribromide relevant to AEGL-3 end points were available.

7.3. Derivation of AEGL-3 Values

No human or animal data on boron tribromide were available to derive AEGL-3 values. On the basis that one mole of boron tribromide hydrolyzes to form three moles of hydrogen bromide in moist air, the AEGL-3 values for boron tribromide were derived by dividing the hydrogen bromide AEGL-3 values by three. See Chapter 8 of this report for how AEGL-3 values were derived for hydrogen bromide. AEGL-3 values for boron tribromide are presented in Table 9-8.

TABLE 9-7 AEGL-2 Values for Boron Tribromide

10 min	30 min	1 h	4 h	8 h
83 ppm (850 mg/m^3)	28 ppm (290 mg/m^3)	13 ppm (130 mg/m^3)	3.3 ppm (34 mg/m^3)	1.7 ppm (17 mg/m^3)

TABLE 9-8 AEGL-3 Values for Boron Tribromide

10 min	30 min	1 h	4 h	8 h
250 ppm (2600 mg/m^3)	83 ppm (850 mg/m^3)	40 ppm (410 mg/m^3)	10 ppm (100 mg/m^3)	5 ppm (51 mg/m^3)

The toxicity of boric acid liberated during hydrolysis of boron tribromide was considered. The intake of boric acid at the AEGL-3 values by infants, the most susceptible population, can be calculated. The 8-h AEGL-3 is 51 mg/m^3. The breathing rate of a child is 12 m^3/day. Boron tribromide is 4.32% boron. Assuming complete uptake of boron from the respiratory tract, the resulting uptake for a child is:

$$51 \text{ mg/m}^3 \times 12 \text{ m}^3/24 \text{ h} \times 8 \text{ h} \times 0.0432 = 8.8 \text{ mg of boron potentially absorbed.}$$

This value is low when compared with the 2-5 g of boron needed for lethality in a child.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for boron tribromide are presented in Table 9-9.

8.2. Comparison with Other Standards and Guidelines

Workplace guidelines exist for boron tribromide (see Table 9-10). The American Conference of Governmental Industrial Hygienists has established a TLV-ceiling value of 1 ppm for boron tribromide, which is based on analogy with hydrogen bromide (ACGIH 2012, 2001). ACGIH recommends ceiling values for primary irritants with no known chronic effects. The ceiling value is a concentration that should not be exceeded during any part of the working day. The National Institute for Occupational Safety and Health (NIOSH 2011) recommended exposure limit-ceiling and the Netherlands MAC value are also 1 ppm (MSZW 2004). These guidelines are higher than the AEGL-1 value of 0.33 ppm. The ACGIH TLV-ceiling for hydrogen bromide is 2 ppm (ACGIH 2012), and the ACGIH TLV-TWA for boric acid is 2 mg/m^3 as inhalable particulate mass (ACGIH 2012).

TABLE 9-9 AEGL Values for Boron Tribromide

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)
AEGL-2 (disabling)	83 ppm (850 mg/m^3)	28 ppm (290 mg/m^3)	13 ppm (130 mg/m^3)	3.3 ppm (34 mg/m^3)	1.7 ppm (17 mg/m^3)
AEGL-3 (lethal)	250 ppm (2600 mg/m^3)	83 ppm (850 mg/m^3)	40 ppm (410 mg/m^3)	10 ppm (100 mg/m^3)	5 ppm (51 mg/m^3)

TABLE 9-10 Standards and Guidelines for Boron Tribromide

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm
AEGL-2	83 ppm	28 ppm	13 ppm	3.3 ppm	1.7 ppm
AEGL-3	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
TLV-C (ACGIH)[a]	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
REL-C (NIOSH)[b]	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
MAC (The Netherlands)[c]	–	–	–	–	10 mg/m^3 1 ppm

[a]TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is a concentration that should not be exceeded during the working day.
[b]REL-C (recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-ceiling.
[c]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

The reactive nature of boron tribromide precludes toxicity testing. In the absence of empirical data on boron tribromide, and on the basis that one mole of boron tribromide theoretically hydrolyzes into three moles of hydrogen bromide, the AEGL values for boron tribromide were based on those for hydrogen bromide. The database for hydrogen bromide was combined with the more robust data base for the related chemical, hydrogen chloride.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Documentation of the Threshold Limit Values and Biological Exposure Indices: Boron tribromide. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2005. Documentation of the Threshold Limit Values and Biological Exposure Indices: Borate compounds, inorganic. ACGIH, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. 2012 Threshold Limit Values and Biological Exposure Indices Based on the Documentation of the TLVs for Chemical Substances and Physical Agents and BEIs. ACGIH, Cincinnati, OH.

Alam, F., F. Evans, G. Mani, and J.R. Papcun. 2003. Boron halides. Pp. 138-168 in Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 4. New York: John Wiley & Sons, Inc.

Albemarle Corporation. 2004. Boron tribromide (chemical data sheet). Baton Rouge, LA: Albemarle Corporation.

ATSDR (Agency for Toxic Substances and Disease Registry). 2010. Toxicological Profile for Boron. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA[online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp26.pdf [accessed Apr. 9, 2014].

Ball, R.W., M.C. Harass, and B.D. Culver. 2012. Boron tribromide. Pp. 885 - 933 in Patty's Toxicology, 6th Ed., Vol. 1, E. Bingham, and B. Cohrssen, eds. New York: Wiley.

Barber, W.F., C.F. Boynton, and P.E. Gallagher. 1964. Physical properties of boron tribromide. J. Chem. Eng. Data 9(1):137-138.

Barrow, C.S., Y. Alarie, M. Warrick, and M.F. Stock. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health 32(2):68-76.

BOC (British Oxygen Company) Gases. 1996. BOC Gases: Boron tribromide. Material Safety Data Sheet. London, UK: BOC.

Brooke, C., and T. Boggs. 1951. Boric acid poisoning: Report of a case and review of the literature. AMA Am. J. Dis. Child. 82(4):465-472.

Doyaguez, E.G. 2005. Boron tribromide. Synlett 10:1636-1637.

Ducey, J., and D.B. Williams. 1953. Transcutaneous absorption of boric acid. J. Pediatr. 43(6):644-651.

Goldbloom, R.B., and A. Goldbloom. 1953. Boric acid poisoning: Report of four cases and a review of 109 cases from the world literature. J. Pediatr. 43(6):631-643.

HSDB (Hazardous Substances Data Bank). 2013. Boron Tribromide (CAS Reg. No. 10294-33-4). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Jan. 8, 2013].

Hubbard, S.A. 1998. Comparative toxicity of borates. Biol. Trace Elem. Res. 66(1-3):343-357.

Johnstone, D.E., N. Basila, and J. Glaser. 1955. Study of boric acid absorption in infants from use of baby powder. J. Pediatr. 46(2):160-167.

Jordan, J.W., and J.T. Crissey. 1957. Boric acid poisoning: A report of a fatal adult case from cutaneous use. A critical evaluation of the use of this drug in dermatologic practice. AMA Arch. Dermatol. 75(5):720-728.

Krystofiak, S.P., and M.M. Schaper. 1996. Prediction of an occupational exposure limit for a mixture on the basis of its components: Application to metalworking fluids. Am. Ind. Health Assoc. J. 57(3):239-244.

Krzystowczyk, N. 2007. Letter to Dr. George Rusch, AEGL Committee Chairman, from Dr. Niomi Krzystowczyk, Director, Corporate Product Stewardship, Albemarle Corporation, Baton Rouge, LA, Dated June 18, 2007.

Kusewitt, D.F., D.M. Stavert, G. Ripple, T. Mundie, and B.E. Lehnert. 1989. Relative acute toxicities in the respiratory tract of inhaled hydrogen fluoride, hydrogen bromide, and hydrogen chloride. Toxicologist 9:36 [Abstract 144].

Locksley, H.B., and W.H. Sweet. 1954. Tissue distribution of boron compounds in relation to neutron-capture therapy of cancer. Proc. Soc. Exp. Biol. Med. 86(1):56-63.

MacEwen, J.D., and E.H. Vernot. 1972. Acute inhalation toxicity of hydrogen bromide. Pp. 62-66 in Toxic Hazards Research Unit Annual Technical Report, 1972. AMRL-TR-72-62, AD 755 358, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH. [online]. Available: http://www.dtic.mil/dtic/tr/fulltext/u2/755358.pdf [accessed Apr. 9, 2014].

McIntyre, A.R., and J.C. Burke. 1937. Intravenous boric acid poisoning in man. J. Pharmacol. Exp. Ther. 60:112-113.

McNally, W.D., and C.A. Rust. 1928. The distribution of boric acid in human organs in six deaths due to boric acid poisoning. J. Am. Med. Assoc. 90(5):382-383.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Boriumtribromide. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Apr. 9, 2014].

NIOSH (National Institute of Occupational Safety and Health). 2011. Pocket Guide to Chemical Hazards: Boron tribromide. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0061.html [accessed January 2013].

NRC (National Research Council). 1991. Hydrogen chloride. Pp. 37-51 in Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2004. Hydrogen chloride; Hydrogen fluoride. Pp. 77-197 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

O'Neil, M.J., P.E. Heckelman, C.B. Koch, and K.J. Roman, eds. 2006. Boron tribromide. P. 220 in The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th Ed. Whitehouse Station, NJ: Merck.

Rosen, F.S., and R.J. Haggerty. 1956. Fatal poisoning from topical use of boric acid powder. N. Engl. J. Med. 255(11):530-531.

Rusch, G.M., G.M. Hoffman, R.F. McConnell, and W.E. Rinehart. 1986. Inhalation toxicity studies with boron trifluoride. Toxicol. Appl. Pharmacol. 83(1):69-78.

Sciarra, J.J. 1958. A selective review of boric acid toxicity. J. Am. Pharm. Assoc. 19(8):494-495.

Stavert, D.M., D.C. Archuleta, M.J. Behr, and B.E. Lehnert. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol. 16(4):636-655.

Valdes-Dapena, M.A., and J.B. Arey. 1962. Boric acid poisoning: Three fatal cases with pancreatic inclusions and a review of the literature. J. Pediatr. 61(4):531-546.

Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2):417-432.

Wong, L.C., M.D. Heimbach, D.R. Truscott, and B.D. Duncan. 1964. Boric acid poisoning: Report on 11 cases. Can. Med. Assoc. J. 90:1018-1023.

Young, E.G., R.P. Smith, and O.C. MacIntosh. 1949. Boric acid as a poison. Report of six accidental deaths in infants. Can. Med. Assoc. J. 61(5):447-450.

APPENDIX A

DERIVATION OF AEGL VALUES FOR BORON TRIBROMIDE

Derivation of AEGL-1 Values

Inadequate data were available on boron tribromide, so AEGL-1 values were based on the AEGL-1 values for hydrogen bromide.

Calculation:	On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-1 value was divided by 3. For all AEGL-1 durations: 1 ppm ÷ 3 = 0.33 ppm

Derivation of AEGL-2 Values

Inadequate data were available on boron tribromide, so AEGL-2 values were based on the AEGL-2 values for hydrogen bromide.

Calculation:	On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-2 values were divided by 3.
10-min AEGL-2:	250 ppm ÷ 3 = 83 ppm
30-min AEGL-2:	83 ppm ÷ 3 = 28 ppm
1-h AEGL-2:	40 ppm ÷ 3 = 13 ppm
4-h AEGL-2	10 ppm ÷ 3 = 3.3 ppm
8-h AEGL-2:	5 ppm ÷ 3 = 1.7 ppm

Derivation of AEGL-3 Values

Inadequate data were available on boron tribromide, so AEGL-3 values were based on the AEGL-3 values for hydrogen bromide.

Calculation:	On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-3 values were divided by 3.
10-min AEGL-3:	740 ppm ÷ 3 = 250 ppm
30-min AEGL-3:	250 ppm ÷ 3 = 83 ppm

1-h AEGL-3	120 ppm ÷ 3 = 40 ppm
4-h AEGL-3:	31 ppm ÷ 3 = 10 ppm
8-h AEGL-3:	15 ppm ÷ 3 = 5 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR BORON TRIBROMIDE

Derivation Summary

AEGL-1 VALUES

10min	30 min	1 h	4 h	8 h
0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm

Data adequacy: Inadequate data were available on boron tribromide, so values were based on the AEGL-1 values for hydrogen bromide. On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-1 values were divided by 3.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
83 ppm	28 ppm	13 ppm	3.3 ppm	1.7 ppm

Data adequacy: Inadequate data were available on boron tribromide, so values were based on the AEGL-2 values for hydrogen bromide. On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-2 values were divided by 3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
250 ppm	83 ppm	40 ppm	10 ppm	5 ppm

Data adequacy: Inadequate data were available on boron tribromide, so values were based on the AEGL-3 values for hydrogen bromide. On the basis that one mole of boron tribromide hydrolyzes into three moles of hydrogen bromide, the hydrogen bromide AEGL-3 values were divided by 3.