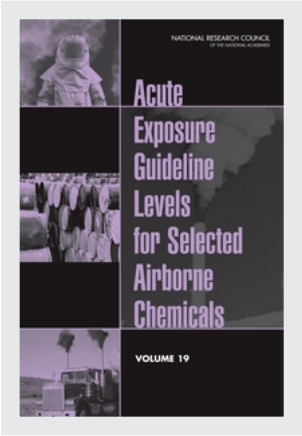

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 19

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)[1] 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 nineteenth volume in that

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

series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene 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.

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 report of the committee that led to this report was 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 report, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), 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 release. The review of the interim report was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim report 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

DEDICATION

The Committee on Acute Exposure Guideline Levels dedicates this volume to our late colleague Dr. Donald E. Gardner. Don was a member of the committee for 12 years, and served as chair for 8 of those years. He was a distinguished toxicologist, respected leader, and valued friend.

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 19

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

This report is the nineteenth 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 eighteen 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, 2014a,b,c). This report is the nineteenth volume in that series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene 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.

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Appendixes

1

Cyanide Salts[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 Cheryl Bast (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Ralph Gingell (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

Sodium cyanide, potassium cyanide, and calcium cyanide are simple inorganic cyanide salts with an almond-like odor. They may react with water or moist air to release toxic, corrosive, or flammable gases. Reaction with water may generate heat which will increase the concentration of hydrogen cyanide fumes in the air (HSDB 2005a,b; 2014).

Even though the cyanide salts are solids, inhalation of dusts may result in ionization in the nasal or pulmonary mucosal fluids to yield cyanide. The salts may also react with water in humid air and be inhaled as hydrogen cyanide. In both cases, there will be systemic absorption of cyanide ion, which is the toxic moiety. Cyanide inhibits cellular respiration by blocking electron transfer from cytochrome oxidase to oxygen, causing tissue hypoxia and cell death. Low concentrations or low dose rates of cyanide are tolerated by detoxification by rhodanese to thiocyanate (Kopras 2012).

In the absence of appropriate chemical-specific data on the three cyanide salts, the AEGL-1, AEGL-2, and AEGL-3 values for hydrogen cyanide (NRC 2002) were used to obtain the AEGL values for the salts. Hydrogen cyanide was used as a surrogate for data on the cyanide salts because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} [lethal dose, 50% lethality] values) data suggest that the cyanide moiety is responsible for the acute toxicity of the cyanide salts. Thus, the concentrations of the cyanide salts that would generate hydrogen cyanide concentrations equivalent to that chemical's AEGL values was calculated. The calculations assumed a temperature of 25°C, a pressure of

760 mm Hg, and complete hydrolysis (one mole of sodium cyanide or potassium cyanide yields one mole of hydrogen cyanide, and one mole of calcium cyanide will yield two moles of hydrogen cyanide).

The calculated AEGL values for the cyanide salts are presented Table 1-1.

1. INTRODUCTION

Sodium cyanide, potassium cyanide, and calcium cyanide are simple inorganic cyanide salts with an almond-like odor. They may react with water or moist air to release toxic, corrosive, or flammable gases. Reaction with water may generate heat which will increase the concentration of hydrogen cyanide fumes in the air (HSDB 2005a,b; 2014).

Even though the salts are solids, inhalation of dusts may result in ionization in the nasal or pulmonary mucosal fluids to yield cyanide. The salts may also react with water in humid air and be inhaled as hydrogen cyanide. In both cases, there will be systemic absorption of cyanide ion, which is the toxic moiety. Cyanide inhibits cellular respiration by blocking electron transfer from cytochrome oxidase to oxygen, causing tissue hypoxia and cell death. Low concentrations or low dose rates of cyanide are tolerated by detoxification by rhodanese to thiocyanate (Kopras 2012).

TABLE 1-1 AEGL Values for Cyanide Salts[a]

Classification	10 min	30 min	1 h	4 h	8 h
Sodium Cyanide					
AEGL-1	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
AEGL-2	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
AEGL-3	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium Cyanide					
AEGL-1	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
AEGL-2	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
AEGL-3	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium Cyanide[b]					
AEGL-1	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3
AEGL-2	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3
AEGL-3	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

[a]Airborne concentrations of these salts will produce the equivalent AEGL values for hydrogen cyanide.

[b]Although the adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound), the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

The rate of cyanide generation depends on ambient temperature, humidity, pH, and the particular cyanide salt; sodium and potassium cyanide behave differently than calcium cyanide. In moist air and at normal temperature, sodium and potassium cyanide slowly decompose and generate hydrogen cyanide (Gail et al. 2011). In the presence of strong acids, complete decomposition and release of hydrogen cyanide occurs (Gail et al. 2011). In dry air, both sodium and potassium cyanide are stable even at high temperatures (Gail et al. 2011).

The alkaline earth cyanides (such as calcium cyanide) are less stable than the alkali metal cyanides (sodium or potassium cyanides) (Gail et al. 2011). Alkaline earth metal cyanides decompose at high temperature, generating hydrogen cyanide. In addition, alkaline earth metal cyanides readily hydrolyze in moist air to release hydrogen cyanide (Pesce 2010; Gail et al. 2011). The amount of hydrogen cyanide released from commercially-produced calcium cyanide (for fumigation purposes) is about 50% of the weight of the cyanide in granular formulation (FAO 1965; Bond 1984).

Hydrolysis constants for sodium and potassium cyanide are similar (2.51×10^{-5} and 2.54×10^{-5}, respectively, at 25°C) (Pesce 2010); data on the hydrolysis of calcium cyanide were not found. Hydrolysis reactions for the three cyanide salts are shown below (Pesce 2010). One mole of sodium cyanide or potassium cyanide may react with water or moisture to produce a maximum of one mole of hydrogen cyanide by the following reactions:

$$NaCN + H_2O \rightarrow HCN + NaOH$$
$$KCN + H_2O \rightarrow HCN + KOH$$

One mole of calcium cyanide may react with water or moisture to produce a maximum of two moles of hydrogen cyanide by the following reaction:

$$Ca(CN)_2 + 2H_2O \rightarrow 2HCN + Ca(OH)_2$$

Sodium cyanide is a white crystalline solid, and may be prepared by heating sodium amide with carbon or by melting sodium chloride and calcium cyanamide together in an electric furnace. It is used for extracting gold and silver from ores, heat treating of metals, electroplating, various organic reactions, and the manufacturing of adiponitrile (Kopras 2012). US production of sodium cyanide was reported as "at least" 1.14×10^{11} grams in 1977, and US imports were reported as 2.77×10^{7} pounds in 1986 (HSDB 2005a).

Potassium cyanide, a white crystalline solid, is prepared by reaction of an aqueous solution of potassium hydroxide with hydrogen cyanide. It is used for fine silver plating, dyes and specialty products, and fumigation of fruit trees, ships, railway cars, and warehouses. US production information was not available; however, US imports were reported as 1,468,423 pounds in 1987 (HSDB 2005b).

Calcium cyanide is a white powder, and is prepared from lime, calcium oxide, coke, and nitrogen in an electric furnace. The commercial product is dark

gray because of the presence of carbon. It is used in the extraction of precious metal ores, adsorption of gold complexes on carbon, as a fumigant, and as a rodenticide (Kopras 2012). US production information on calcium cyanide was not available; however, US imports were reported as 468,246 pounds in 1986 (HSDB 2014).

The chemical and physical properties of the three cyanide salts are presented in Tables 1-2, 1-3, and 1-4.

TABLE 1-2 Chemical and Physical Properties of Sodium Cyanide

Parameter	Value	References
Synonyms	Cyanogran; cyanide of sodium; cymag; hydrocyanic acid sodium salt; cyanobrik; white cyanide	Kopras 2012
CAS registry no.	143-33-9	HSDB 2005a
Chemical formula	NaCN	HSDB 2005a
Molecular weight	49.0	HSDB 2005a
Physical state	White crystalline solid	HSDB 2005a
Melting point	563°C	HSDB 2005a
Boiling point	1,496°C	HSDB 2005a
Density /specific gravity	1.595 g/cm^3 at 20°C	HSDB 2005a
Solubility in water	48 g/100 mL water at 10°C; forms HCN	HSDB 2005a
Vapor pressure	1 mm Hg at 817°C	HSDB 2005a
Hydrolysis constant	2.51×10^{-5} per second at 25°C; yields calculated half-life of 7.7 h	Pesce 2010
Conversion factors	1 ppm = 2.0 mg/m^3 1 mg/m^3 = 0.50 ppm	

TABLE 1-3 Chemical and Physical Properties of Potassium Cyanide

Parameter	Value	References
Synonyms	Hydrocyanic acid potassium salt	Kopras 2012
CAS registry no.	151-50-8	HSDB 2005b
Chemical formula	KCN	HSDB 2005b
Molecular weight	65.11	HSDB 2005b
Physical state	White crystalline solid	HSDB 2005b
Melting point	634°C	HSDB 2005b
Density/specific gravity	1.55 at 20°C	HSDB 2005b
Solubility in water	100 g/100 mL water at >176°F; forms HCN	HSDB 2005b
Hydrolysis constant	2.54×10^{-5} per sec at 25°C; calculated half-life of 7.6 h	Pesce 2010
Conversion factors	1 ppm = 2.7 mg/m^3 1 mg/m^3 = 0.38 ppm	

TABLE 1-4 Chemical and Physical Properties of Calcium Cyanide

Parameter	Value	References
Synonyms	Calcyanide; cyanogas; black cyanide, aero; calcium cyanide, tech grade	Kopras 2012
CAS registry no.	592-01-8	HSDB 2014
Chemical formula	$Ca(CN)_2$	HSDB 2014
Molecular weight	92.12	HSDB 2014
Physical state	White powder, solid	HSDB 2014
Melting point	640°C (estimated by extrapolation because of decomposition)	HSDB 2014
Density/specific gravity	1.853 at 20°C	HSDB 2014
Solubility in water	Soluble in water, gradual liberation of HCN	HSDB 2014
Conversion factors	1 ppm = 3.8 mg/m^3 1 mg/m^3 = 0.27 ppm	

2. HUMAN TOXICITY DATA

No human toxicity data on sodium, potassium, or calcium cyanide were found. There are numerous reports of occupational exposure to hydrogen cyanide (see NRC 2002).

3. ANIMAL TOXICITY DATA

No animal toxicity data on sodium, potassium, or calcium cyanide were found. However, the toxicity data base for hydrogen cyanide is robust. Lethality data are available from studies of dogs, rats, mice, and rabbits, and nonlethal toxicity data are available from studies of nonhuman primates, rats, and mice (see NRC 2002).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Solid cyanide salts deposited on moist respiratory-tract surfaces may hydrolyze and release absorbable cyanide. Another scenario would involve atmospheric hydrolysis of metal cyanides to hydrogen cyanide vapor. Metabolism and disposition information on hydrogen cyanide is summarized in NRC (2002).

Dermal absorption of cyanide salts depends on the form of the salt and the condition of the skin. Dermal exposure to cyanide salts in solution, or exposure of moist or abraded skin to dry cyanide salts, can result in significant absorption of cyanide ion or hydrogen cyanide (Ballantyne 1987). The permeability of cyanide ion across human skin in vitro was estimated to be 3.5×10^{-4} cm/h, and the

permeability of hydrogen cyanide was 100×10^{-4} cm/h (Dugard 1987). In addition, skin exposure to very high air concentrations of hydrogen cyanide has resulted in human poisoning (Potter 1950).

4.2. Mechanism of Toxicity

Hydrogen cyanide is a systemic poison that acts on the central nervous system. Hydrogen cyanide interrupts cellular respiration by blocking electron transfer from cytochrome oxidase to oxygen. Tissue concentrations of oxygen rise, resulting in increased tissue oxygen tension and decreased unloading for oxyhemoglobin. As a consequence, oxidative metabolism may slow to a point where it cannot meet metabolic demands. This 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. 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 (Smith 1996; Kopras 2012). Brain lesions in animals have been associated with exposure to hydrogen cyanide at high concentrations (ATSDR 2006).

4.3. Structure-Activity Relationships

As noted earlier, no acute inhalation toxicity data on the cyanide salts were available. However, acute oral toxicity data suggest both qualitatively (clinical signs) and quantitatively (rat LD_{50} values) that the cyanide moiety is responsible for the acute toxicity of the cyanide salts. Cyanide-induced clinical effects are indistinguishable in humans and animals after inhalation or dermal exposure to hydrogen cyanide vapor or after oral exposure to sodium or potassium cyanide. Clinical signs include headaches, dizziness, nausea, inability to concentrate, thoracic oppression, palpitation, numbness, weakness, rapid pulse, face flushing, unconsciousness, and death (Kopras 2012).

Rat oral LD_{50} values support the contention that cyanide is the toxic moiety. The LD_{50} values for the salts and the LD_{50} values adjusted as equivalent doses of cyanide are presented in Table 1-5. The adjusted values for hydrogen, sodium, and potassium cyanide are comparable whereas the adjusted value for calcium cyanide is much greater (suggesting a less toxic compound) than would be expected on a molar basis for cyanide. The difference may be due to a slower hydrolysis rate, allowing for more efficient detoxification, relative to the other cyanide salts. (Although hydrolysis rates were not found, water solubility/reactivity is described as “forms hydrogen cyanide” for sodium and potassium cyanides [HSDB 2005a,b], and “gradually liberates hydrogen cyanide” for calcium cyanide [HSDB 2014]).

TABLE 1-5 Lethality in Rats Exposed Orally to Hydrogen Cyanide and Cyanide Salts

Compound	LD_{50}, mg/kg (sex)	Adjusted LD_{50}, mg/kg CN^-	Reference
HCN	4.2 (F)	4.1	Ballantyne 1987
NaCN	5.7 (F)	3.0	Ballantyne 1987
	15 (M)	8.0	Smyth et al. 1969
KCN	7.5 (F)	3.0	Ballantyne 1987
	10 (M)	4.0	Hayes 1967
	6 (M)	2.4	Lorke 1983
$Ca(CN)_2$	39 (M)	22	Smyth et al. 1969

4.4. Other Relevant Information

4.4.1. Concurrent Exposure Issues

Because hydrogen cyanide is the toxic moiety of all three salts, and may also be generated by other compounds, coexposure to multiple cyanide salts or other sources of cyanide will result in greater cumulative exposure to cyanide. Exposures should be expressed as cyanide ion and compared with the AEGLs expressed in the same manner to ensure that cumulative exposure is evaluated.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to developing AEGL-1 values for the cyanide salts were found.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to developing AEGL-1 values for the cyanide salts were found.

5.3. Derivation of AEGL-1 Values

In the absence of appropriate chemical-specific data for the cyanide salts, the AEGL-1 values for hydrogen cyanide (NRC 2002) were used to obtain AEGL-1 values for them. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for the acute toxicity of the cyanide salts. In addition, because hydrolysis of cyanide salts in the air or moist respiratory tract may be incomplete (whereas hydrolysis is likely complete after oral exposure due to the low pH of the stomach), the use of hydrogen cyanide as a surrogate for derivation of AEGL values is expected to be conservative.

The hydrogen cyanide AEGL-1 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis. The AEGL-1 values for the cyanide salts are presented in Table 1-6, the calculations are presented in Appendix A, and derivation summary tables are provided in Appendix C. For comparison, the calculations and AEGL derivation summary tables for hydrogen cyanide are presented in Appendix B and Appendix D, respectively.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to developing AEGL-2 values for the cyanide salts were found.

6.2. Animal Data Relevant to AEGL-2

No animal data relevant to developing AEGL-2 values for the cyanide salts were found.

6.3. Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data for the cyanide salts, the AEGL-2 values for hydrogen cyanide (NRC 2002) were used to obtain AEGL-2 values for the title cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for acute toxicity of the cyanide salts. In addition, because hydrolysis of cyanide salts in the air or moist respiratory tract may be incomplete (whereas hydrolysis is likely complete after oral exposure due to the low pH of the stomach), the use of hydrogen cyanide as a surrogate for derivation of AEGL values is expected to be conservative.

The hydrogen cyanide AEGL-2 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis. The AEGL-2 values for the cyanide salts are presented in Table 1-7, the calculations are presented in Appendix A, and derivation summary tables for the cyanide salts are provided in Appendix C. For comparison, the calculations and AEGL derivation summary tables for hydrogen cyanide are presented in Appendix B and Appendix D, respectively.

TABLE 1-6 AEGL-1 Values for Cyanide Salts[a]

Compound	10 min	30 min	1 h	4 h	8 h
Sodium cyanide	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
Potassium cyanide	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
Calcium cyanide[b]	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3

[a]Airborne concentrations of these salts will produce the equivalent AEGL values for hydrogen cyanide.
[b]Although the adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound), the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

TABLE 1-7 AEGL-2 Values for Cyanide Salts[a]

Compound	10 min	30 min	1 h	4 h	8 h
Sodium cyanide	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
Potassium cyanide	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
Calcium cyanide[b]	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3

[a]Airborne concentrations of these salts will produce the equivalent AEGL values for hydrogen cyanide.
[b]Although the adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound), the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to developing AEGL-3 values for the cyanide salts were found.

7.2. Animal Data Relevant to AEGL-3

No animal data relevant to developing AEGL-3 values for the cyanide salts were found.

7.3. Derivation of AEGL-3 Values

In the absence of appropriate chemical-specific data for the title cyanides, the AEGL-3 values for hydrogen cyanide (NRC 2002) were used to obtain AEGL-3 values for the title cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for acute toxicity of the cyanide salts. In addition,

because hydrolysis of cyanide salts in the air or moist respiratory tract may be incomplete (whereas hydrolysis is likely complete after oral exposure due to the low pH of the stomach), the use of hydrogen cyanide as a surrogate for derivation of AEGL values is expected to be conservative.

The hydrogen cyanide AEGL-3 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis. The AEGL-3 values for the cyanide salts are presented in Table 1-8, the calculations are presented in Appendix A, and derivation summary tables for cyanide salts are provided in Appendix C. For comparison, the calculations and AEGL derivation summary tables for hydrogen cyanide are presented in Appendix B and Appendix D, respectively.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for the cyanide salts are presented in Table 1-9. They are based on molar adjustments of the AEGL values for hydrogen cyanide (NRC 2002).

8.2. Comparison with Other Standards and Guidelines

Exposure standards and guidelines for the cyanide salts are presented in Table 1-10, and are expressed in terms of cyanide ion. The 10-min AEGL-1 value for the cyanide salts (2.7 mg/m^3) is in reasonably good agreement with the short-term exposure limit of 5 mg/m^3 established by the American Conference of Governmental Industrial Hygienists (ACGIH 2001, 2013) and the National Institute for Occupational Safety and Health (NIOSH 2011). Likewise, the 30-min AEGL-3 value of 22 mg/m^3 for the cyanide salts is similar to the NIOSH (1994) immediately dangerous to life or health value of 25 mg/m^3.

TABLE 1-8 AEGL-3 Values for Cyanide Salts[a]

Compound	10 min	30 min	1 h	4 h	8 h
Sodium cyanide	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium cyanide	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium cyanide[b]	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

[a]Airborne concentrations of these salts will produce the equivalent AEGL values for hydrogen cyanide.

[b]Although the adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound), the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

TABLE 1-9 AEGL Values for Cyanide Salts[a]

Classification	10 min	30 min	1 h	4 h	8 h
Sodium Cyanide					
AEGL-1	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
AEGL-2	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
AEGL-3	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium Cyanide					
AEGL-1	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
AEGL-2	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
AEGL-3	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium Cyanide[b]					
AEGL-1	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3
AEGL-2	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3
AEGL-3	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

[a]Airborne concentrations of these salts will produce the equivalent AEGL values for hydrogen cyanide.
[b]Although the adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound), the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

TABLE 1-10 Standards and Guidelines for Cyanide Salts (Expressed as CN^-)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.7 mg/m^3	2.7 mg/m^3	2.1 mg/m^3	1.3 mg/m^3	1.1 mg/m^3
AEGL-2	18 mg/m^3	11 mg/m^3	7.5 mg/m^3	3.8 mg/m^3	2.7 mg/m^3
AEGL-3	29 mg/m^3	22 mg/m^3	16 mg/m^3	9.1 mg/m^3	7.0 mg/m^3
IDLH (NIOSH)[a]	–	25 mg/m^3	–	–	–
PEL-TWA (OSHA)[b]	–	–	–	–	11 mg/m^3
TLV-STEL (ACGIH)[c]	5.0 mg/m^3	–	–	–	–
REL-STEL (NIOSH)[d]	5.0 mg/m^3	–	–	–	–
MAK (Germany)[e]	–	–	–	–	2.0 mg/m^3
MAC-Peak Category (The Netherlands)[f]	10 mg/m^3 [15 min]	–	–	–	1.0 mg/m^3
CLV (Sweden)[g]	–	–	–	–	5.0 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 Safety and Health Administration) (OSHA 1978) is the time-weighted average concentrations for a 10-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2013) is defined as a 15-min time-weighted average exposure which should not be exceeded at any time during the workday even if the 8-h time-weighted average is within the threshold-limit value–time-weighted average. Exposures above the threshold-limit value–time-weighted average 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 that range. Value is for hydrogen cyanide and sodium, potassium, and calcium cyanides (as cyanide).
[d]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-STEL.
[e]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2007) is the time-weighted average concentrations 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.
[f]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration - peak category], Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands (MSZW 2007) is defined analogous to the ACGIH-ceiling.
[g]CLV (ceiling limit value, Swedish Work Environment Authority) (SWEA 2005) is the maximum acceptable average concentration limit value (time-weighted average) for a workday. Value is for cyanides and hydrogen cyanide (as CN) total dust.

8.3. Data Adequacy and Research Needs

There are no human or animal inhalation data for sodium, potassium, or calcium cyanide. However, data suggest that the cyanide moiety is responsible for the acute toxicity of these compounds, and the hydrogen cyanide data set is fairly robust.

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APPENDIX A

DERIVATION OF AGEL VALUES FOR CYANIDE SALTS

Derivation of AEGL-1 Values

The AEGL-1 values for hydrogen cyanide were used as target values for calculating the concentrations of the cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis (one mole of sodium cyanide or potassium cyanide will yield one mole of hydrogen cyanide, and one mole of calcium cyanide will yield two moles of hydrogen cyanide).

Sodium Cyanide

10-min AEGL-1:
2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 49.0 ÷ 24.5 = 5.0 mg/m^3

30-min AEGL-1:
2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 49.0 ÷ 24.5 = 5.0 mg/m^3

1-h AEGL-1:
2.0 ppm ÷ 1 = 2.0 ppm
2.0 ppm × 49.0 ÷ 24.5 = 4.0 mg/m^3

4-h AEGL-1:
1.3 ppm ÷ 1 = 1.3 ppm
1.3 ppm × 49.0 ÷ 24.5 = 2.6 mg/m^3

8-h AEGL-1:
1.0 ppm ÷ 1 = 1.0 ppm
1.0 ppm × 49.0 ÷ 24.5 = 2.0 mg/m^3

Potassium Cyanide

10-min AEGL-1:
2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 65.1 ÷ 24.5 = 6.6 mg/m^3

30-min AEGL-1:
2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 65.1 ÷ 24.5 = 6.6 mg/m^3

1-h AEGL-1:
2.0 ppm ÷ 1 = 2.0 ppm
2.0 ppm × 65.1 ÷ 24.5 = 5.3 mg/m^3

4-h AEGL-1:
1.3 ppm ÷ 1 = 1.3 ppm
1.3 ppm × 65.1 ÷ 24.5 = 3.5 mg/m^3

8-h AEGL-1:
1.0 ppm ÷ 1 = 1.0 ppm
1.0 ppm × 65.1 ÷ 24.5 = 2.7 mg/m^3

Calcium Cyanide

10-min AEGL-1: 2.5 ppm ÷ 2 = 1.25 ppm
1.25 ppm × 92.1 ÷ 24.5 = 4.7 mg/m^3

30-min AEGL-1: 2.5 ppm ÷ 2 = 1.25 ppm
1.25 ppm × 92.1 ÷ 24.5 = 4.7 mg/m^3

1-h AEGL-1: 2.0 ppm ÷ 2 = 1.0 ppm
1.0 ppm × 92.1 ÷ 24.5 = 3.8 mg/m^3

4-h AEGL-1: 1.3 ppm ÷ 2 = 0.65 ppm
0.65 ppm × 92.1 ÷ 24.5 = 2.4 mg/m^3

8-h AEGL-1: 1.0 ppm ÷ 2 = 0.50 ppm
0.50 ppm × 92.1 ÷ 24.5 = 1.9 mg/m^3

Derivation of AEGL-2 Values

The AEGL-2 values for hydrogen cyanide were used as target values for calculating the concentrations of the cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis (one mole of sodium cyanide or potassium cyanide will yield one mole of hydrogen cyanide, and one mole of calcium cyanide will yield two moles of hydrogen cyanide).

Sodium Cyanide

10-min AEGL-2: 17 ppm ÷ 1 = 17 ppm
17 ppm × 49.0 ÷ 24.5 = 34 mg/m^3

30-min AEGL-2: 10 ppm ÷ 1 = 10 ppm
10 ppm × 49.0 ÷ 24.5 = 20 mg/m^3

1-h AEGL-2: 7.1 ppm ÷ 1 = 7.1 ppm
7.1 ppm × 49.0 ÷ 24.5 = 14 mg/m^3

4-h AEGL-2: 3.5 ppm ÷ 1 = 3.5 ppm
3.5 ppm × 49.0 ÷ 24.5 = 7.0 mg/m^3

8-h AEGL-2: 2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 49.0 ÷ 24.5 = 5.0 mg/m^3

Potassium Cyanide

10-min AEGL-2: 17 ppm ÷ 1 = 17 ppm
17 ppm × 65.1 ÷ 24.5 = 45 mg/m^3

30-min AEGL-2: 10 ppm ÷ 1 = 10 ppm
10 ppm × 65.1 ÷ 24.5 = 27 mg/m^3

1-h AEGL-2: 7.1 ppm ÷ 1 = 7.1 ppm
7.1 ppm × 65.1 ÷ 24.5 = 19 mg/m^3

4-h AEGL-2: 3.5 ppm ÷ 1 = 3.5 ppm
3.5 ppm × 65.1 ÷ 24.5 = 9.3 mg/m^3

8-h AEGL-2: 2.5 ppm ÷ 1 = 2.5 ppm
2.5 ppm × 65.1 ÷ 24.5 = 6.6 mg/m^3

Calcium Cyanide

10-min AEGL-2: 17 ppm ÷ 2 = 8.5 ppm
8.5 ppm × 92.1 ÷ 24.5 = 32 mg/m^3

30-min AEGL-2: 10 ppm ÷ 2 = 5 ppm
5 ppm × 92.1 ÷ 24.5 = 19 mg/m^3

1-h AEGL-2: 7.1 ppm ÷ 2 = 3.55 ppm
3.55 ppm × 92.1 ÷ 24.5 = 13 mg/m^3

4-h AEGL-2: 3.5 ppm ÷ 2 = 1.75 ppm
1.75 ppm × 92.1 ÷ 24.5 = 6.6 mg/m^3

8-h AEGL-2: 2.5 ppm ÷ 2 = 1.25 ppm
1.25 ppm × 92.1 ÷ 24.5 = 4.7 mg/m^3

Derivation of AEGL-3 Values

The AEGL-3 values for hydrogen cyanide were used as target values for calculating the concentrations of the cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis (one mole of sodium cyanide or potassium cyanide will yield one mole of hydrogen cyanide, and one mole of calcium cyanide will yield two moles of hydrogen cyanide).

Sodium Cyanide

10-min AEGL-3: 27 ppm ÷ 1 = 27 ppm
27 ppm × 49.0 ÷ 24.5 = 54 mg/m^3

30-min AEGL-3: 21 ppm ÷ 1 = 21 ppm
21 ppm × 49.0 ÷ 24.5 = 42 mg/m^3

1-h AEGL-3: 15 ppm ÷ 1 = 15 ppm
15 ppm × 49.0 ÷ 24.5 = 30 mg/m^3

4-h AEGL-3: 8.6 ppm ÷ 1 = 8.6 ppm
8.6 ppm × 49.0 ÷ 24.5 = 17 mg/m^3

8-h AEGL-3: 6.6 ppm ÷ 1 = 6.6 ppm
6.6 ppm × 49.0 ÷ 24.5 = 13 mg/m^3

Potassium Cyanide

10-min AEGL-3: 27 ppm ÷ 1 = 27 ppm
27 ppm × 65.1 ÷ 24.5 = 72 mg/m^3

30-min AEGL-3: 21 ppm ÷ 1 = 21 ppm
21 ppm × 65.1 ÷ 24.5 = 56 mg/m^3

1-h AEGL-3: 15 ppm ÷ 1 = 15 ppm
15 ppm × 65.1 ÷ 24.5 = 40 mg/m^3

4-h AEGL-3: 8.6 ppm ÷ 1 = 8.6 ppm
8.6 ppm × 65.1 ÷ 24.5 = 23 mg/m^3

8-h AEGL-3: 6.6 ppm ÷ 1 = 6.6 ppm
6.6 ppm × 65.1 ÷ 24.5 = 18 mg/m^3

Calcium Cyanide

10-min AEGL-3: 27 ppm ÷ 2 = 13.5 ppm
13.5 ppm × 92.1 ÷ 24.5 = 51 mg/m^3

30-min AEGL-3: 21 ppm ÷ 2 = 10.5 ppm
10.5 ppm × 92.1 ÷ 24.5 = 39 mg/m^3

1-h AEGL-3: 15 ppm ÷ 2 = 7.5 ppm
7.5 ppm × 92.1 ÷ 24.5 = 28 mg/m^3

4-h AEGL-3: 8.6 ppm ÷ 2 = 4.3 ppm
4.3 ppm × 92.1 ÷ 24.5 = 16 mg/m^3

8-h AEGL-3: 6.6 ppm ÷ 2 = 3.3 ppm
3.3 ppm × 92.1 ÷ 24.5 = 12 mg/m^3

APPENDIX B

DERIVATION OF THE AEGL VALUES FOR HYDROGEN CYANIDE (NRC 2002)

Derivation of AEGL-1 Values

Key studies:	Leeser et al. 1990
Supporting studies:	Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970; El Ghawabi et al. 1975
Toxicity end point:	No adverse effect in healthy adult humans occupationally exposed at geometric mean concentration of ≤1 [range 0.01-3.3 ppm, personal samplers (up to 6 ppm, area samples)] or 5 ppm; mild headache in adult humans occupationally exposed at 8 ppm. The exposure duration was considered to be 8 h.
Uncertainty factor:	An uncertainty factor was not applied to the Leeser et al. (1990) 1-ppm concentration because it is the lowest NOAEL. A factor of 3 for intraspecies differences was applied to the supporting studies because no susceptible populations were identified. The uncertainty factor was applied to the 8-h 5 ppm and 8 ppm concentrations, which resulted in concentrations close to the 8-h 1-ppm concentration in the Leeser et al. (1990) study.
Time scaling:	$C^3 \times t = k$ (conservative time-scaling relationship because, the relationship between concentration and exposure duration for the headache effect is unknown). An 8-h 1 ppm concentration was used as the starting point for time scaling.
Calculations:	$(C^3 \div \text{uncertainty factors}) \times t = k$ $(1 \text{ ppm})^3 \times 480 \text{ min} = 480 \text{ ppm-min}$
10-min AEGL-1:	$(480 \text{ ppm-min}/10 \text{ min})^{1/3} = 3.6 \text{ ppm}$ Because 3.6 ppm is above the highest exposure concentration in the Leeser et al. (1990) study, as measured by personal monitors, the 10-min value was set equal to the 30-min value.
30-min AEGL-1:	$(480 \text{ ppm-min} \div 30 \text{ min})^{1/3} = 2.5 \text{ ppm}$
1-h AEGL-1:	$(480 \text{ ppm-min} \div 60 \text{ min})^{1/3} = 2.0 \text{ ppm}$

4-h AEGL-1: $(480 \text{ ppm-min} \div 240 \text{ min})^{1/3} = 1.3 \text{ ppm}$

8-h AEGL-1: 1.0 ppm

Derivation of AEGL-2 Values

Key study: Purser 1984

Toxicity end point: Slight central nervous system depression in monkeys inhaling 60 ppm for 30 min.

Time scaling: $C^2 \times t = k$ (this document; based on regression analysis of incapacitation and lethality data for the monkey)

Uncertainty factors: 2 for interspecies differences
3 for intraspecies variability
Total uncertainty factor: 6

Calculations: $(C^2 \div \text{uncertainty factors}) \times t = k$
$(60 \text{ ppm} \div 6)^2 \times 30 \text{ min} = 3{,}000 \text{ ppm-min}$

10-min AEGL-2: $(3{,}000 \text{ ppm-min} \div 10 \text{ min})^{1/2} = 17 \text{ ppm}$

30-min AEGL-2: $60 \text{ ppm} \div 6 = 10 \text{ ppm}$

1-h AEGL-2: $(3{,}000 \text{ ppm-min} \div 60 \text{ min})^{1/2} = 7.1 \text{ ppm}$

4-h AEGL-2: $(3{,}000 \text{ ppm-min} \div 240 \text{ min})^{1/2} = 3.5 \text{ ppm}$

8-h AEGL-2: $(3{,}000 \text{ ppm-min} \div 480 \text{ min})^{1/2} = 2.5 \text{ ppm}$

Derivation of AEGL-3 Values

Key study: Haskell Laboratory 1981

Toxicity end point: 15-min LC_{01} of 138 ppm in the rat
30-min LC_{01} of 127 ppm in the rat
1-h LC_{01} of 88 ppm in the rat
LC_{01} derived by probit analysis

Time scaling: $C^{2.6} \times t = k$ (this document; based on the Haskell Laboratory [1981] rat dataset)

Uncertainty factors: 2 for interspecies
3 for intraspecies
Total uncertainty factor: 6

Calculations:	$(C^{2.6} \div \text{uncertainty factors}) \times t = k$ $(138 \text{ ppm} \div 6)^{2.6} \times 15 \text{ min} = 52{,}069.5 \text{ ppm-min}$ $(127 \text{ ppm} \div 6)^{2.6} \times 30 \text{ min} = 83{,}911 \text{ ppm-min}$ $(88 \text{ ppm} \div 6)^{2.6} \times 60 \text{ min} = 64{,}656.6 \text{ ppm-min}$
10-min AEGL-3:	$(52{,}069.5 \text{ ppm-min} \div 10 \text{ min})^{1/2.6} = 27 \text{ ppm}$
30-min AEGL-3:	$127 \text{ ppm} \div 6 = 21 \text{ ppm}$
1-h AEGL-3:	$88 \text{ ppm} \div 6 = 15 \text{ ppm}$
4-h AEGL-3:	$(64{,}656.6 \text{ ppm-min} \div 240 \text{ min})^{1/2.6} = 8.6 \text{ ppm}$
8-h AEGL-3:	$(64{,}656.6 \text{ ppm-min} \div 480 \text{ min})^{1/2.6} = 6.6 \text{ ppm}$

APPENDIX C

ACUTE EXPOUSRE GUIDELINES FOR CYANIDE SALTS

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Sodium cyanide				
5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
Potassium cyanide				
6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
Calcium cyanide				
4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3

Key reference: NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 2. Washington, DC: The National Academies Press.

End point/Concentration/Rationale: AEGL-1 values for hydrogen cyanide were used to obtain AEGL-1 values for the three cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for the acute toxicity of the cyanide salts. The hydrogen cyanide AEGL-1 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis.

Molar adjustment factor:
1 (sodium cyanide and potassium cyanide); 2 (calcium cyanide)

Data adequacy: AEGL-1 values for the cyanide salts were derived by analogy to the AEGL-1 values for hydrogen cyanide. The database on hydrogen cyanide is robust. The adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound). However, the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
Sodium cyanide				
34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
Potassium cyanide				
45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
Calcium cyanide				
32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3

Key reference: NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 2. Washington, DC: The National Academies Press.

(Continued)

AEGL-2 VALUES Continued

End point/Concentration/Rationale: AEGL-2 values for hydrogen cyanide were used to obtain AEGL-2 values for the three cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for acute toxicity of the cyanide salts. The hydrogen cyanide AEGL-2 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis.

Molar adjustment factor:
1 (sodium cyanide and potassium cyanide); 2 (calcium cyanide)

Data adequacy: AEGL-2 values for the cyanide salts were derived by analogy to the AEGL-2 values for hydrogen cyanide. The database on hydrogen cyanide is robust. The adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound). However, the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
Sodium cyanide				
54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium cyanide				
72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium cyanide				
51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

Key reference: NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 2. Washington, DC: The National Academies Press.

End point/Concentration/Rationale: AEGL-3 values for hydrogen cyanide were used to obtain AEGL-3 values for the three cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts is deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for acute toxicity of the cyanide salts. The hydrogen cyanide AEGL-3 values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. The calculations assumed a temperature of 25°C, a pressure of 760 mm Hg, and complete hydrolysis.

Molar adjustment factor:
1 (sodium cyanide and potassium cyanide)
2 (calcium cyanide)

Data adequacy: AEGL-3 values for the cyanide salts were derived by analogy to the AEGL-3 values for hydrogen cyanide. The database on hydrogen cyanide is robust. The adjusted rat oral LD_{50} value for calcium cyanide is much greater than would be expected on a molar basis for cyanide (suggesting that it is a less toxic compound). However, the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide. That assumption will yield protective AEGL values.

APPENDIX D

ACUTE EXPOUSRE GUIDELINES FOR HYDROGEN CYANIDE

Derivation Summary (NRC 2002)

AEGL-1 VALUES FOR HYDROGEN CYANIDE

10 min	30 min	1 h	4 h	8 h
2.5 ppm (2.8 mg/m^3)	2.5 ppm (2.8 mg/m^3)	2.0 ppm (2.2 mg/m^3)	1.3 ppm (1.4 mg/m^3)	1.0 ppm (1.1 mg/m^3)

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, Macclesfield, 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(September):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(25):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 y (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: 1 ppm from the Leeser (1990) study; 8 ppm from the El Ghawabi et al. (1975) study; or 5 ppm from the Hardy et al. (1950), Grabois (1954), and Maehly and Swensson (1970) studies were considered no-adverse-effect to mild effect concentrations for an 8-h workday. 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

(Continued)

AEGL-1 Continued

Intraspecies: 3, an uncertainty factor was not applied to the Leeser et al.(1990) 1 ppm concentration, as it is the lowest NOAEL. A factor of 3 was applied to the supporting studies as 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.

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 supports 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, supports 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.

AEGL-2 VALUES FOR HYDROGEN CYANIDE

10 min	30 min	1 h	4 h	8 h
17 ppm (19 mg/m^3)	10 ppm (11 mg/m^3)	7.1 ppm (7.8 mg/m^3)	3.5 ppm (3.9 mg/m^3)	2.5 ppm (2.8 mg/m^3)

Key references: (1) Purser, D.A. 1984. A bioassay model for testing the incapacitating effects of exposure to combustion product atmospheres using cynomolgus monkeys. J. Fire Sci. 2:20-36.
(2) Purser, D.A., P. Grimshaw and K.R. Berrill. 1984. Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile. Arch. Environ. Health 39(6):393-400.

Test species/Strain/Sex/Number: Cynomolgus monkeys, 4 per exposure group (sex not stated)

Exposure route/Concentrations/Durations: Inhalation, 60, 100, 102, 123, 147, or 156 ppm for 30 min

Effects: (30-min exposures)
60 ppm - increased respiratory minute volume and slight changes in EEGs near end of exposure
100 ppm - incapacitation (semi-conscious state) in 19 min
102 ppm - incapacitation in 16 min
123 ppm - incapacitation in 15 min
147 ppm - incapacitation in 8 min
156 ppm - incapacitation in 8 min

(Continued)

AEGL-2 Continued

End point/Concentration/Rationale: The 30-min exposure to 60 ppm, a NOAEL, was chosen because the next higher tested concentration, 100 ppm, resulted in incapacitation within the 30-min exposure period.
Uncertainty factors/Rationale: Total uncertainty factor: 6 Interspecies: 2–The monkey is an appropriate model for humans, the small size and higher respiratory rate of the monkey may result in more rapid uptake and greater sensitivity than in humans. Intraspecies: 3–No specific susceptible populations were identified during monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals including newborns.
Modifying Factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data.
Time scaling: $C^n \times t = k$, where n = 2 and k = 3,000 ppm-min on the basis of regression analysis of time-concentration relationships for both incapacitation times of 8 to 19 min and lethality data (3-60 min) for the monkey.
Data adequacy: Although human data are limited to primarily occupational monitoring studies, the data base on animal studies is good. The test atmosphere in the key study was supplied via a face mask to the restrained test subjects; restrained animals have been shown to be more sensitive than unrestrained animals to inhaled toxicants. Relative species sensitivity to inhaled HCN may be related to breathing rate. Compared to rodents, the slower breathing rate of humans and monkeys may make them less sensitive to the effects of HCN. The following two supporting studies were located: 1. A 30-min exposure of rats to 55 ppm resulted in changes in lung phospholipids and lung dynamics. Use of an uncertainty factor of 6 results in a 30-min AEGL-2 of 9.2 ppm, which is similar to the AEGL value. 2. Humans inhaling mean concentrations of 10 or 15 ppm in electroplating or silver-reclaiming factories for up to 15 y reported symptoms including headache, fatigue, effort dyspnea, and syncopes. There was no evidence that these symptoms occurred on the first day of employment.

AEGL-3 VALUES FOR HYDROGEN CYANIDE

10 min	30 min	1 h	4 h	8 h
27 ppm (30 mg/m^3)	21 ppm (23 mg/m^3)	15 ppm (17 mg/m^3)	8.6 ppm (9.7 mg/m^3)	6.6 ppm (7.3 mg/m^3)

Key reference: Haskell Laboratory. 1981. Inhalation Toxicity of Common Combustion Gases. Haskell Laboratory Report No. 238-81. E.I. du Pont de Nemours and Company, Haskell Laboratory, Newark, DE.
Test species/Strain/Sex/Number: Crl:CD male rats, 10/exposure group
Exposure route/Concentrations/Durations: Inhalation 273, 328, 340, 353, 441, 493, or 508 ppm for 5 min 110, 175, 188, 204, 230, 251, 283, or 403 ppm for 15 min 128, 149, 160, 183, 222, or 306 ppm for 30 min 76, 107, 154, 183, or 222 ppm for 60 min

(Continued)

AEGL-3 Continued

Effects (LC_{01} values were calculated by Haskell Laboratory using probit analysis):
5-min LC_{01}: 283 ppm
15-min LC_{01}: 138 ppm
30-min LC_{01}: 127 ppm
60-min LC_{01}: 88 ppm

End point/Concentration/Rationale:
The LC_{01}, the threshold for lethality, was used as the basis for the derivation of the AEGL-3.
The 15-min LC_{01} was used to calculate the 10 min value; the 30-min LC_{01} was used for the 30-min value; and the 60-min LC_{01} was used to derive the 1-, 4- and 8-h AEGL-3 values.

Uncertainty factors/Rationale:
Total uncertainty factor: 6
Interspecies: 2 - LC_{50} values for the same exposure durations for several species (rat, mouse, and rabbit) were within a factor of approximately 1.5 of each other. Based on relative respiration rates, humans are expected to be less sensitive than rodents. The mechanism is the same for all species.
Intraspecies: 3 - No specific susceptible populations were identified during monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals, including newborns.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data.

Time scaling: $C^n \times t = k$, where n = 2.6 was derived from empirical data and used in a regression analysis of time-concentration relationships for rat LC_{50} values conducted at time periods of 5, 15, 30, and 60 min in the key study. However, the 15-, 30-, and 60-min values were calculated directly from the empirical (LC_{01}) data. The k value of 52,069.5 $ppm^{2.6}$-min, based on the 15-min LC_{01}, was used for the 10-min value and the k value of 64,656.6 $ppm^{2.6}$-min, based on the 1-h LC_{01}, was used for the 4- and 8-h AEGL-3 values.

Data adequacy: The study was well conducted. The HCN concentrations were continuously monitored using infrared spectrophotometry and validated by gas chromatography.
One supporting study was located: exposure of rats to 30 ppm for 24 h resulted in lung congestion but no deaths. Use of a total uncertainty factor of 6 and extrapolation across time to 30 min results in a 30-min AEGL-3 of 22 ppm which is similar to the derived value of 21 ppm.

2

Diketene[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 Kowetha Davidson (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Heather Carlson-Lynch (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).

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

Diketene is a non-hygroscopic, light-colored or colorless liquid that is polymerized on standing. It is flammable and has a moderate fire risk. Diketene has a pungent odor. It is an irritant, causing mild irritation of the eyes, nose, and throat after occupational exposure at 0.58 ppm for 1 min. Inhalation of diketene was not lethal to rats at 250 ppm for 1 h or to rabbits at 194 ppm for 10 min, but deaths occurred in rats exposed at 500 or 750 ppm for 1 h. Rats exposed to diketene at 250-750 ppm for 1 h showed signs of ocular and respiratory-tract irritation. Deaths occurred in mice exposed to diketene at 870 ppm for 10 min and in guinea pigs exposed at 194 ppm for 10 min. Pulmonary edema was found in the animals that died. The 1-h LC_{50} (lethal concentration, 50% lethality) values for rats were 548 ppm for males, 689 ppm for females, and 612 ppm for both sexes combined.

Data were insufficient for deriving AEGL-1 values for diketene. Therefore, AEGL-1 values are not recommended.

Data were also insufficient for deriving AEGL-2 values for diketene. The standing operating procedures for deriving AEGL values specify that AEGL-2 values for chemicals with steep concentration-response curves may be estimated by dividing the AEGL-3 values by a factor of 3. The steepness of the lethality concentration-response curve for diketene indicates that a factor of 3 should be adequate for reducing the AEGL-3 values to a level consistent with the definition of AEGL-2.

AEGL-3 values were derived on the basis of an acute inhalation study in which rats were exposed to diketene at 250, 500, or 750 ppm for 1 h (Katz

1987). The point-of-departure was the lethality $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 181 ppm, which was calculated using a log-probit model. A total uncertainty factor of 30 was applied; a factor of 10 for interspecies differences and a factor of 3 for intraspecies variability. Diketene is irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue; that type of portal-of-entry effect is not expected to vary greatly among individuals. The intraspecies uncertainty factor of 3 is further supported by the similarity in mortality incidence and clinical signs between male and female rats exposed to diketene (Katz 1987). A modifying factor of 2 was also applied because of the limited database on diketene. Time scaling was performed using the equation $C^n \times t = k$. Data on diketene were insufficient for determining an empirical value for the exponent n, so default values of n = 3 for extrapolating to shorter durations (10 and 30 min) and n = 1 for extrapolating to longer durations (4 and 8 h) were used.

The AEGL values for diketene are presented in Table 2-1.

1. INTRODUCTION

Diketene is a light-colored or colorless non-hygroscopic liquid that polymerizes on standing (AIHA 2000; Lewis 2007). It is flammable and has a moderate fire risk. Diketene is used in the production of pigments and toners, pesticides, food preservatives, and pharmaceutical intermediates (HSDB 2003; Lewis 2007). The odor of diketene has been described as pungent (Lewis 2007).

The chemical and physical properties of diketene are presented in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Human Lethality

No data regarding exposure of humans to lethal concentrations of diketene were found.

TABLE 2-1 AEGL Values for Diketene

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)	1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)	One-third of the AEGL-3 values.
AEGL-3 (lethal)	5.5ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 mg/m^3)	$BMCL_{05}$ for lethality (Katz 1987)

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

TABLE 2-2 Chemical and Physical Properties of Diketene

Parameter	Value	Reference
Synonyms	3-Butenoic acid, 3-hydroxy-, beta-lacone; ethenone, dimer; ketene, dimer; 4-methylene-2-oxetanone; vinylaceto-beta-lactone	HSDB 2003
CAS registry no.	674-82-8	HSDB 2003
Chemical formula	$C_4H_4O_2$	HSDB 2003
Molecular weight	84.08	HSDB 2003
Physical state	Light-colored or colorless liquid	AIHA 2000; Lewis 2007
Melting point	-6.5°C	HSDB 2003
Boiling point	127.4°C	HSDB 2003
Density/Specific gravity (water = 1)	1.096 (20/20°C) 1.0897	Lewis 2007 HSDB 2003
Vapor density (air = 1)	2.9	HSDB 2003
Solubility	Soluble in common organic solvents; soluble in water	Lewis 2007
Vapor pressure	10 mm Hg at 24.3°C 1.07 kPa at 20°C	AIHA 2000 HSDB 2003
Flash point (tagged closed cup)	34°C	AIHA 2000
Autoignition temperature	310°C	AIHA 2000
Conversion factors	1 mg/m^3 = 0.29 ppm; 1 ppm = 3.44 mg/m^3	AIHA 2000

2.2. Nonlethal Toxicity

Occupational exposure to diketene at a concentration of 2 mg/m^3 (0.58 ppm) for 1 min caused mild irritation of the conjunctiva and mucosa of the nose and throat (Danishevskii 1948,1951; Feldman 1967).

2.3. Summary

No studies were found on human exposure to lethal concentrations of diketene. A concentration of 0.58 ppm caused mild ocular, nasal, and throat irritation.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rat

Groups of five male and five female CRL:CD®(SD)BR rats were exposed to diketene at concentrations of 0, 250, 500, or 750 ppm for 1 h and observed for 14 days after exposure (Katz 1987). The analytic concentrations were 271 ± 2.4, 466 ± 13.7, and 778 ± 16.9 ppm, respectively. The rats were exposed in a 420-L

stainless steel and glass chamber with 10-13 air changes per hour. The chamber atmosphere was analyzed four or five times using an infrared analyzer; the nominal concentration was calculated on the basis of the amount of diketene used and the air flow rate. All rats were subjected to gross examination, but no tissues were collected for microscopic examination.

Mortality and clinical signs are summarized in Table 2-3. The mortality rate was 0/10, 3/10, and 7/10 rats (sexes combined) in the 250-, 500-, and 750-ppm groups, respectively. All deaths occurred within 48 h after exposure, except for one male rat exposed at 750 ppm that died on day 6. The LC_{50} values were 548 ppm for male rats, 689 ppm for female rats, and 612 ppm for both sexes combined. LC_{10} values calculated by the investigators were 346 ppm for males, 410 ppm for females, and 370 ppm for both sexes combined. All rats exposed to diketene exhibited excessive tearing (lacrimation) during exposure and for a few hours after exposure. Porphyrin discharge from the nose was observed in male and female rats for up to 48 h after exposure at 500 and 750 ppm. Effects on the respiratory tract consisted of gasping in all rats at all concentrations and wheezing in one or two rats per group. Rales were observed in one male rat in each exposure group and one female in the 500-ppm group, but the effect might not have been due to diketene, because no increase in the incidence of rales occurred with a 15-fold increase in the exposure concentration. No gross lesions were found in any rats exposed to diketene.

3.1.2. Mice

Wooster et al. (1947) exposed groups of 4, 30, and 20 mice to diketene at concentrations of 194, 580, or 870 ppm, respectively, for 10 min. Diketene was prepared at a known concentration in acetone and sprayed into the chamber from a glass atomizer; the concentration of diketene in inhaled air was 0.67 mg/L (194 ppm). The animals were observed for up to 15 days after exposure. No additional details on the experimental protocol were provided. One mouse died

TABLE 2-3 Mortality and Clinical Signs in Rats Exposed to Diketene

	Exposure Concentration							
	0	250	500	750	0	250	500	750
Parameter	No. males				No. females			
No. exposed	0	5	5	5	0	5	5	5
Mortality	0	0	2	4	0	0	1	3
Excessive tearing	0	5	5	5	0	5	5	5
Porphyrin discharge	0	0	2	2	0	0	2	3
Gasping	0	5	5	5	0	5	5	5
Rales	0	1	1	1	0	0	1	0
Wheezing	0	1	0	0	0	0	1	2
Poor condition	0	0	0	4	0	0	0	1

Source: Katz 1987.

after exposure at 870 ppm, but no deaths occurred in mice exposed at 580 or 194 ppm. No specific clinical signs or pathologic findings were described. The investigators noted that the findings in the animals that died were similar to those described for animals (particularly the cat) exposed to ketene. Microscopically, animals that died after ketene exposure had proteinaceous edematous fluid in the alveoli of the lungs and in the perivascular connective tissue of the bronchial and bronchiolar vessels. After describing the microscopic lesions in animals that died after ketene exposure, Wooster et al. (1947) stated that "the findings in the few animals dying after diketene poisoning were similar." That suggests that the mice that died after exposure to diketene had alveolar and bronchial edema (pulmonary edema).

3.1.3. Other Species

All three guinea pigs died after exposure to diketene at 194 ppm under the same conditions as described for mice (see Section 3.1.2) (Wooster et al. 1947). No clinical signs or pathologic effects were described. From the investigators' description that the findings in the dead animals were similar to those of animals that died from ketene exposure, it was implied that the guinea pigs also had pulmonary edema.

3.2. Nonlethal Toxicity

Wooster et al. (1947) exposed four rats and three rabbits to diketene at 0.67 mg/L (194 ppm) for 10 min under the same conditions as described for mice (see Section 3.1.2). All of the animals survived to the end of the study. No clinical signs or pathologic lesions were described.

3.3. Other End Points of Toxicity

No data were found on the neurotoxicity, developmental toxicity, reproductive toxicity, genetic toxicity, or carcinogenicity of inhaled diketene in experimental animals.

3.4. Summary

Table 2-4 summarizes the lethal effects of acute inhalation exposure to diketene in several species. The LC_{50} for a 1-h exposure of rats to diketene ranged from 548 to 689 ppm. Rats died after exposure to diketene at concentrations 500 or 750 ppm for 1 h, guinea pigs died after exposure at 194 ppm for 10 min, and mice died after exposure at 870 ppm for 10 min. No deaths occurred in rats and rabbits after exposure to diketene at 194 ppm for 10 min. Ocular and respiratory-tract irritation were observed in rats exposed at lethal and nonlethal concentrations

of diketene greater than 250 ppm. The primary findings in mice and guinea pigs exposed to diketene were the same as those found in the cat that died after exposure to ketene (alveolar and bronchial edema or pulmonary edema).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the uptake, metabolism, disposition, or excretion of inhaled diketene were found.

4.2. Mechanism of Toxicity

Diketene is an irritant (Lewis 2007). Wooster et al. (1947) noted that the pathologic changes caused by ketene were similar to those of phosgene.

4.3. Structure-Activity Relationships

Diketene is the dimeric form of ketene, and is similar to but less toxic than ketene. At high temperatures (510-603°K), diketene undergoes thermal decomposition to form ketene, cyclobuta-1,3-dione, and cyclobuta-1,2-dione (Bui et al. 2007). Wooster et al. (1947) exposed rats, cats, guinea pigs, and rabbits to ketene for 10 min and observed the survivors for up to 15 days. Ketene exposure caused severe damage to the respiratory tract (pulmonary edema), but the pathologic effects were described only for cats. The lowest concentrations associated

TABLE 2-4 Summary of Acute Lethality Data from Studies of Laboratory Animals Exposed to Diketene by Inhalation

Species (sex)	Concentration	Exposure Time	Effect (% lethality)	Reference
Rat	194	10 min	0%	Wooster et al. 1947
Rat (females)	689	1 h	LC_{50}	Katz 1987
Rat (males and females)	612	1 h	LC_{50}	Katz 1987
Rat (males)	548	1 h	LC_{50}	Katz 1987
Rat (females)	410	1 h	LC_{10}	Katz 1987
Rat (males and females)	370	1 h	LC_{10}	Katz 1987
Rat (males)	346	1 h	LC_{10}	Katz 1987
Mouse	870	10 min	5%	Wooster et al. 1947
Mouse	194-580	10 min	0%	Wooster et al. 1947
Guinea pig	194	10 min	100%[a]	Wooster et al. 1947
Rabbit	194	10 min	0%	Wooster et al. 1947

[a]Only three animals exposed.

with mortality were 35 ppm for the mouse, 125 ppm for the rat, 183 ppm for the cat and guinea pig, and 325 ppm for the rabbit. In contrast, no deaths were observed in mice exposed to diketene at 194-580 ppm for 10 min, and 100% mortality occurred in rabbits exposed to diketene at 194 ppm for 10 min (Wooster et al. 1947).

4.4. Species Variability

According to Wooster et al. (1947), guinea pigs died after exposure to diketene at 194 ppm for 10 min, but mice, rats, and rabbits survived a 10-min exposure at 194 ppm. Thus, the guinea pig appears to be more sensitive than other species to diketene.

4.5. Susceptible Populations

No data are available on populations that might be susceptible to diketene.

4.6. Concentration-Exposure Duration Relationship

Lethality data from the study by Katz (1987) was used to create Figure 2-1, which shows a steep concentration-response curve. See Section 3.1.1. for a description of the study.

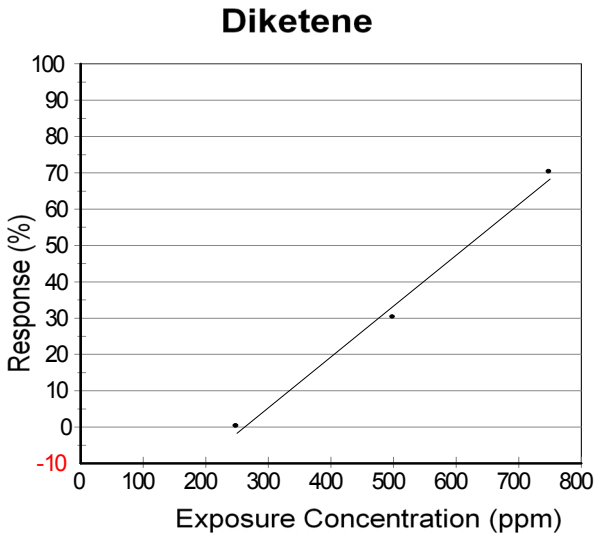

FIGURE 2-1 Concentration-response relationship between diketene and lethality in rats.

4.7. Concurrent Exposure Issues

No concurrent exposure issues for diketene were found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Humans occupationally exposed to diketene at 0.58 ppm for 1 min experienced mild irritation of the eyes, nose, and throat (Danishevskii 1948, 1951).

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to deriving AEGL-1 values for diketene were found.

5.3. Derivation of AEGL-1 Values

No AEGL-1 values were derived for diketene. The only data available for deriving AEGL-1 values are from a study in which workers exposed to diketene at 0.58 ppm were reported to experience mild irritation of the eyes, nose, and throat. That information is from a secondary source and could not be verified, so the data are considered insufficient for deriving AEGL-1 values. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to deriving AEGL-2 values for diketene were found.

6.2. Animal Data Relevant to AEGL-2

Lacrimation and gasping were observed in rats exposed to diketene at 250 ppm for 1 h, and none of the animals died (Katz 1987). No deaths occurred among groups of mice exposed to diketene at 194-580 ppm for 10 min (Wooster et al. 1947).

6.3. Derivation of AEGL-2 Values

The experimental data from animal studies were not appropriate for deriving AEGL-2 values for diketene. Although rats exposed at 250 ppm for 1 h

showed clinical signs indicative of ocular and respiratory-tract irritation and no deaths occurred (Katz 1987), the $BMCL_{05}$ for lethality (used as the point-of-departure for deriving AEGL-3 values) was lower than the highest concentration causing no lethality in rats. Therefore, the rat study should not be used to derive AEGL-2 values. The standing operating procedures for deriving AEGL values specify that AEGL-2 values for chemicals with steep concentration-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Because diketene is judged to have a steep concentration-response relationship for lethality, that approach was used to determine AEGL-2 values for diketene. The AEGL-2 values for diketene are presented in Table 2-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to deriving AEGL-3 values for diketene were found.

7.2. Animal Data Relevant to AEGL-3

In an acute inhalation study using rats exposed to diketene vapor (250, 500, and 750 ppm) for 1 h (Katz 1987), deaths occurred at the two highest concentrations. The exposure conditions and results of the study were well documented. Wooster et al. (1947) reported that one of 20 mice died after exposure to diketene at 870 ppm for 10 min and all three guinea pigs exposed to diketene at 194 ppm for 10 min died. These data show that the guinea pig is the more sensitive species to diketene.

7.3. Derivation of AEGL-3 Values

The AEGL-3 values were derived on the basis of the mortality study of rats exposed to diketene at 250, 500, or 750 ppm for 1 h (Katz 1987). A $BMCL_{05}$ of 181 ppm was calculated using the log-probit model in EPA's Benchmark Dose Software (v. 1.3.2), and an LC_{01} (lethality threshold, 1% lethality) of 276 ppm was calculated by probit regression analysis. The $BMCL_{05}$ of 181 ppm was used as point-of-departure for deriving AEGL-3 values. A total uncertainty factor of 30 was applied; a factor of 10 for interspecies differences and a factor of 3 for intraspecies variability. The factor of 3 was applied because diketene is

TABLE 2-5 AEGL-2 Values for Diketene

10 min	30 min	1 h	4 h	8 h
1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)

irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue. That type of portal-of-entry effect is not expected to vary greatly among individuals. A factor of 3 is further supported by the fact that mortality incidences and clinical signs were similar between male and female rats exposed to diketene (Katz 1987). A modifying factor of 2 was also applied because of the limited database on diketene. Time scaling was performed using the equation $C^n \times t = k$. The data on diketene were inadequate to determine an empirical value for the exponent n, so default values of n = 3 when extrapolating to shorter durations (10 and 30 min) and n = 1 when extrapolating to longer durations (4 and 8 h) were used. The AEGL-3 values for diketene are presented in Table 2-6.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for diketene are presented in Table 2-7. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were estimated by reducing the AEGL-3 values by a factor of 3. AEGL-3 values were derived from the $BMCL_{05}$ for lethality calculated from an acute inhalation study in rats.

8.2. Other Standards and Guidelines

The Russian occupational exposure limit for diketene is 1 mg/m^3 (0.29 ppm) (RTECS 2006). The AEGL-2 and AEGL-3 values for 1-h exposures are similar to the emergency response planning guidelines (ERPG-2 and ERPG-3) of the American Industrial Hygiene Association (AIHA 2000) (Table 2-8). No other standards or guidelines for diketene were found.

TABLE 2-6 AEGL-3 Values for Diketene

10 min	30 min	1 h	4 h	8 h
5.5 ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 mg/m^3)

TABLE 2-7 AEGL Values for Diketene

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)	1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)
AEGL-3 (lethal)	5.5 ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 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 2-8 Standards and Guidelines for Diketene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.8 ppm	1.3 ppm	1.0 ppm	0.25 ppm	0.13 ppm
AEGL-3	5.5ppm	3.8 ppm	3.0 ppm	0.75 ppm	0.38 ppm
ERPG-1 (AIHA)[a]	–	–	1 ppm	–	–
ERPG-2 (AIHA)	–	–	5 ppm	–	–
ERPG-3 (AIHA)	–	–	20 ppm	–	–

[a]ERPG (emergency response planning guideline, American Industrial Hygiene Association) (AIHA 2000).
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-1 for diketene is based on the threshold-limit value for ketene.
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-2 for diketene is based on clinical signs from a 1-h rat lethality study.
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. The ERPG-3 is based on 1-h lethality data (LC_{50} of 612 ppm) in the rat.

8.3. Data Adequacy and Research Needs

Additional animal studies with exposure durations relevant to the AEGL durations other than 1 h and with at least one species other than rat are needed to better characterize the acute inhalation toxicity of diketene. The diketene concentrations tested should encompass the entire spectrum of AEGL end points, ranging from 90-100% lethality to no lethality and no-effect-levels for clinical signs and pathologic findings.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR DIKETENE

Derivation of AEGL-1 Values

Insufficient data were available for deriving AEGL-1 values for diketene. Therefore, 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

The AEGL-2 values for diketene were estimated by dividing the respective AEGL-3 values by 3. That procedure is in accordance with the standing operating procedures for deriving AEGL values for chemicals with steep concentration-response curves (NRC 2001).

Calculations:

10-min AEGL-2:	5.5 ppm ÷ 3 = 1.8 ppm
30-min AEGL-2:	3.8 ppm ÷ 3 = 1.3 ppm
1-h AEGL-2:	3.0 ppm ÷ 3 = 1.0 ppm
4-h AEGL-2:	0.75 ppm ÷ 3 = 0.25 ppm
8-h AEGL-2;	0.38 ppm ÷ 3 = 0.13 ppm

Derivation of AEGL-3 Values

Key study:	Katz, G.V. 1987. Acute Inhalation Toxicity and One-Hour LC10 Value of Diketene in the Rat. Study No. TX-86-265, February 4, 1967. Toxicological Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY.
Toxicity end point:	Lethality (1-h $BMCL_{05}$ of 181 ppm)
Time scaling:	$C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations $(181 \text{ ppm} \div 60)^3 \times 60 \text{ min} = 1{,}647 \text{ ppm-min}$ $(181 \text{ ppm} \div 60)^1 \times 60 \text{ min} = 181 \text{ ppm-min}$
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability

Modifying factor:	2 for limited database
Calculations:	
10-min AEGL-3:	C^3 = (1,647 ppm-min ÷ 10 min) C = 5.5 ppm
30-min AEGL-3:	C^3 = (1,647 ppm-min ÷ 30 min) C = 3.8 ppm
1-h AEGL-3:	C = (181 ppm-min ÷ 60 min) C = 3.0 ppm
4-h AEGL-3:	C^1 = 181 ppm-min ÷ 240 min C = 0.75 ppm
8-h AEGL-3:	C^1 = 181 ppm-min ÷ 480 min C = 0.38 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR DIKETENE

AEGL-1 VALUES

Insufficient data were available for deriving AEGL-1 values for diketene. Therefore, 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
1.8 ppm	1.3 ppm	1.0 ppm	0.25 ppm	0.13 ppm

Data adequacy: No adequate studies were available for deriving AEGL-2 values for diketene. The AEGL-2 values were estimated by dividing the respective AEGL-3 values by 3. That procedure is in accordance with the standing operating procedures for deriving AEGL values for chemicals with steep concentration-response curves (NRC 2001).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
5.5 ppm	3.8 ppm	3.0 ppm	0.75 ppm	0.38 ppm

Key reference: Katz, G.V. 1987. Acute Inhalation Toxicity and One-Hour LC10 Value of Diketene in the Rat. Study No. TX-86-265, February 4, 1967. Toxicological Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY.

Test species/Strain/Number: Rat; CRL:CD®(SD)BR; 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 250, 500, and 750 ppm for 1 h

Effects:
250 ppm: Signs of ocular (lacrimation) and respiratory tract irritation (gasping and rales).
500 ppm: Three rats died (2 male, 1 female); clinical signs were the same as those observed at 250 ppm, plus porphyrin discharge from the nose.
750 ppm: Seven rats died (4 male, 3 female); clinical signs were same as those observed at 500 ppm.

End point/Concentration/Rationale: Lethality, 1-h $BMCL_{05}$ of 181 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10
Intraspecies: 3, because diketene is irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue. That type of portal-of-entry effect is not expected to vary greatly among individuals. A factor of 3 is further supported by the fact that mortality incidences and clinical signs were similar between male and female rats exposed to diketene (Katz 1987).

Modifying factor: 2 for limited database

Animal-to-human dosimetric adjustment: None

(Continued)

AEGL-3 VALUES Continued

Time scaling: $C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.
Data adequacy: Only one adequate animal study was available for evaluating the acute inhalation toxicity of diketene. Additional studies in rats exposed for other durations and studies in at least one other species are needed to better characterize the acute inhalation toxicity of diketene.

APPENDIX C

CATEGORY PLOT FOR DIKETENE

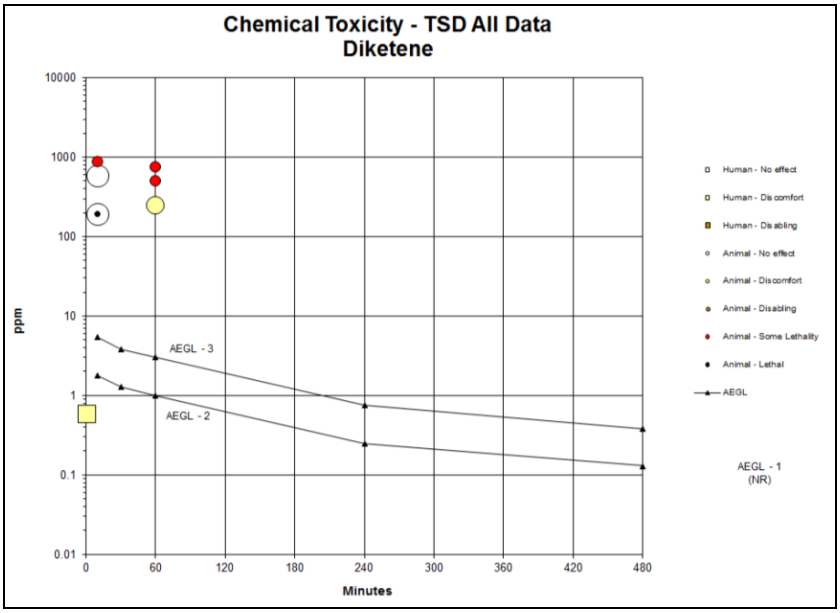

FIGURE C-1 Category plot of toxicity data and AEGL values for diketene.

TABLE C-1 Data Used in Category Plot for Diketene

Source	Species	ppm	Minutes	Category	Comments
AEGL-2		1.8	10	AEGL	
AEGL-2		1.3	30	AEGL	
AEGL-2		1.0	60	AEGL	
AEGL-2		0.25	240	AEGL	
AEGL-2		0.13	480	AEGL	
AEGL-3		5.5	10	AEGL	
AEGL-3		3.8	30	AEGL	
AEGL-3		3.0	60	AEGL	
AEGL-3		0.75	240	AEGL	
AEGL-3		0.38	480	AEGL	
Danishevskii 1948, 1951; Feldman 1967	Human	0.58	1	1	Mild irritation of the conjunctiva and mucosa of nose and throat

(Continued)

TABLE C-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Katz 1987	Rat	250	60	1	No mortality, lacrimation
Katz 1987	Rat	500	60	SL	30% mortality
Katz 1987	Rat	750	60	SL	70% mortality
Wooster et al. 1947	Mouse	194	10	0	No mortality
Wooster et al. 1947	Mouse	580	10	0	No mortality
Wooster et al. 1947	Mouse	870	10	SL	1/20 died
Wooster et al. 1947	Guinea pig	194	10	3	3/3 died

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethality.

APPENDIX D

BENCHMARK CONCENTRATION CALCULATION

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\DIKETENE.(d)
Gnuplot Plotting File: C:\BMDS\DATA\DIKETENE.plt
Mon Apr 09 09:49:14 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 = -13.4507
slope = 2.10082

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

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-16.3675	5.52762	-27.2014	-5.53353
Slope	2.55065	0.87102	0.843482	4.25782

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)	# Parameters	Deviance	Test d.f.	P-value
Full model	-12.2173	4			
Fitted model	-12.5124	2	0.590315	2	0.7444
Reduced model	-22.4934	1	20.5522	3	0.0001304

AIC: 29.0249

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0.000
271.0000	0.0188	0.188	0	10	-0.438
466.0000	0.2433	2.433	3	10	0.418
778.0000	0.7296	7.296	7	10	-0.211

Chi-square = 0.41 d.f. = 2 P-value = 0.8142

Benchmark Dose Computation
Specified effect = 0.05
Risk type = Extra risk
Confidence level = 0.95

BMD = 321.212
BMDL = 180.893

3

Methacrylaldehyde[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 Tom Marshall (Oak Ridge National Laboratory), Lisa Ingerman (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).

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

Methacrylaldehyde is a colorless liquid at ambient temperature and pressure. It is an intermediate in the production of methacrylonitrile and methacrylic acid, and has been found in the emissions from automobile exhaust, liquid floor wax, steel-protective paints, and trees. Production of methacrylaldehyde in the United States (other than as a chemical intermediate) was discontinued in the late 1970s because better catalysts in propylene oxidation became available for the production of copolymers and resins. Methacrylaldehyde is highly irritating to mucous membranes, especially the upper respiratory tract and eyes (HSDB 2002). Data on the acute lethality of methacrylaldehyde in animals are sparse. Inhalation studies indicate that it is an irritant and that the upper respiratory tract is the target for toxicity in laboratory animals. Irritant effects were evident in studies of durations ranging from a single 6-h exposure to repeated exposures for 2-13 weeks.

The AEGL-1 values for methacrylaldehyde are based on ocular irritation in healthy human subjects (Nojgaard et al. 2005). The nondominant eyes of 10 men were exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm in eight sessions. Blinking frequency was recorded as a measure of irritation and the subjects described the intensity of any ocular discomfort or irritation during the exposures. The number of complaints about irritation and its intensity were not different at any concentration relative to that described by the control group. The relative change in blinking frequency was statistically higher (18%; $p = 0.001$) during exposure at 0.286 ppm. The no-

observed-adverse-effect level (NOAEL) for blinking frequency was 0.189 ppm, which served as the point-of-departure for all of the AEGL-1 values for methacrylaldehyde. No uncertainty factors were applied because the blinking frequency is not a perceived effect but an objective measurement that precedes perceived irritation. The same AEGL-1 value was used for all durations because mild irritation is not expected to vary over time.

The AEGL-2 values are based on sensory irritation observed in a study by Coombs et al. (1994), in which Sprague-Dawley rats were exposed to methacrylaldehyde at 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. Animals exposed at the two highest concentrations were observed keeping their eyes half-closed or closed during exposure and animals exposed at 15.3 ppm occasionally exhibited salivation. No signs of ocular irritation were observed at 1 ppm. Lesions of the upper airways were evidence that the upper respiratory tract is also a target for toxicity. No relevant single exposure or short-term exposure studies were available. Because half-closed or closed eyes may be impairments for escape, 1 ppm was used as the point-of-departure. Typically, two uncertainty factors of 3 would be used for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, the concentration which did not result in perceived irritation or change in blinking frequency in the Nojgaard et al. (2005) study used as the basis of the AEGL-1 values. Thus, a total uncertainty factor of 3 was used. Time scaling was not performed because half-closed or closed eyes are signs of contact irritation.

The AEGL-3 values are based on a study of a single 6-h exposure to methacrylaldehyde at 77 ppm, which resulted in 90% mortality in rats (Coombs et al. 1992). No deaths were observed in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks (Coombs et al. 1992) or in rats exposed at 15.3 ppm for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1994). The concentration of 19 ppm was selected as the point-of-departure for AEGL-3 values. Selecting a no-effect level as the basis of the AEGL-3 values is supported by the steep concentration-response relationship; a 4-fold increase in concentration resulted in a 90% increase in mortality. AEGL-3 values were time-scaled using the equation $C^n \times t = k$ (ten Berge et al. 1986). Default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used. The 30-min AEGL-3 value was adopted as the 10-min value because extrapolation from a 6-h point-of-departure to a 10-min guideline is not recommended (NRC 2001). A total uncertainty factor of 10 was applied; a factor of 3 was used to account for interspecies differences and a factor of 3 was used to account for intraspecies variability. Factors of 10 were considered unnecessary because the toxic effects of methacrylaldehyde appear to be related to contact irritation, so effects are not expected to differ substantially between species or among individuals.

The AEGL values for methacrylaldehyde are presented in Table 3-1.

1. INTRODUCTION

Methacrylaldehyde is a colorless liquid at ambient temperature and pressure. It is highly irritating to mucous membranes, especially the upper respiratory tract and eyes (HSDB 2002). Production of methacrylaldehyde in the United States other than as a chemical intermediate was discontinued in the late 1970s because better catalysts in propylene oxidation became available in the production of copolymers and resins. It is an intermediate in the production of methacrylonitrile and methacrylic acid. It has been found in the emissions from automobile exhaust, liquid floor wax, steel protective paints, and trees. The chemical and physical properties of methacrylaldehyde are presented in Table 3-2.

TABLE 3-1 AEGL Values for Methacrylaldehyde

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	Eye blinking frequency in human subjects (Nojgaard et al. 2005)
AEGL-2 (disabling)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	No-effect level for ocular irritation in rats (Coombs et al. 1994)
AEGL-3 (lethal)	4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)	No deaths in rats (Coombs et al. 1992)

TABLE 3-2 Chemical and Physical Properties of Methacrylaldehyde

Parameter	Value	References
Synonyms	Methacrolein; 2-methylpropenal; methacraldehyde; 2-methyl-2-propenal; 2-methylacrolein; isobutenal; methacrolein	Borchers 2012
CAS registry no.	78-85-3	Borchers 2012
Chemical formula	C_4H_6O	HSDB 2002
Molecular weight	70.09	Borchers 2012
Physical state	Colorless liquid	HSDB 2002
Melting point	-81°C	HSDB 2002
Boiling point	68.4°C	HSDB 2002
Density/specific gravity (water = 1)	0.849 at 25°C	HSDB 2002
Vapor density (air = 1)	2.4	HSDB 2002
Solubility in water	5.9% (59,000 mg/L) at 20°C; miscible with water, ethanol, and ether	HSDB 2002
Vapor pressure	155 mm Hg at 25 °C	HSDB 2002
Lower explosive limit (volume % in air)	2.6	IPCS 1995
Conversion factors	1 ppm = 2.9 mg/m^3 1 mg/m^3 = 0.35 ppm	HSDB 2002

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No studies of the acute lethality of methacrylaldehyde in humans were found.

2.2. Nonlethal Toxicity

2.2.1. Clinical Studies

The nondominant eye of 10 healthy men was exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm (Nojgaard et al. 2005). Methacrylaldehyde vapors were mixed with clean air that was adjusted to a flow rate that generated the desired concentration. Exposures were conducted using a clear plastic eyepiece though which the vapors passed after mixing with clean air at 20% relative humidity. Concentrations delivered to the eyepiece were measured at a point in the delivery system before reaching the eyepiece. Blinking frequency was recorded as a measure of irritation and the subjects reported the perceived intensity of any eye discomfort or irritation during the exposure sessions. The subjects were recorded by a digital video camera and the same researcher viewed all of the videos and counted the number of blinks per session. The subjects were asked to rate perceived irritation of the eye, eyelid, or skin as none, weak, moderate, or strong. A baseline for blinking frequency was established by having four successive stages in each exposure session: an acclimatization stage, which included 3 min of clean air; an initial baseline recording with 8 min of clean air; a 20 min stage of chemical or clean air; and a final 8 min of clean air. The latter stage was divided into 4 min of recovery and 4 min of a final baseline recording. The number of complaints about irritation and its perceived intensity were not different at any concentration relative to the control exposure (see Table 3-3). The relative change in blinking frequency was statistically higher (18%; $p = 0.001$) during exposure at the highest concentration of 0.286 ppm. The NOAELs were 0.286 ppm for perceived irritation and 0.189 ppm for blinking frequency. A mixture of limolene oxidation products and ozone was tested separately in this study. The results showed that those materials increased blinking frequency by as much as 34%, and also showed that lower relative humidity (20% vs. 50%) exacerbated the response.

2.3. Neurotoxicity

No studies of the neurotoxicity of methacrylaldehyde in humans were found.

TABLE 3-3 Results of Blinking Frequency Tests in Humans Exposed to Methacrylaldehyde

Test Parameter	Control	0.089 ppm	0.189 ppm	0.286 ppm
Subjects perceiving irritation	3/10	4/10	5/10	4/10
Perceived intensity	<weak	<weak, weak	<weak, weak	<weak, weak
Relative change in blinking frequency (%)[a]	-9	10	8	18[b]
95% Confidence interval (%)	-19 to 3	-2 to 23	-2 to 20	7 to 30
p-value[c]	0.14	0.09	0.13	0.001

[a]Change relative to baseline of each subject calculated using log-transformed data.
[b]p = 0.001.
[c]Calculated by repeated-analysis using ANOVA software program.
Source: Adapted from Nojgaard et al. 2005.

2.4. Developmental and Reproductive Toxicity

No studies of the developmental or reproductive toxicity of methacrylaldehyde in humans were found.

2.5. Genotoxicity

No studies of the genotoxicity of methacrylaldehyde in humans were found.

2.6. Carcinogenicity

No studies of the carcinogenicity of methacrylaldehyde in humans were found.

2.7. Summary

The single human study on methacrylaldehyde indicates that it is a direct-acting irritant, confirming that effects in people are similar to those observed in animal studies.

3. ANIMAL TOXICITY DATA

The results of toxicity studies of laboratory animals exposed to methacrylaldehyde by inhalation are summarized in Table 3-4.

TABLE 3-4 Result of Toxicity Studies of Methacrylaldehyde

Species	Exposure Duration	Concentration (ppm)	End Point	Reference
Mouse	30 min	2.0	NOAEL (10% decrease in respiratory rate)	Larsen and Nielsen 2000
		4.4	LOAEL (30% decrease in respiratory rate)	
		6.6	40% decrease in respiratory rate	
		10.2	50% decrease in respiratory rate	
		13.1	55% decrease in respiratory rate	
		26.3	70% decrease in respiratory rate	
		1.3 (95% CI: 0.8-2.1)	RD_0	
Rat	4 h	125	Lethal to 2/6, 3/6, or 4/6 rats	Carpenter et al. 1949
Rat	4 h	195	LC_{50}; severe irritation of respiratory tract	BG Chemie 1995
Rat	6 h	77	Lethal to 9/10 in 48 h; acute irritation, pulmonary lesions	Coombs et al. 1992
		5	NOAEL; eyes half-closed during exposure	
	6 h/d, 5 d/wk for 2 wk	19	LOAEL; multiple clinical signs related to respiratory irritation, respiratory tract lesions	
Rat	6 h/d, 5 d/wk for 13 wk	1.0	NOEL	Coombs et al. 1994
		4.9	NOAEL; eyes half-closed during exposure	
		15.3	LOAEL; multiple clinical signs related to respiratory irritation, respiratory tract lesions, evidence of reversal 4 wk after exposure	
Rat	Unknown	10	Maternal toxicity	BG Chemie 1995
		20	Maternal and fetal toxicity (reduced birth weight)	

Abbreviations: CI, confidence interval; LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; RD_0, extrapolated threshold concentration for reduction in respiratory rate.

3.1. Acute Lethality

3.1.1. Rats

Carpenter et al. (1949) exposed six Sherman rats (sex not specified) to methacrylaldehyde at a nominal concentration of 125 ppm for 4 h in a glass inhalation chamber, and observed the survivors for 14 days. The report indicates that two, three, or four of the rats died. No other information was provided. The concentration of 125 ppm is assumed to be an approximate LC_{50} in Sherman rats.

An unconfirmed 4-h LC_{50} of 195 ppm is reported in a secondary source (BG Chemie 1995). BG Chemie is the German Employment Accident Insurance Fund of the Chemical Industry. The organization, which includes a scientific advisory committee, assesses the hazard of chemicals in the workplace, plans toxicity studies, and contracts the conduct of those studies to laboratories.

3.2. Nonlethal Toxicity

3.2.1. Rats

In a 2-week inhalation exposure study in Sprague-Dawley rats, a single 6-h exposure to methacrylaldehyde at 77 ppm, the highest concentration tested, resulted in death or a moribund condition in nine of 10 rats (five male, four female) within 2 days of exposure (Coombs et al. 1992). The cause of death was lesions in the respiratory tract, which were comprised of necrosis of the olfactory and respiratory epithelium in the nasal turbinates, extensive epithelial ulceration of the larynx and trachea, and necrosis of the bronchiolar epithelium of the lungs. The other two concentrations tested were 5 and 19 ppm, and groups of five male and five female rats were exposed at those concentrations for 6 h/day, 5 days/week for the full 2 weeks. Closed eyes or half-closed eyes were noted in the rats during each exposure period; rats in the 19-ppm group also adopted a hunched position during the exposure. Minimal hyperplasia of the respiratory epithelium of the nasal turbinates and laryngeal epithelia were observed at 19 ppm; no respiratory lesions were observed at 5 ppm.

Coombs et al. (1994) exposed groups of 10 male and 10 female Sprague-Dawley rats by inhalation to methacrylaldehyde at 0, 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. Additional groups of control rats and rats exposed at 15.3 ppm were maintained and observed for 4 weeks after exposure ended. Animals exposed at 4.9 or 15.3 ppm were observed keeping their eyes half-closed during exposure days 1-6 or for most of the study, respectively; salivation was observed occasionally in the 15.3-ppm group. Weight gain and food consumption were decreased in both males and females at the highest concentration. Lesions in the respiratory tract comprised of inflammation of the olfactory epithelium and metaplastic changes in the dorsal meatus and dorsal central nasal septum were observed in male and female rats exposed at 15.3 ppm. Similar changes were found in the larynx of some animals at that concentration. Clear

signs of repair and recovery from the lesions were found during the 4-week observation period. The NOAEL was 4.9 ppm and the LOAEL was 15.3 ppm for olfactory lesions. For ocular irritation, the NOAEL was 1 ppm.

3.2.2. Mice

Larsen and Nielsen (2000) studied the effects of inhaled methacrylaldehyde on the respiratory tract of male mice (strain not specified; four per group) exposed at 0, 2.0, 4.4, 6.6, 10.2, 13.1, or 26.3 ppm for 30 min. Sensory irritation as indicated by a decreased respiratory rate, airflow limitation as indicated by the expiration flow rate at half of the tidal volume, and pulmonary irritation as indicated by the time-of-pause between the end of expiration and the beginning of inspiration were evaluated. Methacrylaldehyde caused a concentration-dependent decrease in respiratory rate of about 30, 40, 50, 55, and 70% at 4.4, 6.6, 10.2, 13.1, and 26.3 ppm, respectively. An RD_{50} (concentration that reduces the respiratory rate by 50%) of 10.4 ppm and an RD_0 (extrapolated threshold concentration for reduction in respiratory rate) of 1.3 ppm were calculated for that indicator of sensory irritation. No response was seen in the indicators for pulmonary irritation. The investigators concluded that methacrylaldehyde is a potent sensory irritant and that desensitization does not occur in mice because the level of sensory irritation was constant during exposure.

3.3. Developmental and Reproductive Toxicity

No studies of the developmental or reproductive toxicity of methacrylaldehyde were found.

3.4. Genotoxicity

Only in vitro mutagenicity data are available on methacrylaldehyde and the results are equivocal. Methacylaldehyde produced positive results in *Salmonella typhimurium* strains TA100 (Eder et al. 1990, 1993, 1994) and TA104 (Mersch-Sunderman et al. 1992) without S-9 activation, but had negative results in strain TA 98 (Kato et al. 1989). Neudecker et al. (1991) showed that the addition of S-9 activation reduced methacrylaldehyde mutagenicity even when the liver preparation was boiled or when epoxide hydrolase was inhibited. That indicates that the positive results seen in this bacterial assay are of a direct-acting nature. Methacrylaldehyde was weakly positive in an *Escherichia coli* WP2 *uvr*A assay without activation (Kato et al. 1989). Several studies have shown methacrylaldehyde to be inactive in the SOS chromotest (Benamira and Marnett 1992; Mersch-Sunderman 1992; Eder et al. 1990, 1993, 1994). Weak activity for DNA damage was indicated in the comet assay using rat hepatocytes (Kuchenmeister et al. 1998), and a marginally positive result was obtained in studies of DNA adduct formation (Eder et al. 1993).

3.5. Chronic Toxicity and Carcinogenicity

No studies of the chronic toxicity or carcinogenicity of methacrylaldehyde were found.

3.6. Summary

Acute lethality data from animal studies are sparse. Nonlethal inhalation studies indicate that methacrylaldehyde is an irritant and that the upper respiratory tract is the target for toxicity. Signs of respiratory irritation in rats were gasping and closed or half-closed eyes during inhalation exposure. At higher concentrations, lesions of the upper airways were evident. Data in mice show that methacrylaldehyde suppresses respiration in a manner that indicates significant irritation. Genotoxicity data are equivocal. No data on the reproductive toxicity, developmental toxicity, or carcinogenicity of methacrylaldehyde were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No studies on the metabolism and disposition of methacrylaldehyde were available. According to HSDB (2002), the fate of methacrylaldehyde is probably similar to other short chain aldehydes that are readily oxidized by aldehyde dehydrogenase to organic acids, which can then serve as substrates for fatty oxidation and the Krebs cycle. A second pathway is for aldehydes to be inactivated by reaction with sulfhydryl groups, particularly glutathione.

4.2. Mechanism of Toxicity

The short chain alkenes related to acrolein are known to react with sulfhydryl groups (Beauchamp et al. 1985). Acrolein is the most toxic of the 2-alkenals (including methacrylaldehyde, crotonaldehyde, pentenal, and hexenal) and is also the most reactive toward sulfhydryl groups. The respiratory irritancy of acrolein and related aldehydes may be due to reactivity toward sulfhydryl groups in receptor proteins in the nasal mucosa.

4.3. Structure-Activity Relationships

Neudecker et al. (1991) showed that relative to acrolein the size of the alkylating substituent influences the direct mutagenicity of the aldehyde, with activity decreasing in the order of 2-methylacrolein, 2-ethylacolein, and 2-propylacrolein.

4.4. Other Relevant Information

4.4.1. Species Variability

Studies in rats and mice (Table 3-4) do not indicate much variability in the toxic effects of methacrylaldehyde. That is likely due to the direct irritating effect of methacrylaldehyde on the airways.

4.4.2. Concentration-Exposure Duration Relationship

The 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). To obtain health-protective AEGL values in the absence of an empirically derived scaling exponent, temporal scaling may be performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The only human toxicity study of methacrylaldehyde shows that the chemical has the potential for ocular irritation (Nojgaard et al. 2005). The nondominant eyes of 10 men were exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm in eight sessions. Blinking frequency was recorded as a measure of irritation and the subjects described the intensity of any ocular discomfort or irritation during the exposures. The number of complaints about irritation and its intensity were not different at any concentration relative to that described by the control group. The relative change in blinking frequency was statistically higher (18%; p = 0.001) during exposure at 0.286 ppm. The NOAEL for blinking frequency was 0.189 ppm.

5.2. Animal Data Relevant to AEGL-1

Data in rats show that inhaled methacrylaldehyde is a contact irritant. For a 2-week exposure, the NOAEL was 4.9 ppm and the LOAEL was 19 ppm for respiratory-tract lesions (Coombs et al. 1992). A 13-week study in rats demonstrated a NOAEL of 5 ppm and a LOAEL of 15.3 ppm for olfactory lesions and a NOAEL of 1 ppm for ocular irritation (Coombs et al. 1994).

5.3. Derivation of AEGL-1 Values

The point-of-departure for the AEGL-1 values for methacrylaldehyde is the NOAEL of 0.189 ppm for blinking frequency in human subjects (Nojgaard et al. 2005). No uncertainty factors were applied because blinking frequency is not a perceived effect, but is rather an objective measurement that precedes perceived irritation. The same concentration was used for all durations because mild irritation is not expected to vary over time. The AEGL-1 values for methacrylaldehyde are presented in Table 3-5.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to deriving AEGL-2 values for methacrylaldehyde were found.

6.2. Animal Data Relevant to AEGL-2

Data in rats show that inhaled methacrylaldehyde is a contact irritant. For a 2-week exposure to methacrylaldehyde, the NOAEL and LOAEL for respiratory-tract lesions in rats was 5 and 19 ppm, respectively (Coombs et al. 1992). In another study, Sprague-Dawley rats were exposed to methacrylaldehyde at 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. At the two highest concentrations, the animals kept their eyes half-closed or closed during exposure. Salivation (indicative of substantial sensory irritation) was observed occasionally in animals exposed at 15.3 ppm. No signs of ocular irritation were observed at 1 ppm. The upper respiratory tract is also a target of toxicity for methacrylaldehyde, as evidenced by olfactory lesions found in rats exposed at 15.3 ppm. Data in mice show that methacrylaldehyde suppresses respiration in a manner that indicates significant irritation (Larsen and Nielsen 2000).

6.3. Derivation of AEGL-2 Values

The AEGL-2 values for methacrylaldehyde are based on a NOAEL of 1 ppm for ocular irritation in rats (Coombs et al. 1994). Typically, two uncertainty factors of 3 would be applied to determine AEGL values for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, which is a NOAEL for ocular irritation in humans (Nojgaard et al. 2005) and the basis of the AEGL-1 values for methacrylaldehyde. Thus, a total uncertainty factor of 3 was applied instead. Time scaling was not performed because mild ocular irritation is not expected to vary over time. The AEGL-2 values for methacrylaldehyde are presented in Table 3-6, and the calculations are presented in Appendix A.

TABLE 3-6 AEGL-2 Values for Methacrylaldehyde

10 min	30 min	1 h	4 h	8 h
0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to deriving AEGL-3 values for methacrylaldehyde were found.

7.2. Animal Data Relevant to AEGL-3 Values

Data in rats show that inhaled methacrylaldehyde is a sufficiently severe contact irritant that it causes serious effects, including lethality (Table 3-4). A single exposure of rats to methacrylaldehyde at 77 ppm for 6 h resulted in 90% mortality (Coombs et al. 1992). No deaths were observed in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks or in rats exposed at 15.3 ppm 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1994). Other supporting studies include an assumed 4-h LC_{50} in Sherman rats of about 125 ppm (nominal) reported by Carpenter et al. (1949), and an unconfirmed 4-h LC_{50} of 195 ppm reported in a secondary source (BG Chemie 1995).

7.3. Derivation of AEGL-3 Values

On the basis of the study by Coombs et al. (1992), the 2-week NOAEL for lethality of 19 ppm was selected as the point-of-departure for AEGL-3 values for methacrylaldehyde. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on methacrylaldehyde were inadequate for deriving an empirical value for the exponent n, so default values of n = 3 to extrapolate to shorter durations and n = 1 to extrapolate to longer durations were used. A total uncertainty factor of 10 was applied; a factor of 3 to account for interspecies differences and a factor of 3 to account for intraspecies variability. Factors of 10 were considered unnecessary because the toxic effects of methacrylaldehyde appear to be related to contact irritation, so effects are not expected to differ substantially between species or among individuals. Furthermore, use of a factor of 10 for either the interspecies or intraspecies uncertainty factor would result in AEGL-3 values that are less consistent with the available data. (A total uncertainty factor of 30 yields AEGL-3 values of 1.4 ppm for the 10- and 30-min durations, 1.1 ppm for the 1-h duration, 0.7 ppm for the 4-h duration, and 0.47 ppm for the 8-h duration. No effects were observed in rats exposed at 1.0 ppm for 6 h/day, 5 days/week for 13 weeks, and half-closed eyes and respiratory irritation were observed in rats similarly exposed at 4.9 ppm).

The AEGL-3 values for methacrylaldehyde are presented in Table 3-7, and the calculations are provided in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for methacrylaldehyde are presented in Table 3-8. The AEGL-1 values are based on a study of ocular irritation in healthy human subjects, which identified a NOAEL and a LOAEL for blinking frequency (Nojgaard et al. 2005). The AEGL-2 values are based on a study by Coombs et al. (1994), in which Sprague-Dawley rats exposed to methacrylaldehyde had clinical signs of ocular irritation. The AEGL-3 values are based on a concentration of methacrylaldehyde not resulting in deaths in rats exposed for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1992).

8.2. Other Standards and Guidelines

No other standards or guidelines for methacrylaldehyde were found.

8.3. Data Adequacy and Research

Human data appropriate for derivation of AEGL-1 values for methacrylaldehyde were available from a well-conducted study. However, no information was available concerning effects in young, elderly, or asthmatic individuals. Minimal animal data were available for derivation of AEGL-2 or AEGL-3 values.

TABLE 3-7 AEGL-3 Values for Methacrylaldehyde

10 min	30 min	1 h	4 h	8 h
4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

TABLE 3-8 AEGL Values for Methacrylaldehyde

Classification	10 min	30min	1h	4h	8 h
AEGL-1 (nondisabling)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.5860 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)
AEGL-2 (disabling)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)
AEGL-3 (lethal)	4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHACRYLALDEHYDE

Derivation of AEGL-1 Values

Key study:	Nojgaard, J.K., K.B. Christensen, and P. Wolkoff. 2005. The effect on human blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol Lett. 156(2):241-251.
Toxicity end point:	Blinking frequency, NOAEL = 0.189 ppm
Time scaling:	None
Uncertainty factors:	None
Modifying factor:	None
Calculations:	
10-min AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
30-min AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
1-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
4-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
8-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)

Derivation of AEGL-2 Values

Key study:	Coombs, D.W., T.J. Kenny, D. Crook, and W.A. Gibson. 1994. Methacrolein (BG No. 108) 13-week Inhalation Toxicity Study in Rats. BGH 50/932334. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.
Toxicity end point:	No signs of ocular irritation in rats at 1 ppm
Time scaling:	None
Uncertainty factors:	3 for interspecies differences and intraspecies variability

Modifying factor:	None
10-min AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
30-min AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
1-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
4-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
8-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm

Derivation of AEGL-3 Values

Key study:	Coombs, D.W., T.J. Kenny, and C.J. Hardy. 1992. Methacrolein (BG No. 108) 2-week Repeat Dose Preliminary Inhalation Toxicity Study in Rats. BGH 50/932334. BGH 40/920648. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.
Toxicity end point:	No deaths in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks
Time scaling:	$C^n \times t = k$ (ten Berge et al.1986); default values of n = 3 for extrapolation to shorter durations and n = 1 for longer durations. The 30-min value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value (NRC 2001). $(19 \text{ ppm})^3 \times 6 \text{ h} = 41{,}154 \text{ ppm-h}$ $(19 \text{ ppm})^1 \times 6 \text{ h} = 114 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Modifying factor:	None
10-min AEGL-3:	4.3 ppm (same as the 30-min AEGL-3 value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 41{,}154 \text{ ppm-h}$ $C^3 = 82{,}308 \text{ ppm}$ $C = 43.5 \text{ ppm}$ $43.5 \text{ ppm} \div 10 = 4.3 \text{ ppm}$

1-h AEGL-3:	$C^3 \times 1$ h = 41,154 ppm-h C^3 = 41,154 ppm C = 34.5 ppm 34.5 ppm ÷ 10 = 3.5 ppm
4-h AEGL-3:	$C^3 \times 4$ h = 41.154 ppm-h C^3 = 10,288 ppm C = 21.7 ppm 21.7 ppm ÷ 10 = 2.2 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 114 ppm-h C = 14.25 ppm 14.25 ppm ÷ 10 = 1.4 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHACRYLALDEHYDE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)

Key reference: Nojgaard, J.K., K.B. Christensen, and P. Wolkoff. 2005. The effect on human blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol Lett. 156(2):241-251.

Test species/Strain/Number: 10 healthy men

Exposure route/Concentration/Duration: Ocular exposure via eyepiece; 0, 0.089, 0.189, and 0.286 ppm for 20 min.

Effects:
0.089 ppm = NOAEL
0.189 ppm = NOAEL for increased blinking frequency
0.286 ppm = LOAEL for increased blinking frequency
0.286 ppm = NOAEL for perceived ocular irritation

End point/Concentration/Rationale: Blinking frequency as a measure of ocular irritation; NOAEL = 0.189 ppm

Uncertainty factors/Rationale: No uncertainty factors were necessary because blinking frequency is not a perceived effect, but an objective measurement that precedes perceived irritation.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: None; the same value was applied to all durations because mild irritation is not expected to vary over time.

Data adequacy: Well-conducted human study.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.33 ppm (0.96 mg/m^3)	0.33 ppm 0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)

Key reference: Coombs, D.W., T.J. Kenny, D. Crook, and W.A. Gibson. 1994. Methacrolein (BG No. 108) 13-week Inhalation Toxicity Study in Rats. BGH 50/932334. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

Test species/Strain/Number: Rat; Sprague-Dawley; 10 males and 10 females/group

(Continued)

AEGL-2 VALUES Continued

Exposure route/Concentrations/Durations: Inhalation; 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks

Effects: Half-closed or closed eyes were observed during exposure days 1-6 in rats exposed at 4.9 ppm and for most of the study in rats exposed at 15.3 ppm. Histopathologic evidence of respiratory-tract irritation was found at the end of the 13-week exposure period in rats exposed at 15.3 ppm.

End point/Concentration/Rationale: NOAEL for ocular irritation of 1 ppm, because ocular irritation could impair ability to escape.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Studies of human volunteers and rodents indicate that methacrylaldehyde is a direct-acting irritant. Repeated exposure studies in rats show that the eyes and upper respiratory tract are targets for acute and subchronic toxicity. Data in mice show that methacrylaldehyde suppresses respiration in a manner consistent with significant irritation. Typically, two factors of 3 would be used for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, the NOAEL for ocular irritation in humans (Nojgaard et al. 2005) and the basis for the AEGL-1 values for methacrylaldehyde.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: Not performed because mild ocular irritation is unlikely to vary with exposure duration.

Data adequacy: Well-conducted subchronic study. No single or short-term exposure studies were available.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

Key reference: Coombs, D.W., T.J. Kenny, and C.J. Hardy. 1992. Methacrolein (BG. No. 108) 2-week repeat dose preliminary inhalation toxicity study in rats BGH 50/932334. BGH 40/920648. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

Test species/Strain/Number: Rat; Sprague-Dawley; 5 males and 5 females/group

Exposure route/Concentrations/Durations: Inhalation; 5, 19, and 77 ppm for 6 h/day, 5 days/week for 2 weeks.

Effects: No deaths observed at 19 ppm. After a single exposure to methacrylaldehyde at 77 ppm for 6 h, nine of 10 rats died or were moribund within 48 h.

End point/Concentration/Rationale: No deaths at 19 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10

(Continued)

AEGL-3 VALUES Continued

Interspecies: 3, because methacrylaldehyde is a direct-acting irritant and its effects are unlikely to differ substantial between species.
Intraspecies: 3, because methacrylaldehyde is a direct-acting irritant and its effects are unlikely to differ among individuals.
Studies of human volunteers and rodents indicate that methacrylaldehyde is a direct-acting irritant. Repeated exposure studies in rats show that the eyes and upper respiratory tract are targets for acute and subchronic toxicity. Data in mice show that methacrylaldehyde suppresses respiration in a manner consistent with significant irritation. Furthermore, use of a default value of 10 for either the interspecies or intraspecies uncertainty factor would result in AEGL-3 values that are less consistent with the available data. (Use of a total uncertainty factor of 30 would yield AEGL-3 values of 1.4 ppm for the 10- and 30-min durations, 1.1 ppm for the 1-h duration, 0.7 ppm for the 4-h duration, and 0.47 ppm for the 8-h duration. No effects were found in rats exposed at 1.0 ppm for 6 h/day, 5 days/week for 13 weeks. Half-closed eyes were observed during exposure and reversible respiratory lesions were found in rats similarly exposed at 4.9 ppm).

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$ (ten Berge et al.1986); data on methacrylaldehyde were in adequate to derive an empirical value for the exponent n, so default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations were used (NRC 2001). The 30-min value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value (NRC 2001).

Data adequacy: The inhalation study that demonstrated lethality after a single 6-h exposure to methacrylaldehyde was well conducted. The cause of death was lesions in the respiratory tract, comprised of necrosis of the olfactory and respiratory epithelium in the nasal turbinates, extensive epithelial ulceration of the larynx and trachea, and necrosis of the bronchiolar epithelium in the lung. No deaths were observed at the other two concentrations tested (5 and 19 ppm for 6 h/day, 5 days/week) for the full 2 weeks.

APPENDIX C

CATEGORY PLOT FOR METHACRYLALDEHYDE

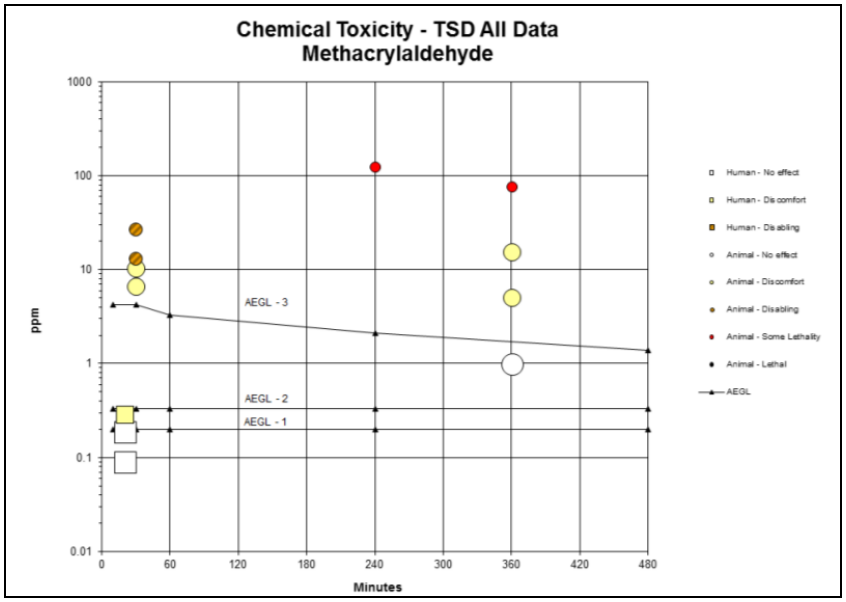

FIGURE C-1 Category plot of toxicity data and AEGL values for methacrylaldehyde.

TABLE C-1 Date Used in Category Plot for Methacrylaldehyde

Source	Species	ppm	Minutes	Category	Comments
AEGL-1		0.2	10	AEGL	
AEGL-1		0.2	30	AEGL	
AEGL-1		0.2	60	AEGL	
AEGL-1		0.2	240	AEGL	
AEGL-1		0.2	480	AEGL	
AEGL-2		0.33	10	AEGL	
AEGL-2		0.33	30	AEGL	
AEGL-2		0.33	60	AEGL	
AEGL-2		0.33	240	AEGL	
AEGL-2		0.33	480	AEGL	
AEGL-3		4.2	10	AEGL	
AEGL-3		4.2	30	AEGL	
AEGL-3		3.5	60	AEGL	

(Continued)

TABLE C-1 Continued

AEGL-3		2.2	240	AEGL	
AEGL-3		1.4	480	AEGL	
Nojgaard et al. 2005	Human	0.089	20	0	
Nojgaard et al. 2005	Human	0.189	20	0	
Nojgaard et al. 2005	Human	0.286	20	1	Increased blinking frequency
Coombs et al. 1992	Rat	1.0	360	0	
Coombs et al. 1992, 1994	Rat	5	360	1	Half-closed or closed eyes
Coombs et al. 1992	Rat	15.3	360	1	Ocular and respiratory irritation
Coombs et al. 1994	Rat	19	360	1	Ocular and respiratory irritation
Coombs et al. 1992	Rat	77	360	SL	90% lethality
Carpenter et al. 1949	Rat	125	240	SL	2/6, 3/6, or 4/6 deaths
Larsen and Nielsen 2000	Mouse	2.0	30	0	
Larsen and Nielsen 2000	Mouse	4.4	30	1	30% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	6.6	30	1	40% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	10.2	30	1	50% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	13.1	30	2	55% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	26.3	30	2	70% decrease in respiratory rate

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethality.

4

Pentaborane[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 Milanez (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Lisa Ingerman (SRC, Inc.), 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).

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

Pentaborane is a very flammable, colorless liquid that is insoluble in water, but hydrolyzes over several hours to form boric acid, hydrogen, and heat. It is a strong reducer and reacts with ammonia, organic amines, and unsaturated hydrocarbons. Human and animal studies have shown that pentaborane primarily causes central nervous system (CNS) toxicity. Symptoms in humans include dizziness, drowsiness, headache, hiccups, impaired judgment, incoordination, muscle spasms, and convulsions. Animals experience tremors, salivation, miosis (constriction of pupils), lethargy, aggressiveness, and convulsions.

AEGL-1 values were not developed for pentaborane because no relevant human or animal studies were available. Human studies found either no effects or CNS toxicity that was more severe than those defined by AEGL-1.

The AEGL-2 values are based on a no-effect level for CNS toxicity in dogs. The end point was selected to avoid even minor effects on CNS function, which could impair judgment and result in accidents and injury (Mindrum 1964). Dogs were exposed to pentaborane for 60 min for 5 days, and neurotoxicity was assessed through their performance in a conditioned avoidance response (CAR) test and through behavioral observations (Weir et al. 1964). A single exposure to pentaborane at 1.4 ppm caused no neurologic signs or delays in the CAR test, and was used as the point-of-departure. Dogs exposed at 1.4 ppm a second time (the following day), however, began to exhibit CNS effects, including decreased activity, miosis, and CAR delays, and additional exposures caused irritability and aggres-

siveness. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used because pentaborane causes similar effects (CNS toxicity) in humans and four species of laboratory animals, and acute lethality values varied less than 3-fold among the species. An intraspecies uncertainty factor of 3 was applied because the homogeneous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans. Concentrations were scaled across time using the equation $C^n \times t = k$ (ten Berge et al. 1986). An empirical value for n of 1.3 was determined by linear-regression analysis of acute lethality data from studies of rats (Weir et al. 1961, 1964). The AEGL-2 values are supported by studies in monkeys exposed for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. These studies were not used because the exposure durations were too short, and the monkeys were not subjected to the CAR test.

The AEGL-3 values are based on an acute lethality study in which mice were exposed to pentaborane at 6.9-11.6 ppm for 60 min (Weir et al. 1961, 1964). Mice had tremors, ataxia, convulsions, and red exudate around the mouth and nose, and death occurred within 24 h. Benchmark dose software (EPA Version 2.4.0) was used to calculate LC_{50} (lethal concentration, 50% lethality), $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response), and BMC_{01} (benchmark concentration with 1% response) values of 7.75, 5.08, and 6.04 ppm, respectively. The AEGL-3 point-of-departure was the $BMCL_{05}$ of 5.08 ppm, which was considered an estimate of the threshold for lethality in mice. A total uncertainty factor of 10 was applied and concentrations were scaled across time for the same reasons as described for the AEGL-2 values. The AEGL-3 values are supported by the lethality data from mice exposed for 4 h (Feinsilver et al. 1960), rats exposed for 5-60 min (Weir et al. 1961, 1964), monkeys exposed for 2 min (Weeks et al. 1964), and dogs exposed for 2-15 min (Weeks et al. 1964), which would have yielded similar AEGL-3 values.

The AEGL values for pentaborane are presented in Table 4-1.

TABLE 4-1 AEGL Values for Pentaborane

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)	0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)	No-effect level for CNS toxicity in dogs (Weir et al. 1964)
AEGL-3 (lethal)	2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)	Lethality threshold ($BMCL_{05}$) for mice (Weir et al. 1961, 1964)

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

1. INTRODUCTION

Pentaborane is a very flammable liquid and has a pungent odor (HSDB 2006). It is used in catalysts, corrosion inhibitors, and fluxing agents, and as an experimental jet and rocket fuel in air-breathing engines and (HSDB 2006; Lewis 2007). Pentaborane is manufactured by the hydrogenation of diborane. Two US manufacturers of pentaborane are listed in the Hazardous Substances Data Bank (HSDB 2006), but no production volumes are specified. A different source indicates that pentaborane is not commercially available in significant quantities (Schubert 2000).

Pentaborane is not soluble in water, but hydrolyzes over a period of several hours to form boric acid, hydrogen, and heat. It is a member of a class of chemicals known as the boron hydrides or boranes, which are strong reducers and react with ammonia, organic amines, and unsaturated hydrocarbons.

Selected chemical and physical properties of pentaborane are presented in Table 4-2.

TABLE 4-2 Chemical and Physical Properties of Pentaborane

Parameter	Value	References
Synonyms	Pentaboron nonahydride; pentaborane 9; dihydropentaborane	HSDB 2006
CAS registry no.	19624-22-7	HSDB 2006
Chemical formula	B_5H_9	HSDB 2006
Molecular weight	63.17	HSDB 2006
Physical state	Colorless liquid	HSDB 2006
Melting point	-46.6°C	HSDB 2006
Boiling point	60°C; 58°C	HSDB 2006; Lewis 2007
Density/specific gravity	0.61 at 0-4°C	HSDB 2006
Vapor density (air = 1)	2.2	HSDB 2006
Solubility in water	Decomposes at 150°C; hydrolyzes slowly in water	HSDB 2006
Vapor pressure	171 mmHg at 20°C; 66 mmHg at 0°C	HSDB 2006
Flammability limits	Lower limit = 0.42%; upper limit = 98%; flash point = 30°C (closed cup); autoignition at 35°C	HSDB 2006
Conversion factors	1 ppm = 2.58 mg/m^3 1 mg/m^3 = 0.388 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

During the process of detoxifying old canisters filled with pentaborane gas at an industrial site in Virginia, two workers were seriously injured and one died (Yarbrough et al. 1984). The air concentrations of pentaborane were unknown. The most acutely exposed worker began having convulsions 4 min after dermal contact, and 4 min later had an opisthotonic spasm and went limp. He had erythema and marked congestion of the conjunctiva and oral mucous membranes. An electroencephalogram (EEG) conducted 6 h after the exposure revealed no electrical activity, and the worker died 8 days later. Autopsy revealed severe necrotizing pneumonia, fatty changes with centrilobular degeneration in the liver, brain degeneration, and lack of mature spermatozoa in the testicles. The second worker had similar effects but survived. He was in a coma for 4 months, after which he had muscle weakness, incoordination, limited vision, and severe cortical atrophy and ventricular dilation (detected by a computed tomography [CT] scan). The third worker suffered numerous myoclonic jerks, several grand mal seizures, disorientation, agitation, and hallucinations, and had an abnormal EEG. He was discharged after 11 days with no obvious symptoms. Less serious effects occurred in the emergency medical responders and a bystander to this incident (Hart et al. 1984; Silverman et al. 1985, 1989; see Section 2.2.2.).

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Odor Awareness

Using 17 subjects and 40 measurements, Comstock and Oberst (1953) determined that the median detectable odor concentration of pentaborane was 2.5 mg/m^3 (1.0 ppm). The tested concentrations and the corresponding ability to detect the odor were 0.2 ppm (5%), 0.3 ppm (12.5%), 0.6 ppm (32.5%), 1.0 ppm (57.5%), and 2.0 ppm (100%). The subjects described the odor as garlic-like, acetylene-like, and pungent. Pentaborane's odor also has been characterized as unpleasant, sweetish, and like sour milk or sweet penetrating burning rubber (Mindrum 1964; HSDB 2006). Olfactory fatigue was associated with pentaborane exposure (Mindrum 1964).

Several secondary sources cite odor detection thresholds of 1.0 or 0.97 ppm for pentaborane, but provide no experimental data (Krackow 1953; Amoore and Hautala 1983; Ruth 1986). These sources were probably citing the values determined by Comstock and Oberst (1953). Insufficient data were available to calculate a level of distinct odor awareness for pentaborane.

2.2.2. Case Reports

Four cases of unintentional exposure to pentaborane at a US research laboratory were documented by Rozendaal (1951). The subjects were men, ages 23-31. The concentrations to which they were exposed were unknown. In the two milder cases, the men experienced nervousness, exhaustion, dizziness, and drowsiness typically after exposure ceased, and recovered sufficiently to return to work 3-4 days later. In the two more serious cases, the men were hospitalized and developed intermittent spasms of all voluntary muscles and opisthotonos. They were also confused and disoriented, had impaired recent memory, and EEG tracings showed irritation of the cerebral cortex. Their symptoms improved and they returned to work 7-10 days after the incident.

Lowe and Freeman (1957) described in detail several cases of occupational exposure to unknown concentrations of pentaborane vapor over a 3-year period at a chemical plant. The most common symptoms were drowsiness (78%), dizziness (71%), headache (28%), and cough (15%). In the most severe case, a 28-year old man exposed for about an hour became rigid and unconscious, had involuntary muscular contractions of the extremities, and became comatose with brief periods of restlessness and disorientation. He improved overnight, had light-headedness and headache, and developed periodic persistent hiccups for 6 days. Blood and urine tests revealed abnormalities in hepatic and renal function that in some cases (hepatic function) persisted until his discharge 40 days after exposure. Several exposures at lower concentrations of pentaborane were also described. The men experienced light-headedness, hiccups, flushing, drowsiness, nausea, muscle tremors, profuse perspiration, photophobia, and disorientation for a few hours to a few days. In one case, the worker experienced no symptoms until the day after exposure.

The effects of accidental human exposures to unknown concentrations of pentaborane were characterized in 14 workers by Sim (1958). Common symptoms soon after exposure were dizziness, vertigo, drowsiness, nervousness, restlessness, and hiccups. A number of delayed neurologic findings occurred about 40 h after exposure, including headache, visual disturbance, inability to concentrate, memory loss, incoordination, muscle pain, cramps, tremors, and convulsions. Blood chemistry evaluations suggested hepatic toxicity (positive cephalin-flocculation and thymol-turbidity tests and elevated serum albumin, globulin, and nonprotein nitrogen) in some individuals. Analyses of urinary and hematologic parameters were generally normal. Boron was detected in the urine in cases of severe (undefined) exposure, and persisted for more than a week.

Serial EEG tracings were used to evaluate CNS effects in 15 male workers exposed to pentaborane at two US aircraft facilities (North American Aviation, Inc. and Edwards Air Force Base) (Schoettlin et al. 1961). The exposure concentrations of pentaborane were unknown, but in some cases the men reported that they could briefly smell the gas. All 15 men (ages 23-43) had abnormalities in their EEG tracings (generalized slow response on the resting period and theta- or delta-activity in response to hyperventilation), even though six of them did not

experience any symptoms from exposure. In many cases, the EEGs returned to normal after 5-18 months without exposure. Reported symptoms included mental confusion, lack of coordination, and sleepiness.

Cordasco et al. (1962) studied the pulmonary effects of exposure to several boranes, including pentaborane, in workers exposed occupationally from 1956-1960. Of 166 exposed workers, only three had bronchopulmonary effects. However, all subjects had neurologic symptoms, including clonic movement of the extremities and neck, muscle spasms, diffuse fasiculations, opisthotonos, and catatonic state.

CNS toxicity occurred at a pentaborane-production facility where area air concentrations were measured using an MSA portable boranes detector (Roush et al. 1962). The detector could not measure concentrations greater than 1.0 ppm, which occurred infrequently (≤0.3 h/day). In "contaminated" areas, pentaborane concentrations were approximately 0.3-1.0 ppm (detection limit of 0.01 ppm). Exposure durations were estimated to be 0.1-1.6 h/day on the basis of job descriptions and locations; the C × t range was 0.02-0.64 ppm-h. No correlations were made, however, between exposure concentration, duration, and resulting symptoms. Potentially exposed workers wore protective gear, including full face masks with canister or air line, but could still occasionally smell pentaborane. Over a 12-month period there were 13 cases of intoxication. The most common toxic effects were dizziness, drowsiness and lethargy, headache, stiff neck, poor coordination, nervousness, apprehension, and muscle spasms. Workers recovered within a few hours or days.

Mindrum (1964) characterized the effects of pentaborane exposures at a company where air concentrations of pentaborane were monitored with a detector that registered "positive" upon reaching 1 ppm. The men wore a gas mask (self-contained or air line) or air pack when anticipating exposure, or after smelling pentaborane. In many cases of intoxication, there was no positive detector reading for pentaborane but its odor was detected. In some cases, symptoms occurred when the workers were unaware that they were exposed; the investigators speculated that this could have been due to other masking odors or olfactory fatigue. Signs of toxicity occurred up to 24 h after exposure. Mild symptoms, such as lethargy, confusion, fatigue, inability to concentrate especially when doing ordinary tasks (e.g., driving), chest constriction, headache, lightheadedness, lack of coordination, and inappropriate behavior (e.g., laughing uproariously during cranial nerve examination, driving through five stop signs on the way home from work) resolved after a few days. Moderate exposures caused slurred speech, sleepy appearance, difficulty focusing the eyes, sleeping for long periods, anorexia, and conjunctivitis; the effects resolved in about one week. Severe exposures caused incoordination, muscle spasms and tremors, areas of numbness, drooling, nausea, vomiting, convulsions (30-120 seconds), opisthotonus, increased blood pressure, tachycardia, fever, and profuse perspiration. The neurologic symptoms resolved within 3 weeks of exposure. The men

had abnormal EEGs; the severity of the abnormality increased with exposure severity and returned to normal within 5 weeks. No notable effects on pulmonary, cardiac, or hepatic function were found.

The effects of exposure to unknown concentrations of pentaborane on 13 emergency responders and a bystander during and after an industrial accident in 1982 were described by Hart et al. (1984) and Silverman et al. (1985, 1989). Persons examined within an hour of exposure had conjunctivitis and skin reddening, and those admitted to the hospital the next day reported dizziness, blurred vision, fatigue, myoclonic jerks, hallucinations, and memory loss, and had abnormal EEGs. All but one of the subjects had normal EEGs 4-12 weeks after exposure, although approximately half of the subjects had CT-scan abnormalities and mild brain dysfunction, as measured by deficits in functional tests (sustained attention, memory and learning, and constructional skills). The subjects had higher concentrations of neurotransmitters (as measured by homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenolglycol) in their plasma or cerebrospinal fluid than reference values. Many subjects reported psychologic symptoms indicative of posttraumatic stress disorder and depression, which were not correlated with CT-scan abnormalities. A follow-up 18 months later showed that neuropsychologic functioning improved and that CT scans and the ventricular-brain ratio remained relatively unchanged, but that psychologic symptoms generally persisted or became worse.

2.3. Neurotoxicity

Pentaborane was shown to be a potent neurotoxin in all reports of accidental human exposure to the chemical (Rozendaal 1951; Lowe and Freeman 1957; Sim 1958; Schoettlin et al. 1961; Cordasco et al. 1962; Roush et al. 1962; Mindrum 1964; Hart et al. 1984; Yarbrough et al. 1984; Silverman et al. 1985, 1989). The exposure concentrations of pentaborane were not known with certainty in any of the cases, but neurotoxic effects occurred below the odor threshold of 1 ppm. The ability to detect the smell of pentaborane is subject to olfactory fatigue (Mindrum 1964). Common symptoms were dizziness, drowsiness, headache, nervousness, restlessness, exhaustion, hiccups, flushing, nausea, cough, profuse perspiration, photophobia, visual disturbance, and inability to concentrate. EEG tracings revealed abnormalities, even in cases when the individuals had no symptoms. More serious symptoms included memory loss, disorientation, incoordination, muscle pain, muscle spasms, and convulsions. In a number of cases, the neurologic symptoms occurred 1-2 days after exposure. In the most severe case documented, a worker had convulsions and spasms within 10 min of exposure and no electrical brain activity (measured by EEG) 6 h later (Yarbrough et al. 1984). He died 8 days after exposure, and autopsy revealed brain degeneration and pulmonary, hepatic, and testicular lesions.

Hart et al. (1984) and Silverman et al. (1985, 1989) found that in addition to the physiologic effects associated with pentaborane, exposed persons developed psychologic and emotional changes consistent with posttraumatic stress disorder, which in some cases persisted for 18 months after exposure.

2.4. Developmental and Reproductive Toxicity

No human developmental or reproductive toxicity studies of pentaborane were found. One case report of a 38-year old worker who died after acute exposure (inhalation and dermal) to pentaborane found a lack of mature spermatozoa in his testicles (Yarbrough et al. 1984).

2.5. Genotoxicity

No human studies of the genotoxic potential of pentaborane were found.

2.6. Carcinogenicity

No human studies of the carcinogenic potential of pentaborane were found.

2.7. Summary

Pentaborane has a pungent odor that has been characterized as unpleasant, sweetish, or smelling like sour milk, with a detection threshold of 0.97 ppm. A number of accidental occupational exposures to pentaborane have been documented, with unknown or uncertain exposure concentrations. These studies consistently show that neurotoxicity is the primary and most sensitive effect of exposure, and occurs below the odor threshold for pentaborane. Symptoms included dizziness, drowsiness, headache, nervousness, restlessness, exhaustion, hiccups, cough, nausea, flushing, profuse perspiration, visual disturbances, inability to concentrate, memory loss, incoordination, muscle spasms, and convulsions. EEG tracings revealed abnormalities, even in cases when the individuals had no symptoms. In some cases neurologic symptoms were delayed for one or two days after exposure. In the most severe cases, convulsions and spasms occurred within minutes, and there was evidence of brain, hepatic, pulmonary, and renal lesions. Some individuals exposed to pentaborane developed symptoms of posttraumatic stress disorder that persisted for at least 18 months after exposure.

No human studies were found that evaluated pentaborane genotoxicity, carcinogenicity, or developmental or reproductive toxicity, except that a 38-year old worker who died 8 days after acute exposure to pentaborane lacked mature spermatozoa.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Non-human Primates

Sooty mangabey monkeys of unspecified sex and age were exposed to pentaborane for 2 min in both an acute study (five unspecified concentrations; three animals per group) and a nonlethal toxicity study (described in Section 3.2.1) (Weeks et al. 1964). The test vapor was generated by passing nitrogen gas through chilled (-18 to -20°C) liquid pentaborane, followed by dilution with air. The concentration of pentaborane in the 0.4-m^3 dynamic exposure chamber was determined by a carmine method using air collected in Edgewood collection bubblers. Animals were placed into and removed from the chamber using a sliding carriage, which was not further described. The animals were observed for 7 days. Observations included tremors, ataxia, and convulsions, which ended with death within 24 h after exposure (data for individual test concentrations were not provided). The 2-min LC_{50} was 248 ppm, as determined by the method of Finney (1952).

3.1.2. Dogs

Weir et al. (1964) conducted a series of single- and repeat-exposure studies in which beagles (two to six per group) were exposed to pentaborane at 1.4-55 ppm for 5-60 min. These studies were not designed to be acute lethality studies, although death occurred in several cases. These studies are described in Section 3.2.2.

Weeks et al. (1964) determined LC_{50} values and characterized nonlethal toxicity in mongrel dogs (age and sex not specified) exposed to pentaborane for 2, 5, or 15 min, using methods very similar to that of Weir et al. (1964). The nonlethal toxicity study is described in Section 3.2.2. In the acute lethality study, groups of four dogs were exposed to five unspecified concentrations of pentaborane using a sliding carriage assembly. Animals were observed for toxicity and weight changes for 7 days after exposure. Toxic signs began with tremors and proceeded to ataxia, convulsions, and death within 24 h (data for individual test concentrations were not provided). LC_{50} values calculated by the method of Finney (1952) were 284, 126, and 36 ppm for the 2-, 5-, and 15-min exposures, respectively.

3.1.3. Rats

Rats of unspecified sex and strain had a 2-h LC_{50} of 17 ppm for a 2-h post-exposure observation period (Krackow 1953). Signs of CNS toxicity included weakness, incoordination, tremors, convulsions, coma, and ultimately death.

There was no evidence of pulmonary damage. No other experimental details were provided.

Svirbely (1954a) exposed male Carworth Farms Wistar (CFW) rats to pentaborane at 4.6-285 ppm for 15-240 min in a preliminary experiment, and at 10.0-20.2 ppm for 120 min in a second trial designed to determine the LC_{50}. The animals were exposed in an 18.5-L glass dynamic exposure chamber, and were observed for 2 weeks after exposure. Pentaborane vapor was generated by passing nitrogen gas through chilled (-40°C) liquid pentaborane, followed by dilution with air, and its chamber concentrations were calculated. The following observations occurred "to a greater or less degree depending on concentration and duration of exposure": tremors, jitteriness, convulsions, spasms, corneal opacity, decreased breathing, bulging eyes, abdominal distension, cyanosis, seminal ejaculate, running-like movements of the upper body, and "normal state." The tremors and jitteriness persisted for a "considerable" time after cessation of exposure. All deaths occurred within 24 h. The individual exposure concentrations and mortality rates are presented in Table 4-3. It is unclear why the investigators presented some mortality incidences as two data points instead of one (e.g., mortality of 4/5 at 20.2 ppm reported twice for male rats, instead of 8/10 once); the only difference between the two groups appeared to be mean body weight. The investigators calculated a 2-h LC_{50} of 19.5 ppm using Thompson's (1947) method of moving averages; only the deaths that occurred during the first 2 h of exposure were used in the calculation. Using benchmark dose software (EPA Version 1.3.2) to model the mortality that occurred over the 2-week observation period in the second experiment, an LC_{50} of 16.6 ppm ($BMCL_{05}$ = 13.1 ppm, BMC_{01} = 14.6 ppm) was calculated. When the data from both experiments were combined, the 2-h LC_{50} was 15.7 ppm ($BMCL_{05}$ = 8.3 ppm, BMC_{01} = 10.2 ppm).

In a separate experiment, Svirbely (1954b) examined the effect of repeated exposures on 15 adult male CFW rats. Animals were exposed to pentaborane vapor at 3.3 ppm (calculated concentration) for 5 h/day for up to 5 days, using exposure conditions as described for Svirbely (1954a). The first rat died 4.5 h after the beginning of exposure, and had mild convulsions and delayed, gasping breathing. The survivors appeared dazed and did not move. Neurotoxic effects increased with additional exposures. During the second exposure, some rats displayed a "belligerent" attitude and had mild tremors and convulsions, and nine more died. During the third exposure, the belligerent behavior was more pronounced and animals became very aggressive ("rage" behavior, biting others), and the rats had tremors, gasping, salivation, convulsions, and hyperexcitability. Four more rats died during or after the third exposure, and the remaining rat died after the fourth exposure. There was a dose-related decrease in weight of the treated rats (20-48 g), whereas a control group of three rats gained weight (3 g) over the same time period. Gross pathologic findings included dark-colored adrenal glands and congested liver and spleen after one exposure, congested lungs after two or more exposures, and corneal opacity and seminal ejaculate after four exposures.

TABLE 4-3 Mortality in Rats Exposed to Pentaborane

Experiment	Concentration (ppm)	Duration (min)	Mortality	2-h LC_{50}
First (preliminary)	235-285, 56.0, 24.0, 20.2, 20.2, 16.0, 16. 0, 13.2 (12-15), 13.2 (12-15), 4.3, 4.3, 4.6	15, 18, 85, 80, 80, 81, 81, 120, 120, 120, 120, 240	3/3, 2/3, 3/3, 4/5, 4/5, 2/5, 2/5, 2/6, 3/4, 0/7, 0/3, 0/10	15.7 ppm for all 120-min data, 2-wk observation period
Second (LC_{50})	10.0, 10.0, 12.6, 12.6, 16.0, 16.0, 20.2, 20.2	120	0/5, 1/5, 0/5, 0/5, 0/5, 3/5, 5/5, 5/5	

Source: Adapted from Svirbely 1954a.

Long et al. (1957) determined a mean survival time of 62-67 min for three male CFW rats exposed to pentaborane at 13.6 ppm. Pentaborane vapor was generated as described above for Svirbely et al. (1954a,b), and the concentrations were calculated. Other study details were not provided.

Groups of 8-10 week old male white rats (10/group) were exposed to pentaborane at 3.2-7.5 ppm for 4 h in a 400-L dynamic gassing chamber (Feinsilver et al. 1960). Additional groups of animals (number not specified) were "similarly" exposed and periodically killed and examined for pathologic changes in the lungs, trachea, liver, kidneys, spleen, and testes and compared with untreated controls. Pentaborane concentration was determined by hydrolysis of pentaborane collected with absorption bubblers containing cellosolve, and titration of the resulting boric acid with NaOH. The test concentrations (and resulting mortalities) for the 7-day observation period were 3.2 ppm (0/10), 3.8 ppm (0/10), 4.5 ppm (0/10), 4.8 ppm (1/10), 5.4 ppm (4/10), 5.9 ppm (4/10), 6.2 ppm (6/10), 7.1 ppm (9/10), and 7.5 ppm (10/10). The investigators determined a 4-h LC_{50} of 5.8 ppm using the Bliss-Finney method (Finney 1952); benchmark dose analyses (EPA Version 1.3.2) estimated LC_{50}, $BMCL_{05}$, and BMC_{01} values of 5.8, 4.2, and 4.3 ppm, respectively. Animals were irritable and aggressive and had respiratory distress, depression, ataxia, prostration, protruding eyeballs, diarrhea, tremors, clonic convulsions, and corneal opacity after death. Rats that died during or within a few hours after exposure to pentaborane at concentrations of 7.0 ppm or greater had alveolar edema and hemorrhage. Rats that survived 6-10 days had no pathologic changes.

Male Sprague-Dawley rats (350-450 g) were exposed to pentaborane vapor at approximately 0.25-0.6 mg/kg (approximately 6.5-15 ppm; see below) for 40 min in an 8-L static exposure chamber (Dost et al. 1963). The post-exposure observation period was not specified. The dose was determined by measuring the amount of pentaborane present in the chamber before and after the exposure, and assuming that the difference between the two values was due to absorption by the animals. Negligible amounts of pentaborane were adsorbed to the chamber walls and animal hair (data not provided). The LD_{50} was determined to be 0.42 mg/kg (0.38-0.46 mg/kg) by "probit analysis of percentage of test subjects responding below each dose level." (The chamber concentration of pentaborane was back-calculated to have been 11 ppm, assuming 100% absorption, an inha-

lation rate of 0.22 m^3/day, a body weight of 0.4 kg, and a 40-min exposure; the investigators refer to the air concentration as 10-20 ppm.)

Groups of 10 young male white rats (100-120 g; strain not specified) were exposed to pentaborane for 5 min (62.2-84.7 ppm), 15 min (29.0-34.3 ppm), 30 min (13.0-19.3 ppm), or 60 min (7.5-15.1 ppm) (Weir et al. 1961, 1964). Animals were placed into and removed from the 0.4-m^3 dynamic exposure chamber using a sliding carriage assembly, which was not further described. Animals were observed for 7 days after exposure. The test vapor was generated by passing nitrogen gas through chilled (2.0°C) liquid pentaborane, followed by dilution with air, and the concentration of pentaborane was determined by a carmine method using air collected in Edgewood collection bubblers. Toxic signs began with tremors, ataxia, convulsions, and red exudate around the mouth and nose. All deaths occurred within 24 h after exposure. The exposure concentrations and respective mortalities and LC_{50} values calculated by the method of Bliss (1952) are shown in Table 4-4. Identical LC_{50} values were obtained using benchmark dose software (EPA Version 1.3.2). The $BMCL_{05}$ values for the 5-, 15-, 30-, and 60-min exposures were 56.7, 24.5, 8.1, and 7.0 ppm, respectively, and the respective BMC_{01} values were 58.6, 26.4, 9.8, and 7.5 ppm.

3.1.4. Mice

All mice (10/10; unspecified sex and strain) exposed to pentaborane at 5 ppm for 4 h died within 24 h, the majority dying within 4 h (Krackow 1953). Mice exposed for 2 h had an LC_{50} of 11 ppm for a 2-h post-exposure observation period. Animals had signs of CNS toxicity (weakness, incoordination, tremors, convulsions, and coma) but no evidence of pulmonary damage. No other experimental details were provided.

Male CFW mice were exposed to pentaborane at 4.6-285 ppm for 15-240 min in a preliminary experiment, and at 10.0-20.2 ppm for 120 min in a second trial designed to determine the LC_{50} (Svirbely 1954a). The animals were exposed in an 18.5-L glass dynamic exposure chamber, and were observed for 2 weeks after exposure. Pentaborane vapor was generated by passing nitrogen gas through chilled liquid pentaborane, followed by dilution with air, and its chamber concentrations were calculated. Effects included tremors, jitteriness, convulsions, spasms, corneal opacity, running-like movements of legs, bulging eyes, abdominal distension, seminal ejaculate, cyanosis, and huddling. The tremors and

TABLE 4-4 Mortality in Rats Exposed to Pentaborane

Time (min)	Concentration (ppm)	Mortality	LC_{50} (ppm)
5	62.2, 66.5, 65.3, 70.2, 84.7	0/10, 4/10, 6/10, 8/10, 10/10	66.6
15	29.0, 32.5, 32.8, 34.3, 31.4	0/10, 7/10, 7/10, 8/10, 9/10	31.2
30	13.0, 14.7, 15.5, 17.1, 19.3	2/10, 4/10, 6/10, 7/10, 9/10	15.2
60	7.5, 9.8, 10.7, 12.9, 15.1	0/10, 3/10, 7/10, 9/10, 10/10	10.4

Source: Adapted from Weir et al. 1961.

jitteriness persisted for a "considerable" time after cessation of exposure. Effects were not reported in relation to exposure concentrations other than a general statement that severity depended on concentration and duration of exposure. All deaths occurred within 24 h. The individual exposure concentrations and mortality rates are shown in Table 4-5. The investigators calculated a 2-h LC_{50} of 14.1 ppm using Thompson's (1947) method of moving averages; only the deaths that occurred during exposure were included in the calculation. Using benchmark dose software (EPA Version 1.3.2) to model data combined from both experiments on mortality that occurred during the 2-week observation period, an LC_{50} of 12.4 ppm ($BMCL_{05}$ = 7.9 ppm, BMC_{01} = 8.6 ppm) was calculated.

Long et al. (1957) determined a mean survival time of 145-147 min for three male CFW mice exposed to pentaborane at 13.6 ppm. Pentaborane vapor was generated as by Svirbely et al. (1954a,b), and concentrations were calculated. No further study details were provided.

Mice of unspecified strain and sex were exposed to pentaborane for various durations in a dynamic exposure chamber by Weatherby (1958). The pentaborane concentration was measured analytically by collecting the air in cellosolve, water, and chromotropic acid, and measuring the formation of the resulting boric acid-chromotropate complex by spectrophotometry. All mice (six per group) exposed to pentaborane at 40, 20, and 10 ppm died after 29, 50, and 90 min of exposure, respectively; the first deaths occurred after 16, 26, and 72 min, respectively. Of 12 mice exposed to pentaborane for 60 min and observed for 5 days, 10 died (not specified when) and two survived and appeared normal. Two mice exposed to pentaborane at 5 ppm for 177 min had convulsions, but neither died and both appeared to recover after 24 h. No further experimental details were provided.

Groups of 10 female white mice (8-10 weeks old) were exposed to pentaborane at 3.0-5.6 ppm for 4 h, and additional groups of animals were similarly exposed and killed periodically to evaluate pathologic organ changes (Feinsilver et al. 1960), as described for male rats in Section 3.1.3. The exposure concentrations (and resulting mortalities) for the 7-day observation period were 3.0 ppm (2/10), 3.2 ppm (2/10), 3.3 ppm (5/10), 3.7 ppm (7/10), 5.6 ppm (10/10). The investigators determined a 4-h LC_{50} of 3.4 ppm using the Bliss-Finney method (Finney 1952). Benchmark dose analysis (EPA Version 1.3.2) of the data resulted in LC_{50}, $BMCL_{05}$, and BMC_{01} values of 3.5, 2.2, and 2.6 ppm, respectively. The animals were irritable and had respiratory distress, ataxia, depression, pros-

TABLE 4-5 Mortality in Mice Exposed to Pentaborane

Experiment	Concentration (ppm)	Duration (min)	Mortality	2-h LC_{50}
First (preliminary)	235-285, 56.0, 24.0, 20.2, 16.0, 13.2 (12-15), 4.3, 4.6	15, 18, 85, 80, 81, 120, 120, 240	5/5, 5/5, 5/5,10/10, 10/10, 10/10, 0/10, 10/10	12.4 ppm for all 120-min data, 2-wk observations period.
Second (LC_{50})	10.0, 12.6, 16.0, 20.2	120	2/10, 0/10, 10/10, 10/10	

Source: Adapted from Svirbely 1954a.

tration, protruding eyeballs, diarrhea, tremors, clonic convulsions, corneal opacity, and abdominal distension after death. Animals had "occasional" alveolar edema or hemorrhage at unspecified concentrations "soon" after exposure, but pathologic changes were absent in animals examined after 6-10 days.

Groups of 10 young female mice (20-24 g; strain not specified) were exposed to unspecified concentrations of pentaborane for 5, 15, 30, or 60 min in a 0.4 m^3-dynamic exposure chamber and observed for 7 days (Weir et al. 1961, 1964). Animals were placed into and removed from the chamber using a sliding carriage assembly, which was not further described. The pentaborane vapor was generated from liquid pentaborane and its concentration was determined by a carmine method in air collected in Edgewood collection bubblers. Toxic signs began with tremors, ataxia, convulsions, red exudate around the mouth and nose, and then death within 24 h after exposure. The exposure concentrations, mortalities, and LC_{50} values calculated by the method of Bliss (1952) are shown in Table 4-6. LC_{50} values obtained using benchmark dose software (EPA Version 2.4.0) for the 5-, 15-, and 60-min durations were similar (40.8, 18.7, and 7.8 ppm) to those calculated using the Bliss method. The respective $BMCL_{05}$ values were 27.3, 13.7, and 5.1 ppm, and BMC_{01} values were 28.7, 13.8, and 6.0 ppm. The 30-min data did not provide an adequate fit to the probit model.

Weir et al. (1964) exposed groups of 20 mice to pentaborane at 3.7 ppm for 60 min, 10.2 ppm for 15 min, or 19.8 ppm for 5 min for 4 days. The animals had convulsions after each exposure, but the incidence in each group was not specified. No mice died the first day. Mortality was high in the groups exposed for 15 or 60 min (15/20 and 16/20, respectively), and occurred by the end of the fourth exposure day. In the group exposed for 5 min, 2/20 animals died 5 days after exposure ended.

LC_{50} values were determined for young adult female mice (strain not specified; 10/group) exposed for 0.5, 2, 5, or 15 min in another study at the same institution (Weeks et al. 1964). Five unspecified exposure concentrations were tested using a protocol similar to that described by Weir et al. (1964). Animals were observed for 7 days and weighed daily, as well as before exposure. Toxic signs began with tremors and proceeded to ataxia, convulsions, and death within 24 h (data for individual test concentrations not provided). LC_{50} values calculated by the method of Finney (1952) were 401, 133, 53, and 19 ppm for the 0.5-, 2-, 5-, and 15-min durations, respectively.

The acute lethality studies of pentaborane are summarized in Table 4-7.

TABLE 4-6 Mortality in Mice Exposed to Pentaborane

Time (min)	Concentration (ppm)	Mortality	LC_{50} (ppm)
5	28.7, 33.5, 36.4, 36.4, 38.8, 37.5, 43.5	0/10, 1/10, 1/10, 2/10, 2/10, 5/10, 7/10	40.5
15	15.4, 18.4, 18.8, 20.4, 18.9, 21.9	1/10, 2/10, 5/10, 7/10, 8/10, 10/10	18.6
30	10.5, 13.0, 13.2, 9.6, 12.7, 15.8	2/10, 5/10, 6/10, 7/10, 8/10, 10/10	10.6
60	6.9, 7.3, 6.9, 7.4, 7.5, 11.6	0/10, 1/10, 3/10, 3/10, 5/10, 10/10	7.8

Source: Adapted from Weir et al. 1961.

TABLE 4-7 Summary of Acute Lethality Data on Pentaborane from Animal Studies

Species	Concentrations (ppm)	Duration (min)	Mortality	Effect (Reference)
Monkey	Five tested, but unspecified	2.0	LC_{50} = 248 ppm	Tremors, ataxia, and convulsions (Weeks et al. 1964).
Rat (M)	62.2-84.7	5	LC_{50} = 66.6 ppm	Tremors, ataxia, convulsions, and red exudate from mouth and nose; death within 24 h after exposure (Weir et al. 1961, 1964).
	29.0-34.3	15	LC_{50} = 31.2 ppm	
	13.0-19.3	30	LC_{50} = 15.2 ppm	
	7.5-15.1	60	LC_{50} = 10.4 ppm	
Rat	~6.5-15	40	LC_{50} = ~11 ppm	Not specified (Dost et al. 1963).
Rat	16.0-285	15-85	4/10-3/3 each	Tremors, jitteriness, convulsions, corneal opacity, bulging eyes, decreased breathing, and cyanosis (Svirbely 1954a).
	4.3-20.2	120	LC_{50} = 15.7 ppm	
	4.6	240	0/10	
Rat	3.3	300 × 4	1/15, 10/15, 14/15, 15/15 after 1, 2, 3, 4 exposures	Convulsions, gasping, tremors, aggressiveness, salivation, and organ lesions (Svirbely 1954b).
Rat	Unspecified	120	LC_{50} = 17 ppm (2-h observation)	Weakness, incoordination, tremors, convulsions, and coma (Krackow 1953).
Rat	13.6	145-147	3/3	Mean survival time (Long et al. 1957).
Rat	3.2-7.5	240	LC_{50} = 5.8 ppm	Respiratory distress, ataxia, depression, aggressiveness, tremors, convulsions, corneal opacity, and pulmonary lesions (Feinsilver et al. 1960).
Mouse	Five tested, but unspecified	0.5, 2.0, 5.0, 15.0	LC_{50} = 401, 133, 53, 19 ppm	Tremors, ataxia, convulsions, and death within 24 h (Weeks et al. 1964).
Mouse	28.7-43.5	5	LC_{50} = 40.5 ppm	Tremors, ataxia, convulsions, and red mouth and nasal exudate; death within 24 h after exposure (Weir et al. 1961, 1964).
	15.4-21.9	15	LC_{50} = 18.6 ppm	
	9.6-15.8	30	LC_{50} = 10.6 ppm	
	6.9-11.6	60	LC_{50} = 7.8 ppm	

(Continued)

TABLE 4-7 Continued

Species	Concentrations (ppm)	Duration (min)	Mortality	Effect (Reference)
Mouse	16.0-285	11-81	5/5 or 10/10 each	Tremors, jitteriness, running-like movements, convulsions, spasms, corneal opacity, bulging eyes, cyanosis, and huddling (Svirbely 1954a).
	4.3-20.2	120	LC_{50} = 12.4 ppm	
	4.6	240	10/10	
Mouse	19.8	5 × 4	2/20	Convulsions; death after 2 or more exposures (Weir et al. 1964).
	10.2	15 × 4	15/20	
	3.7	60 × 4	16/20	
Mouse	Unspecified	120	LC_{50} =11 ppm (2-h observation)	Weakness, tremors, incoordination, coma, and convulsions (Krackow 1953).
	5	240	10/10	
Mouse	13.6	62-67	3/3	Mean survival time (Long et al. 1957).
Mouse	40, 20, 10	29, 50, 90	LC_{100}	No details provided.
	5	177	None in 24 h.	Convulsions; appeared normal after 24 h (Weatherby 1958).
	10	60	10/12 in 5 d	Survivors appeared normal (Weatherby 1958).
Mouse	3.0-5.6	240	LC_{50} = 3.4 ppm	Respiratory distress, ataxia, depression, irritability, tremors, convulsions, corneal opacity, and pulmonary lesions (Feinsilver et al. 1960).
Dog	Five tested, but unspecified	2	LC_{50} = 284 ppm	Tremors, ataxia, convulsions, and death within 24 h (Weeks et al. 1964).
		5	LC_{50} = 126 ppm	
		15	LC_{50} = 36 ppm	
Dog	5.0, 10.5	60	1/2 at each concentration	Tremors, salivation, and convulsions (Weir et al. 1964)
	3.7 × 3	60	1/3 after third exposure	Miosis, irritability, aggressiveness, ocular lesions, and convulsions (Weir et al. 1964).

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

Sooty mangabey monkeys of unspecified sex and age were exposed to pentaborane for 2 min in both an acute lethality study (described in Section 3.1.1) and a nonlethal toxicity study (Weeks et al. 1964). In the latter study, groups of three monkeys were exposed for 2 min to pentaborane at 37, 60, or 143 ppm, concentrations intended to be approximately one-half, one-fourth, or one-eighth of the LC_{50} of 248 ppm. Animals were placed into and removed from the exposure chamber using a sliding carriage assembly, which was not further described. Hematology parameters (erythrocytes, packed erythrocyte volume, hemoglobin, and leukocyte counts) were examined one day after exposure and weekly for up to 4 weeks. Bromsulfalein retention was also measured at unspecified intervals. Animals were killed 1, 2, and 4 weeks after treatment for gross and microscopic pathologic analyses. Brain sections were also stained with Nissl to examine the neurons. Monkeys exposed to pentaborane at 37 or 60 ppm had no signs of toxicity. Animals exposed at 143 ppm had convulsions and tremors within 1 h of exposure but not the next day. None of the groups had treatment-related gross or microscopic lesions or alterations in hematologic parameters or bromsulfalein retention.

3.2.2. Dogs

Weir et al. (1964) conducted a series of single- and repeat-exposure studies in which beagles (two to six per group) were exposed to pentaborane at 1.4-55 ppm for 5-60 min. Death occurred in several cases. Dogs were exposed either head-only or whole-body in the single-exposure studies and whole-body in the repeat-exposure studies. The test vapor was generated by passing nitrogen gas through chilled (2.0°C) liquid pentaborane, followed by dilution with air. The concentration of pentaborane was determined by a carmine method using air collected in Edgewood collection bubblers. The dogs were exposed in a 0.4-m^3 dynamic chamber with a port through which the head could be placed either inside or outside the chamber. Dogs were suspended in a harness during exposure to restrict movement, and were observed for 7 days. The dogs were examined before exposure to determine their general physical condition and neurologic, behavioral, and ophthalmoscopic status. In some trials, the boron content in serum and urine samples was measured by a curcumin and carmine method, respectively. The urine was collected for a week before and after exposure.

Some dogs were trained to perform a conditioned avoidance response (CAR) by the method of Solomon and Wynne (1953). In the CAR test, the dogs had to jump over a barrier within 5 seconds after a stimulus (light + buzzer) or they would get an electric shock through the floor (during training only). Each test session consisted of 20 jump trials. Dogs were considered trained when they completed five sessions over a 5-day period without error. The test was con-

ducted 1, 2, and 24 h after exposure, and for a few (unspecified) days thereafter. The harmonic mean of response time was calculated for each session of 20 trials, and compared to pre-exposure values.

The head-only and whole-body single exposures produced consistent results. For exposure durations of 5, 15, and 60 min, no toxic signs were seen at concentrations of 28, 12, and 3.2 ppm, respectively. Severe toxicity was evident at higher (unspecified) concentrations, including apprehensiveness, tremors, salivation, and tonic and clonic convulsions, which increased in severity with the exposure concentration. Death resulted from 60-min exposures at 5.0 or 10.5 ppm; one of two dogs died in each case. Survivors had decreased appetite and were lethargic, apprehensive, and irritable for several days after exposure. Serum boron concentrations increased to 0.2 μg/mL during the first hour after exposure to higher (undefined) concentrations, and then subsided to below detectable concentrations (0.05 μg/mL). The 24-h urinary boron concentrations were increased in a concentration-related manner in all groups, generally subsiding to nearly pre-exposure concentrations by 48 h.

In one series of repeat-exposure studies conducted by Weir et al. (1964) (Experiment 1), beagles were exposed two or three times on successive days to pentaborane at 3.7-19.8 ppm for 5-60 min, except that the third 60-min exposure was terminated after 48 min because one animal had convulsions. After the first exposure, only mild to moderate bloodshot eyes were found in eight of 11 dogs, but there was no concentration-response relationship. After the second exposure, more severe ocular lesions occurred (bloodshot eyes, miosis, and hemorrhage of the iris), as well as severe neurotoxicity (manifest as convulsions during and after exposure) and vicious behavior followed by lethargy. One animal exposed for 60 min died after the third exposure. The study did not report the results of the CAR tests, other than to state that the response time in the CAR test increased to the point that the dogs would not participate for 2-6 days after the last exposure. The boron concentration in the serum of the dogs did not increase, but urinary concentrations increased after each exposure, returning to pre-exposure levels 72 h after the last exposure. A similar study (Experiment 2) was conducted at approximately half the exposure concentration (1.4-9.3 ppm for 5-60 min), but animals were exposed for 5 days. No neurologic effects or CAR impairment occurred after the first exposure. Animals in all the groups began to exhibit CNS effects after the second exposure. By the fifth exposure, effects included increased irritability, aggressiveness, decreased activity, and miosis (concentration related). Latency increased in the CAR test with each exposure, and by the fourth or fifth exposure the dogs were indifferent to the stimuli, although the response was re-established 5-6 days after pentaborane exposure ended.

To determine the effect of retreatment interval on toxicity, Weir (1964) exposed groups of three dogs to pentaborane at 2.5 ppm for 60 min. Dogs were exposed two to five times, with rest periods between exposures varying from 24 to 96 h. Miosis was seen after each exposure, reaching a minimum after the third exposure and then remaining constant. Impaired performance on the CAR test was seen after the second exposure in at least one dog of each group. Signs of

toxicity occurred during or after the second exposure, and were the most severe in dogs exposed on successive days (brief convulsions, tremors, and cyanosis). Signs in dogs exposed to pentaborane on non-successive days included tremors of the neck, apprehensiveness, and increased sensitivity to noise and movement. Toxicity decreased in severity as the interval between exposures increased.

The results of the Weir et al. (1964) dog studies are summarized in Table 4-8.

Weeks et al. (1964) characterized the acute lethality (described in Section 3.1.2.) and nonlethal toxicity in mongrel dogs (age and sex not specified) exposed to pentaborane for 2, 5, or 15 min. The exposure method was as described by Weir et al. (1964). The dogs were exposed to approximately one-eighth, one-fourth, and one-half of the LC_{50} for each exposure duration. The concentrations were 33, 73, and 144 ppm for the 2-min exposures; 16, 33, and 58 ppm for the 5-min exposures; and 5.2, 9.1, and 18 ppm for the 15-min exposures. The dogs were trained to perform CAR tests, and their behavior and performance during the CAR tests (consisting of 20 trials) were evaluated 10 min and 1, 2, and 24 h after exposure, and then daily for another few days. The clinical signs and results of the CAR tests are presented in Table 4-9. Dogs exposed to pentaborane at 33 ppm for 5 min lay down after each exposure. No clinical signs were observed at the other concentrations. Exposure at 5.2 ppm for 15 min resulted in a slight decrease in mean latency response time, but the investigators noted that the decrease was not significant and no alterations were observed in dogs exposed to pentaborane at 9.1 ppm for 15 min. More severe effects occurred at the high concentrations for all three exposure durations, consisting of convulsions, tremors, and CAR performance delays; some animals did not even perform the CAR test (2- and 5-min exposures).

Groups of eight male mongrel dogs were exposed to pentaborane at 14.0-28.0 ppm for either 30 or 60 min, although the specific combinations of exposure concentration and duration were not specified (Weir et al. 1965; Weir and Meyers 1966; further described in Section 4.2.). The observation period also was not specified. Dogs exposed at lower (unspecified) concentrations were cooperative and quiet and appeared sedated, whereas those exposed at higher (unspecified) concentrations exhibited nausea, tremors, convulsions, defecation, miosis, and bradycardia.

3.2.3. Rats

In a mechanistic study, male Sprague-Dawley rats were exposed to pentaborane at 7.6 ppm for 30 min and their brain serotonin and norepinephrine concentrations were measured periodically for 7 days (Weir et al. 1965). The rats were killed 3, 6, 12, 24, 48, 72, 96, and 168 h (serotonin only) after exposure. The brains were immediately removed and homogenized, and serotonin

TABLE 4-8 Effects Observed in Dogs Exposed to Pentaborane

Duration	Concentration (ppm)	Effects
Single Exposure		
5 min	Head only: 28.0 (n = 6)	No toxic signs.
	Head only: 38.0 or 55.0 (n = 2/group)	Tremors, salivation, clonic convulsions, and apprehensiveness.
	Whole body: 14.0 or 26.0 (n = 2/group)	No toxic signs.
	Whole body: 46.0 (n = 2)	Tremors and convulsions.
15 min	Head only: 12.0 (n = 4)	No toxic signs
	Head only: 18.0 (n = 4) or 30.0 (n = 2)	Tremors and apprehensiveness.
	Head only: 19.0 (n = 2)	Clonic convulsions.
60 min	Head only: 3.2 (n = 2)	No toxic signs.
	Head only: 5.0, 5.7, 6.9, or 10.5 (n = 2/group)	Tremors, convulsions, and salivation; one death at 5.0 and 10.5 ppm.
	Whole body: 0.3, 0.4, 0.8, 1.5, or 3.0 (n = 3/group)	No toxic signs.
	Whole body: 4.5 (n = 3)	Convulsions.
	Whole body: 7.5 (n = 3)	Convulsions and two deaths.
Multiple Exposure		
5 min	9.3 × 5 (n = 4)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	19.8 × 2 (n = 4)	Slightly bloodshot eyes, miosis, and convulsions after second exposure.
15 min	5.0 × 5 (n = 4)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	10.2 × 2 (n = 4)	Markedly bloodshot eyes, miosis, and convulsions after second exposure.
60 min	1.4 × 5 (n = 3)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	3.7 × 3 (n = 3)	Convulsions, viciousness, lethargy, ocular lesions after second exposure, and one death after third exposure.
60 min	2.5 (n = 3) × 2; 24 h apart	Convulsions, tremors, CAR-d after second exposure, and miosis.
	2.5 (n = 3) × 5; 48 h apart	Neck tremors, apprehensiveness, CAR-d after second exposure, and miosis.
	2.5 (n = 3) × 4; 72 h apart 2.5 (n = 3) × 4; 96 h apart	Neck tremors, lethargy, noise sensitivity, CAR-d after second exposure, and miosis (72 or 96 h apart).

Abbreviations: CAR-d, conditioned-avoidance-response delay. Source: Data from Weir et al. 1964.

TABLE 4-9 Effects Observed in Dogs Exposed to Pentaborane

Concentration (ppm)	Clinical signs	CAR performance
2-min exposure		
33	None	Not affected.
73	None	1/3, some increase in mean latency response time 2 h after exposure.
144	2/3 convulsions	2/3, increase in CAR mean latency response time; 1/3, no jumps 1 and 2 h after exposure.
5-min exposure		
16	None	Not affected.
33	2/3 lay down after each response	2/3, increase in CAR mean latency response time.
58	2/3 convulsions	2/3, no jumps 1 and 2 h after exposure; 3/3, increase in CAR mean latency response time.
15-min exposure		
5.2	None	3/3, slight, but not significant, increase in mean response time.
9.1	None	Not affected.
18	1/3, convulsions; 2/3, tremors	2/3, increase in mean latency response time.

Source: Adapted from Weeks et al. 1964.

(5-hydroxytryptamine) and norepinephrine were extracted and measured fluorometrically. There was a marked depletion in brain serotonin (≤63% decreased from controls) and a modest decrease in norepinephrine (≤29% decreased from controls) that were maximal 3-12 h after exposure. Concentrations of serotonin and norepinephrine returned to normal 7 and 2 days after exposure, respectively. No other results were reported.

3.2.4. Mice

As part of their experiment to determine the toxic mechanism of pentaborane, Weir et al. (1965) measured the pentobarbital sleeping time in mice exposed to pentaborane at 3.5-4.0 ppm or 8.5-9.0 ppm for 30 min. Groups of 10 mice were injected intraperitoneally with sodium pentobarbital (30.0 or 45.0 mg/kg) 1, 8, 18, or 24 h after inhaling pentaborane. The greatest increase in sleeping time occurred 1-8 h after exposure, and was greater at the higher pentaborane concentration. No other effects on the animals were noted.

The nonlethal toxicity studies of pentaborane are summarized in Table 4-10; the table also shows the lethal responses in the dog studies of Weir et al. (1964).

TABLE 4-10 Summary of Nonlethal Toxicity of Pentaborane from Animal Studies

Species	Concentration (ppm)	Duration (min)	Effects	Reference
Monkey	37, 60	2.0	No toxic signs or organ lesions.	Weeks et al. 1964
	143	2.0	Convulsions and tremors first day, no organ lesions.	
Rat	7.6	30	Decreased (≤63%) brain serotonin and norepinephrine (≤29%) within 3 h, reversible after 7 and 2 d, respectively.	Weir et al. 1965
Mouse	3.5-4.0	30	Increased pentobarbital (45 mg/kg) sleeping time.	Weir et al. 1965
	8.5-9.0	30	Increased pentobarbital (30 mg/kg) sleeping time.	
Dog	14-55	5	Tremors, salivation, and convulsions at ≥38 ppm.	Weir et al. 1964
	18, 30	15	Tremors at 18 ppm; convulsions at 30 ppm.	
	0.3-10.5	60	Convulsions and tremors at ≥ 4.5 ppm; 1/2 died at 5.0 and 10.5 ppm.	
Dog	9.3 × 5 19.8 × 2	5	At all concentrations: miosis, irritability, tremors, bloodshot eyes, aggressiveness, and convulsions after second exposure. One of three dogs died after third exposure at 3.7 ppm.	Weir et al. 1964
	5.0 × 5 10.2 × 2	15		
	1.4 × 4 2.5 × 2 3.7 × 3	60		
Dog	33	2.0	No effects.	Weeks et al. 1964
	73	2.0	No toxic signs and CAR-d.	
	144	2.0	Convulsions and CAR-d.	
	16	5.0	No effects.	
	33	5.0	Lethargy and CAR-d.	
	58	5.0	Convulsions and CAR-d.	
	5.2	15.0	No toxic signs and equivocal CAR-d.	
	9.1	15.0	No effects.	
	18	15.0	Convulsions, tremors, and CAR-d.	
Dog	14.0-28.0	30-60	Dogs appeared sedated at "lower" concentrations. Nausea, tremors, convulsions, defecation, miosis, and bradycardia at "higher" concentrations. Observation period not specified.	Weir et al. 1965; Weir and Meyers 1966

Abbreviations: CAR-d, conditioned-avoidance-response delay.

3.3. Neurotoxicity

Animal studies consistently showed that the CNS is the target of pentaborane toxicity. Toxicity increased with exposure duration and concentration, and was cumulative in multiple-exposure studies. Neurotoxic signs included appre-

hensiveness, drooling, nausea, decreased appetite, weight loss, lethargy, irritability, jitteriness, corneal opacity, aggressiveness, defecation, miosis, ataxia, tremors, spasms, and convulsions. Signs resolved within a day after mild exposure but persisted for several days after more severe intoxication.

3.4. Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies of pentaborane were found, although reproductive toxicity was reported in a subchronic animal study. Exposure to pentaborane at 0.6 ppm for up to 6 months resulted in testicular atrophy in two of 17 hamsters and one of 15 rats, and minimal or absent spermatogenesis in three of 17 hamsters and one of 15 rats, whereas none of these effects were found in the controls (Levinskas et al. 1958). Both species also had neurotoxic effects and pathologic organ changes.

Boric acid, a hydrolysis product of pentaborane, has been shown be a developmental and reproductive toxicant after repeated inhalation or oral exposure (HSDB 2012).

3.5. Genotoxicity

No genotoxicity studies of pentaborane were found.

3.6. Subchronic and Chronic Toxicity

Levinskas et al. (1958) conducted a subchronic toxicity study in which male CFW mice, male albino guinea pigs, male New Zealand albino rabbits, and male CFW rats were exposed to pentaborane at 1.0 ppm for 6 h/day, 5 days/week for 4 weeks (20 exposures). The test concentrations were calculated, but a subsequent publication by this laboratory showed that the analytic measurements were 47-130% of the nominal concentration at 3.0-13.8 ppm, but were 10-80% of the nominal concentration at 0.2 ppm (Hill and Merrill 1960). Levinskas et al. (1958) similarly exposed rabbits, rats, monkeys, dogs, and golden hamsters to pentaborane at 0 or 0.2 ppm for 6 h/day, 5 days/week for 6 months. The 6-month survival in treated animals was 0/2 for monkeys, 3/4 for dogs, 8/12 for rabbits, 24/30 for rats, and 17/20 for hamsters; in controls, the survival was 0/1 for monkeys, 2/3 for dogs, 6/6 for rabbits, 11/15 for rats, and 12/15 for hamsters. The monkeys were the first to die (one died after four exposures), and hamsters required the greatest number of exposures before death occurred (75). The results of this study are summarized in Table 4-11; they are considered equivocal because of the unexplained deaths in the control groups and questionable test concentrations.

3.7. Carcinogenicity

No studies of the potential carcinogenicity of pentaborane were found.

TABLE 4-11 Effects Observed in in Laboratory Animals Exposed to Pentaborane

Concentration	Duration	Species (sex)	Effects
0.2 ppm[a]	6 h/d, 5 d/wk for 6 mo	Monkey (M)	2/2 died after 4 and 15 exposures (1/1 control died after 16 exposures); low appetite, apathy, vomiting, muscle tremors, and impaired mobility.
		Rat (M)	6/30 died after ≥49 exposures (4/15 controls died after ≥47 exposures); nasal and/or ocular discharge, lethargy, viciousness, no grooming, and testicular lesions.
		Dog (F)	1/4 died after 52 exposures (1/3 controls died after 16 exposures); low appetite, ocular and nasal discharge, emaciation, muscle tremors, and impaired mobility.
		Hamster (M)	3/20 died after ≥75 exposures (3/25 controls after ≥10 exposures); brief periods of lethargy and testicular lesions.
		Rabbit (M)	4/12 died after ≥ 21 exposures (0/6 controls died); ocular and nasal discharge, decreased appetite, scrawny, unclean, and aggressive when handled.
1.0 ppm[a]	6 h/d, 5 d/wk for 4 wk	Mouse (M)	Weight loss and 9/11 died after ≥3 exposures.
		Rat (M)	Nasal discharge, lethargy, weight loss, and 9/12 died after ≥12 exposures.
		Rabbit (M)	Ocular irritation, impaired motion, weight loss, and 6/6 died after ≥9 exposures.
		Guinea pig (M)	Nasal discharge, weight loss, and 2/2 died after 10 exposures.

[a]Nominal concentration. A subsequent publication by Hill and Merrill (1960) showed that the analytic measurements were 47-130% of the nominal concentration at 3.0-13.8 ppm, and were 10-80% of the nominal concentration at 0.2 ppm. Source: Data from Levinskas et al. 1958.

3.8. Summary

Single- and multiple-exposure studies of pentaborane were conducted using monkeys, dogs, rats, mice, hamsters, rabbits, and guinea pigs. The studies consistently show that the CNS is the target of pentaborane; toxicity increased with exposure duration and concentration. Neurotoxic signs included apprehensiveness, lethargy, corneal opacity, aggressiveness, miosis, ataxia, tremors, and convulsions. In the single-exposure studies, all deaths occurred within 24 h. The most sensitive test of neurotoxicity was the CAR test for dogs, which found decreased performance from exposures that produced no apparent signs of toxicity (Weeks et al. 1964).

No gross or microscopic pathologic lesions were found in a single-exposure study of monkeys exposed to pentaborane at 37, 60, or 143 ppm for 2 min (Weeks et al. 1964). However, pathologic findings were noted in two multiple-exposure studies (Svirbely 1954b; Levinskas et al. 1958), including lesions in the adrenal glands, liver, spleen, lungs, testes, and eyes of rats. Pentaborane decreased brain concentrations of serotonin markedly and norepinephrine slightly in rats 3-12 h after exposure, and increased the pentobarbital sleeping time in mice (Weir et al. 1965).

No genotoxicity, carcinogenicity, or developmental or reproductive toxicity studies of pentaborane were found, although chronic exposure to pentaborane at 0.2 ppm caused testicular lesions in hamsters and rats.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

The metabolism and disposition of pentaborane has not been elucidated in humans or animals. Pentaborane hydrolyzes after several hours in body-temperature water to produce the much less toxic compounds boric acid (borane) and hydrogen, as well as heat. It is unknown to what extent the hydrolysis products contribute to pentaborane toxicity.

Workers accidentally exposed to high (undefined) concentrations of pentaborane had CNS effects, and boron was detected in their urine (Sim 1958). Urinary concentrations were the highest the first 2 days after exposure, followed by low levels for days 3-6, and slightly higher levels for several days after that (data not provided), suggesting slow elimination of boron.

Several dog studies indicated that the urinary concentrations of pentaborane are a better indicator of exposure than serum concentrations (Weir et al. 1964). Borane was undetectable in the serum after "low" (undefined) exposures, whereas it increased to 0.2 µg/mL during the first hour after exposure at "higher" (undefined) concentrations and then subsided to below detectable levels (0.05 µg/mL). However, the 24-h urinary boron measurements were increased in a concentration-related manner in all groups, generally subsiding to nearly pre-exposure concentrations after 48 h. In a repeat-exposure study, Weir et al. (1964) found that dogs exposed two or three times on successive days to pentaborane at 3.7-19.8 ppm for 5-60 min had unchanged serum boron concentrations, but their urinary boron increased after each exposure, returning to pre-exposure concentrations after 72 h.

Reed et al. (1964) examined the metabolic fate of pentaborane in rats and rabbits injected intraperitoneally with pentaborane-H^3 liquid (2.5 mg/kg). Rats exhaled 37% of the radiolabel as $H_2{}^3$ within 2 h, with negligible additional exhalation of $H_2{}^3$ thereafter. This pattern might reflect initial hydrolysis that formed an acid-labile intermediate containing nonvolatile and nonionizable tritium, which was present mainly in the liver and blood. The subsequent decrease in radiolabel in the liver and blood 3 h after exposure (relative to 10 min after ex-

posure) was postulated to be due to a slow hydrolysis of the nonvolatile intermediate to form ionizable hydrogens that can be exchanged with water. The latter theory is supported by a study in which pentaborane-H^3 radiolabel was incorporated into nonvolatile blood solids of anesthetized rabbits at approximately the same time (about 15 min after exposure) as the initial hydrolysis of pentaborane to form H_2^3 and nonvolatile intermediates in rats.

4.2. Mechanism of Toxicity

The mechanism of pentaborane toxicity is unknown, but might involve decreased brain serotonin and norepinephrine concentrations. Pentaborane is a potent reducer capable of reacting with ammonia, organic amines, and unsaturated hydrocarbons. The mechanism of toxicity appears to be similar among species, as the CNS was consistently the primary target of pentaborane.

A series of experiments in mice, rats, and dogs examined the mechanism of action of pentaborane (Weir et al. 1965; Weir and Meyers 1966). Pentobarbital-induced (intraperitoneal injection) sleeping time in mice was increased maximally 1-8 h after exposure to pentaborane at concentrations of 3.5 ppm or greater for 30 min. Serotonin was markedly decreased and norepinephrine was slightly decreased in brain homogenates of rats 3-168 h after exposure to pentaborane at 7.6 ppm for 30 min. The decreases were maximal 3-12 h after exposure. Concentrations returned to normal after 7 days for serotonin and after 2 days for norepinephrine. A similar effect on brain serotonin concentrations was observed in rats injected intraperitoneally with pentaborane at 8.0 mg/kg, although serotonin concentrations returned to normal more quickly (after 4 days).

Conscious dogs treated with pentaborane at 0.6-3.6 mg/kg by intraperitoneal injection or at 14.0-28.0 ppm by inhalation for 30 or 60 min had signs of neurotoxicity, as well as a large decrease in blood pressure and bradycardia that returned to normal after 4 h (Weir et al. 1965; Weir and Meyers 1966). (Information about the combinations of exposure concentration and duration and the length of the observation periods was not specified.) Anesthetized dogs injected intraperitoneally with pentaborane at 1.2-3.6 mg/kg had an initial increase in arterial blood pressure (after 2-5 min), which then fell slowly over 48 h. The dogs had bradycardia and decreased response (compared to pre-exposure) to bilateral carotid occlusion (20 seconds with hemostats) and intravenously injected tyramine (increases blood pressure and heart rate), but no effects on vagal stimulation (electrodes) or response to epinephrine. Administration of norepinephrine partially restored the decreased blood pressure, pulse rate, and responsiveness to carotid occlusion and tyramine.

4.3. Structure-Activity Relationships

Pentaborane is a member of a class of seven chemicals known as the boron hydrides or boranes, of which only two other chemicals are stable, diborane

(B_2H_6) and decaborane ($B_{10}H_{14}$). They are soluble in organic solvents and insoluble in water, but hydrolyze on contact with water within a few seconds (diborane), within several hours at body temperature (pentaborane), or in about 30 days (decaborane) (Sim 1958).

Krackow (1953) evaluated acute lethality studies conducted with pentaborane, diborane, and decaborane, and concluded that pentaborane was the most toxic. Rats and dogs exposed to diborane had pulmonary edema and hemorrhage, whereas animals exposed to pentaborane (rats and mice) and decaborane (rats, mice, and rabbits) primarily had neurologic effects, including loss of coordination and convulsions.

Because of the differences in toxicity among the boranes, structure-activity comparisons were not used in the derivation of AEGL values for pentaborane.

4.4. Other Relevant Information

4.4.1. Species Variability

The CNS was the target of pentaborane in all tested species, including humans; effects included incoordination, muscle spasms, convulsions, decreased appetite, and drooling. A comparison of animal studies indicates that the mouse is the most sensitive to the acute toxicity of pentaborane. Rats, dogs, and monkeys were similarly sensitivity to pentaborane.

Acute lethality studies in rats and mice were consistent in finding slightly lower LC_{50} values for mice. For example, Weir et al (1961, 1964) reported mouse LC_{50} values of 40.5, 18.6, 10.6, and 7.8 ppm for 5-, 15-, 30-, and 60-min exposures, respectively, whereas the analogous rat LC_{50} values were 66.6, 31.2, 15.2, and 10.4 ppm. Similarly, Svirbely (1954a) reported 120-min LC_{50} values of 12.4 ppm for mice and 15.7 ppm for rats, and Feinsilver et al. (1960) estimated 240-min LC_{50} values of 3.4 ppm for mice and 5.8 ppm for rats.

A comparison of the acute lethality of pentaborane in monkeys, dogs, and mice by Weeks et al (1964) indicated that mice were more sensitive than dogs and monkeys, but the latter two species were similarly sensitive. LC_{50} values for a 2-min exposure were 133 ppm for mice, 248 ppm for monkeys, and 284 ppm for dogs. Comparison of acute lethality between dogs and mice for 5- and 15-min exposures also showed that mice were more sensitive than dogs. Studies of nonlethal concentrations of pentaborane indicated that monkeys and dogs were similarly susceptible. Monkeys exposed for 2 min to pentaborane at 37 or 60 ppm had no toxic signs, but at 143 ppm the animals had convulsions and tremors. Dogs exposed for 2 min to pentaborane at 33 or 73 ppm had no toxic signs, but had convulsions at 144 ppm. The subchronic exposure studies of Levinskas et al. (1958) suggested that monkeys were more susceptible than rats, mice, rabbits, dogs, guinea pigs, and hamsters because the monkeys died after fewer exposures to pentaborane than the other species. However, as noted in Section 3.6, that study is considered unreliable because deaths also occurred in the control groups and the accuracy of the exposure concentrations was questionable.

Thus, the overall species variability in the toxic response to pentaborane was low. The LC_{50} values for exposures of 2-240 min varied by approximately a factor of 2 in four animal species, and similar responses were seen at comparable nonlethal concentrations in dogs and monkeys.

4.4.2. Susceptible Populations

No information on populations especially sensitive to pentaborane was found.

4.4.3. Concentration-Exposure Duration Relationship

ten Berge et al. (1986) determined that 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. The value of n ranged from 1 to 3 for 90% of the chemicals examined in that study.

The value of n for pentaborane was calculated to be 1.3 by linear regression analysis of rat LC_{50} data (5-60 min exposure durations) from the studies of Weir et al. (1961, 1964). See Appendix D for the calculations. Similar values for n can be calculated by linear regression analysis using LC_{50} data from dog and mouse studies: n = 1.0 using the 2-15–min LC_{50} data in dogs (Weeks et al. 1964), n = 1.47 using the 5-60–min LC_{50} values in mice (Weir et al. 1961, 1964), and n = 1.11 using the 0.5-15–min LC_{50} data in mice (Weeks et al. 1964).

If the 4-h LC_{50} values obtained by Feinsilver et al. (1960) for rats and mice are combined with the 5-60–min LC_{50} values of Weir et al. (1961, 1964), the values of n would increase from 1.30 to 1.55 for the rat and from 1.47 to 1.57 for the mouse. The slightly larger n values were not used, however, because Feinsilver et al. (1960) used a different analytic method to determine pentaborane concentrations than Weir et al. (1961, 1964).

Although the AEGL-2 values for pentaborane were derived on the basis of a dog study (Weir et al. 1964), the value of n calculated from dog LC_{50} data (Weeks et al. 1964) was not used to extrapolate across time because the exposure durations for the dogs were for just 2-15 min whereas they were 5-60 min for the rats. Furthermore, a larger number of rats (200) were studied than dogs (60). Using a value of n derived from a rat lethality study was considered appropriate because neurotoxic effects are on the continuum of effects leading to death, neurotoxicity was the primary toxic effect in both species, and dogs and rats were similarly sensitive to pentaborane.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Pentaborane has an odor threshold of approximately 1 ppm. Occupational studies have shown that humans exposed to pentaborane at concentrations with

an undetectable odor developed CNS effects characteristic of pentaborane intoxication (Schoettlin et al. 1961; Mindrum 1964).

5.2. Animal Data Relevant to AEGL-1

No animal studies of pentaborane evaluating end points relevant to AEGL-1 values were found. A study with dogs trained to do the CAR test showed that decrements in performance on the test occurred in dogs otherwise showing no apparent signs of toxicity from pentaborane (Weeks et al. 1964).

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended for pentaborane because no relevant human or animal studies were available. Human studies showed either no effects or CNS toxicity of severity greater than that defined by AEGL-1.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No experimental human studies of pentaborane were found. Occupational exposure studies indicated that the CNS is the target of pentaborane toxicity and that CNS effects can occur at concentrations with an undetectable odor. However, none of the studies determined exposure concentrations, exposure durations, and resulting effects simultaneously.

6.2. Animal Data Relevant to AEGL-2

Dog studies conducted by Weir et al. (1964) and Weeks et al. (1964) were potential candidates for developing AEGL-2 values. Those studies examined the effects of pentaborane on the dogs' behavior and performance in the CAR test. None of the acute lethality studies in rats or mice were used because the studies either did not adequately describe exposure concentrations and responses or tested only one concentration. The study of sooty mangabey monkeys exposed to pentaborane at 37-143 ppm (Weeks et al. 1964) involved just a 2-min exposure, a duration considered too short to serve as the basis of AEGL-2 values.

In the Weir et al. (1964) single-exposure studies, dogs were exposed to pentaborane for 5, 15, or 60 min, but they were either not subjected to the CAR test or the results of the CAR tests were not reported. CNS effects increased in severity with exposure concentration, and death occurred from 60-min exposures at 5.0 and 10.5 ppm.

Three multiple-exposure studies were conducted by Weir et al. (1964); the results reported after the first exposure to pentaborane in each of those cases was

considered. In one study, dogs exposed to pentaborane at 3.7-19.8 ppm for 5-60 min had mildly to moderately bloodshot eyes after one exposure, with no evidence of a concentration-response relationship. Two or more exposures caused bloodshot eyes, miosis, hemorrhage of the iris, CNS effects (convulsions, vicious behavior, and lethargy), and one death (after three exposures of 60 min). The only CAR test result reported was that dogs would not participate for 2-6 days after the last 60-min exposure. In the second experiment, dogs were exposed to pentaborane at 1.4-19.8 ppm for 5-60 min for 5 successive days. No neurologic effects or CAR delays occurred after the first exposure. After the second exposure, all groups began to exhibit CNS effects, including increased irritability, aggressiveness, decreased activity, and miosis (concentration related). Latency increased in the CAR test with each exposure. In the third experiment, dogs were exposed to pentaborane at 2.5 ppm on 2-5 occasions, with a reexposure interval of 24-96 h. Pupil size was decreased after each exposure. After the second exposure, animals had impaired performance on the CAR test and signs of toxicity (brief convulsions, tremors, cyanosis, apprehensiveness, and sensitivity to noise and movement) that decreased in severity as the exposure interval increased.

Weeks et al. (1964) exposed dogs to pentaborane at 33-144 ppm for 2 min, 16-58 ppm for 5 min, and 5.2-18 ppm for 15 min. CNS toxicity was dose-related, ranging from absent to severe. In some cases CAR delays occurred despite the lack of obvious signs (2 min at 73 ppm; 15 min at 5.2 ppm).

6.3. Derivation of AEGL-2 Values

The AEGL-2 values are based on the no-observed-effect level for CNS toxicity. Selection of that end point was intended to avoid even minor effects on CNS function, which could impair judgment of humans and result in accidents and injury (Mindrum 1964). The point-of-departure was a single 60-min exposure to pentaborane at 1.4 ppm (the first exposure in a five-exposure study), which caused no neurologic signs or CAR impairment in dogs (Weir et al. 1964). Dogs similarly exposed a second time (the following day) began to exhibit CNS effects, including decreased activity, miosis, and CAR delays, and additional exposures caused irritability and aggressiveness. This scenario was chosen instead of the 60-min single exposure study in which 3.0 or 3.2 ppm produced no toxic signs (Weir et al. 1964), because the investigators did not state whether the dogs had CAR delays. Furthermore, 3.0 and 3.2 ppm are close to a concentration that caused convulsions (4.5 ppm) after a single 60-min exposure. The 5-min exposure to pentaborane at 16 ppm (Weeks et al. 1964) also could have been used to derive very similar AEGL-2 values, but the Weir et al. (1964) study was chosen because the exposure duration was longer. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was applied because pentaborane caused similar effects (CNS toxicity) in humans and four species of laboratory animals, and because LC_{50} values varied less than 3-fold among species. An intraspecies uncertainty factor of 3 was applied because the

homogeneous response among species and steep concentration-response curve for lethality indicate that there would be little variability among humans.

Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n ranges from 0.8 to 3.5 for many irritant and systemically acting vapors and gases. A value of n = 1.3 was determined by linear regression analysis of acute lethality data from studies of mice exposed for 5-60 min (Weir et al. 1961, 1964), as described in Section 4.4.3. The resulting AEGL-2 values are presented in Table 4-12, and the calculations are detailed in Appendix A. The AEGL-2 values are supported by studies of monkeys exposed to pentaborane for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. The latter were not used because the exposure durations of the studies were too short, and the monkeys were not subjected to the CAR test.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No relevant human data were available for deriving AEGL-3 values for pentaborane.

7.2. Animal Data Relevant to AEGL-3

Acute lethality data were available from studies of monkeys (2 min), rats (5-240 min), mice (0.5-240 min), and dogs (2-15 min). The studies portrayed a consistent picture of pentaborane intoxication, which was manifested as tremors, weakness, ataxia, aggressiveness, and convulsions. LC_{50} values were comparable for monkeys, rats, and dogs, but were consistently lower for mice; however, the values in mice were generally less than 2-fold lower than other tested species.

7.3. Derivation of AEGL-3 Values

Reliable LC_{50} values were identified in several species for durations ranging from 2 min to 4 h. In general, there was less than a 3-fold difference in the LC_{50} values in rats, mice, dogs, and monkeys for a given exposure duration indicating very little species differences. The lowest LC_{50} values were found in mice. The 60-min lethality data from the study by Weir et al. (1961, 1964) and

TABLE 4-12 AEGL-2 Values for Pentaborane

10 min	30 min	1 h	4 h	8 h
0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)

the 4-h data from the study by Feinsilver et al. (1960) were considered possible sources of points-of-departure for AEGL-3 values. Benchmark dose software (EPA Version 1.3.2 and 2.4.0) was used to calculate LC_{50}, $BMCL_{05}$, and BMC_{01} values. The respective values for the 60-min study were 7.75, 5.08, and 6.04 ppm, and for the 4-h study were 3.5, 2.2, and 2.6 ppm. The $BMCL_{05}$ of 5.08 ppm was selected as an estimate of the threshold for lethality. Concentrations were scaled across time using the equation $C^{1.3} \times t = k$ (ten Berge et al. 1986), as described in Section 4.4.3. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used because pentaborane caused similar effects (CNS toxicity) in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species. An intraspecies uncertainty factor of 3 was applied because the homogeneous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Potential AEGL-3 values calculated on the basis of the 4-h $BMCL_{05}$ would have resulted in 10-min, 30-min, 1-h, 4-h, and 8-h values of 2.5, 1.1, 0.64, 0.22, and 0.13 ppm, respectively, which are similar to those calculated from the 60-min data. The 60-min $BMCL_{05}$ of 5.08 ppm was selected as the point-of-departure for the AEGL-3 values because it yielded slightly lower AEGL-3 values. The AEGL-3 values for pentaborane are supported by the LC_{50} values of Weir et al. (1961, 1964) for rats exposed for 60 min, which would have yielded slightly higher AEGL-3 values. The lethality data from studies of monkeys exposed for 2 min and dogs exposed for 2-15 min (Weeks et al. 1964) also would have yielded similar AEGL-3 values, but were not used because of the short exposure durations. The AEGL-3 values for pentaborane are presented in Table 4-13, and the calculations are detailed in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not developed for pentaborane because no relevant human or animal studies were available. The AEGL-2 and AEGL-3 values were based on dog and mouse studies, respectively. Neurotoxicity was considered the critical end point. CNS effects were the predominant toxic effect from exposure to pentaborane, and they were the most sensitive indicator in animals and humans. The CNS toxicity and progression profile was consistent among species. The AEGL values for pentaborane are presented in Table 4-14.

TABLE 4-13 AEGL-3 Values for Pentaborane

10 min	30 min	1 h	4 h	8 h
2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

TABLE 4-14 AEGL Values for Pentaborane

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)	0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)
AEGL-3 (lethal)	2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

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

TABLE 4-15 Standards and Guidelines for Pentaborane

Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	NR	–	NR	NR	NR	NR
AEGL-2	0.56 ppm	–	0.24 ppm	0.14 ppm	0.048 ppm	0.028 ppm
AEGL-3	2.0 ppm	–	0.87 ppm	0.51 ppm	0.17 ppm	0.10 ppm
IDLH (NIOSH)[a]	–	–	1 ppm	–	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	–	0.005 ppm
PEL-TWA (OSHA)[c]	–	–	–	–	–	0.005 ppm
REL-TWA (NIOSH)[d]	–	–	–	–	–	0.005 ppm
TLV-STEL (ACGIH)[e]	–	0.015 ppm	–	–	–	–
REL-STEL (NIOSH)[f]	–	0.015 ppm	–	–	–	–
MAK (Germany)[g]	–	–	–	–	–	0.005 ppm
MAK Peak Limit (Germany)[h]	–	0.015 ppm	–	–	–	–
MAC (The Netherlands)[i]	–	–	–	–	–	0.005 ppm

[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]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2013) 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.

[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Safety and Health Administration) (29 CFR Part 1910 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.

[e]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2013) 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.

[f]REL-STEL (recommended exposure limit – short-term exposure limit) (NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.

[g]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Foundation]) (DFG 2010) is defined analogous to the ACGIH TLV-TWA.

[h]MAK Spitzenbegrenzung (peak limit category II, excursion factor 2, Deutsche Forschungsgemeinschaft [German Research Foundation]) (DFG 2010) constitutes the maximum average concentration to which workers can be exposed for a period 15 min with no more than four exposure periods per work shift with 1-h intervals; total exposure may not exceed 8-h MAK.

[i]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2007) is defined analogous to the ACGIH TLV-TWA.

8.2. Other Standards and Guidelines

A comparison of the AEGL values with other standards and guidelines for pentaborane is presented in Table 4-15. The concentration of pentaborane that is immediately dangerous to life or health was determined by the National Institute for Occupational Safety and Health (NIOSH) to be 1 ppm on the basis of the acute inhalation studies of Jacobson (1958), Levinskas et al. (1958), and Weir et al. (1964). (The data attributed to Jacobson [1958] appear to be those generated by Feinsilver et al. [1960].) The American Conference of Governmental Industrial Hygienists established a threshold limit value–time-weighted average (TWA) of 0.005 ppm and a short-term exposure limit (STEL) of 0.015 ppm, both of which are intended to prevented adverse CNS effects, such as convulsions and neurologic impairment in workers (ACGIH 2001, 2013). The Occupational Safety and Health Administration (OSHA) adopted 0.005 ppm as the permissible exposure limit (PEL)-TWA "to protect exposed workers against the significant risk of CNS neuropathic effects, such as tremors and convulsions, behavioral changes, and loss of judgment, potentially associated with exposure to pentaborane above the PEL" (29CFR 1910 [2006]). In concurrence with OSHA, NIOSH adopted 0.005 ppm as its recommended exposure limit (REL)-TWA and 0.015 ppm as the REL-STEL.

8.3. Data Adequacy and Research Needs

Case reports of occupational exposures to pentaborane are available, but none of them provide quantitative data adequate for deriving AEGL values. They do show, however, that exposure to pentaborane at concentrations below the odor threshold can cause significant CNS toxicity.

Animal data on pentaborane were adequate for deriving AEGL-2 and AEGL-3 values. Studies in four species were available, and consistent results were found among species. Studies conducted in the 1960s were considered more reliable than those conducted in the 1950s, because an analytic method for measuring pentaborane was not available in the 1950s.

The key studies used to derive the AEGL values for pentaborane were well conducted and reported. One shortcoming was that only one study was available in which the exposure duration was longer than 1 h and for which analytic concentrations were available (Feinsilver et al. 1960) for the purpose of determining the exposure concentration-time relationship for pentaborane.

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Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.

Weir, F.W., F.H. Meyers, R.H. Arbuckle, and S. Bennett. 1965. The Similar Pharmacologic and Toxic Effects of Pentaborane, Decaborane, and Reserpine. Report no. AMRL-TR-65-49. Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, OH. May 1965.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PENTABORANE

Derivation of AEGL-1 Values

AEGL-1 values for pentaborane are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

Key study:	Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.
Toxicity end point:	No-observed-effect level for CNS toxicity in dogs; 1.4 ppm for a 60-min exposure. Dogs exposed a second time (the following day), however, began to exhibit CNS effects including decreased activity, miosis, and CAR delays. Additional exposures at 1.4 ppm caused irritability and aggressiveness.
Time scaling:	$C^n \times t = k$; an empirical value for n of 1.3 was determined by linear-regression analysis of rat lethality data (LC_{50} values for exposures of 5-60 min [Weir et al. 1961, 1964]). Acute lethality data from studies in dogs yielded an n = 1.0, but that value was not used because the exposure durations were only 2-15 min (Weeks et al. 1964). Use of the rat studies to determine the value of n was considered appropriate because neurotoxicity was the primary toxic effect in both rats and dogs, and they were similarly sensitive to pentaborane. $(1.4 \text{ ppm})^{1.3} \times 60 \text{ min} = 93 \text{ ppm-min}$
Uncertainty factors:	3 for interspecies differences; similar effects (CNS toxicity) were found in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among the species. 3 for intraspecies variability; the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Modifying factor: None

Calculations:

10-min AEGL-2: $C^{1.3} \times 10$ min = 93 ppm-min
C = 5.6 ppm
5.6 ppm ÷ 10 = 0.56 pm (1.4 mg/m^3)

30-min AEGL-2 $C^{1.3} \times 30$ min = 93 ppm-min
C = 2.4 ppm
2.4 ppm ÷ 10 = 0.24 ppm (0.62 mg/m^3)

1-h AEGL-2 C = 1.4 ppm
1.4 ppm ÷ 10 = 0.14 ppm (0.36 mg/m^3)

4-h AEGL-2 $C^{1.3} \times 240$ min = 93 ppm-min
C = 0.48 ppm
0.48 ppm ÷ 10 = 0.048 ppm (0.12 mg/m^3)

8-h AEGL-2 $C^{1.3} \times 480$ min = 93 ppm-min
C = 0.28 ppm
0.28 ppm ÷ 10 = 0.028 ppm (0.072 mg/m^3)

Derivation of AEGL-3 Values

Key studies: Weir, F.W., D.W. Bath, and M.H. Weeks. 1961. Short-term Inhalation Exposures of Rodents to Pentaborane-9. ASD Technical Report 61-663. Aerospace Medical Laboratory, Wright-Patterson Air Force Base, OH. December 1961.

Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.

Toxicity end point: Lethality threshold in mice; $BMCL_{05}$ = 5.08 ppm

Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear-regression analysis of rat lethality data (LC_{50} values for exposures of 5-60 min [Weir et al. 1961, 1964]).

$(5.08)^{1.3} \times 60$ min = 496 ppm-min

Uncertainty factors: 3 for interspecies differences; similar effects (CNS toxicity) were found in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among the species.

	3 for intraspecies variability; the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.
Modifying factor:	None
Calculations:	
10-min AEGL-3	$C^{1.3} \times 10$ min = 496 ppm-min C = 20 ppm 20 ppm ÷ 10 = 2.0 ppm (5.2 mg/m^3)
30-min AEGL-3	$C^{1.3} \times 30$ min = 496 ppm-min C = 8.7 ppm 8.7 ppm ÷ 10 = 0.87 ppm (2.2 mg/m^3)
1-h AEGL-3	C = 5.1 ppm 5.1 ppm ÷ 10 = 0.51 ppm (1.3 mg/m^3)
4-h AEGL-3	$C^{1.3} \times 240$ min = 496 ppm-min C = 1.7 ppm 1.7 ppm ÷ 10 = 0.17 ppm (0.44 mg/m^3)
8-h AEGL-3	$C^{1.3} \times 480$ min = 496 ppm-min C = 1.0 ppm 1.0 ppm ÷ 10 = 0.10 ppm (0.26 mg/m^3)

APPENDIX B

CATEGORY PLOT FOR PENTABORANE

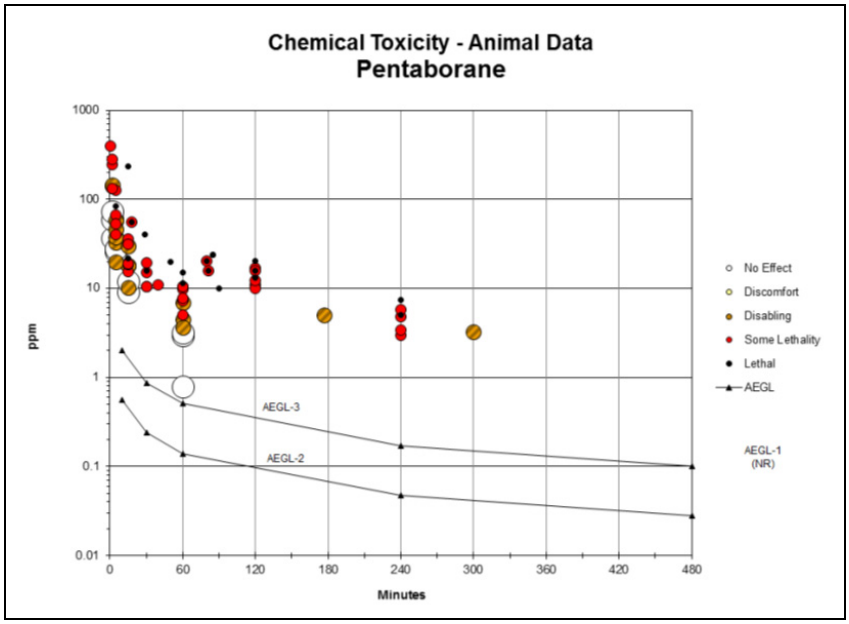


FIGURE B-1 Category plot of toxicity data and AEGL values for pentaborane. The data include single-exposure data from studies of monkeys, dogs, rats, and mice. Results from multiple-exposure studies that have information on effects from the first exposure to pentaborane are also included. No human data on pentaborane were available.

TABLE B-1 Data Used in Category Plot for Pentaborane

Source	Species	ppm	Minutes	Category	Comments
AEGL-2		0.56	10	AEGL	
AEGL-2		0.24	30	AEGL	
AEGL-2		0.14	60	AEGL	
AEGL-2		0.048	240	AEGL	
AEGL-2		0.028	480	AEGL	
AEGL-3		2.0	10	AEGL	
AEGL-3		0.87	30	AEGL	
AEGL-3		0.51	60	AEGL	
AEGL-3		0.17	240	AEGL	
AEGL-3		0.1	480	AEGL	
Weeks et al. 1964	Monkey	37	2	0	No toxic signs
Weeks et al. 1964	Monkey	60	2	0	No toxic signs
Weeks et al. 1964	Monkey	143	2	2	Convulsions and tremors
Weeks et al. 1964	Monkey	248	2	SL	LC_{50}
Weeks et al. 1964	Dog	73	2	0	No toxic signs
Weeks et al. 1964	Dog	144	2	2	Convulsions
Weeks et al. 1964	Dog	284	2	SL	LC_{50}
Weeks et al. 1964	Dog	16	5	0	No toxic signs
Weeks et al. 1964	Dog	33	5	2	Lethargy
Weeks et al. 1964	Dog	58	5	2	Convulsions
Weeks et al. 1964	Dog	126	5	SL	LC_{50}
Weeks et al. 1964	Dog	9.1	15	0	No toxic signs
Weeks et al. 1964	Dog	18	15	2	Convulsions, tremors

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Weeks et al. 1964	Dog	36	15	SL	LC_{50}
Weir et al. 1964	Dog	26	5	0	No toxic signs (head-only exposure)
Weir et al. 1964	Dog	28	5	0	No toxic signs (whole-body exposure)
Weir et al. 1964	Dog	38	5	2	Tremors, salivation, clonic convulsions, apprehension
Weir et al. 1964	Dog	46	5	2	Tremors, convulsions
Weir et al. 1964	Dog	12	15	0	No toxic signs
Weir et al. 1964	Dog	18	15	2	Tremors, apprehension
Weir et al. 1964	Dog	30	15	2	Clonic convulsions
Weir et al. 1964	Dog	0.80	60	0	No toxic signs
Weir et al. 1964	Dog	3.0	60	0	No toxic signs (whole-body exposure)
Weir et al. 1964	Dog	3.2	60	0	No toxic signs (head-only exposure)
Weir et al. 1964	Dog	4.5	60	2	Convulsions
Weir et al. 1964	Dog	5.0	60	SL	Tremors, convulsions, salivation, death (1/2)
Weir et al. 1964	Dog	6.9	60	2	Tremors, convulsions, salivation
Weir et al. 1964	Dog	7.5	60	SL	Convulsions, death (2/3)
Weir et al. 1964	Dog	10.5	60	SL	Tremors, convulsions, salivation, death (1/2)
Dost et al. 1963	Rat	11	40	SL	LC_{50}
Feinsilver et al. 1960	Rat	4.8	240	SL	Mortality: 1/10
Feinsilver et al. 1960	Rat	5.8	240	SL	LC_{50}
Feinsilver et al. 1960	Rat	7.5	240	3	Mortality: 10/10
Krackow 1953	Rat	17	120	SL	LC_{50}
Svirbely 1954a	Rat	235	15	3	Mortality: 3/3
Svirbely 1954a	Rat	56	18	SL	Mortality: 2/3
Svirbely 1954a	Rat	20.2	80	SL	Mortality: 4/5

Svirbely 1954a	Rat	16	81	SL	Mortality: 2/5
Svirbely 1954a	Rat	24	85	3	Mortality: 3/3
Svirbely 1954a	Rat	15.7	120	SL	LC_{50}
Svirbely 1954a	Rat	20.2	120	3	Mortality: 5/5
Svirbely 1954b	Rat	3.3	300	2	Convulsions, gasping, tremors, aggressiveness, salivation, organ lesions
Weir et al. 1961, 1964	Rat	66.6	5	SL	LC_{50}
Weir et al. 1961, 1964	Rat	84.7	5	3	Mortality: 10/10
Weir et al. 1961, 1964	Rat	31.2	15	SL	LC_{50}
Weir et al. 1961, 1964	Rat	15.2	30	SL	LC_{50}
Weir et al. 1961, 1964	Rat	19.3	30	SL	Mortality: 9/10
Weir et al. 1961, 1964	Rat	9.8	60	SL	Mortality: 3/10
Weir et al. 1961, 1964	Rat	10.4	60	SL	LC_{50}
Weir et al. 1961, 1964	Rat	15.1	60	3	Mortality: 10/10
Feinsilver et al. 1960	Mouse	3	240	SL	Mortality: 2/10
Feinsilver et al. 1960	Mouse	3.4	240	SL	LC_{50}
Krackow 1953	Mouse	5	240	3	Mortality: 10/10
Krackow 1953	Mouse	11	120	SL	LC_{50}
Svirbely 1954a	Mouse	56.0	18	3	Mortality: 5/5
Svirbely 1954a	Mouse	20.2	80	3	Mortality: 10/10
Svirbely 1954a	Mouse	16	81	3	Mortality: 10/10
Svirbely 1954a	Mouse	24.0	85	3	Mortality: 5/5
Svirbely 1954a	Mouse	10	120	SL	Mortality: 2/10
Svirbely 1954a	Mouse	12.4	120	SL	LC_{50}
Svirbely 1954a	Mouse	13.2	120	3	Mortality: 10/10
Svirbely 1954a	Mouse	16	120	3	Mortality: 10/10

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Weatherby 1958	Mouse	40	29	3	Mortality: 6/6
Weatherby 1958	Mouse	20	50	3	Mortality: 6/6
Weatherby 1958	Mouse	10	90	3	Mortality: 6/6
Weatherby 1958	Mouse	5.0	177	2	Convulsions, appeared normal after 24 h
Weir et al. 1961, 1964	Mouse	40.5	5	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	15.4	15	SL	Mortality: 1/10
Weir et al. 1961, 1964	Mouse	18.4	15	SL	Mortality: 2/10
Weir et al. 1961, 1964	Mouse	18.6	15	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	21.9	15	3	Mortality: 10/10
Weir et al. 1961, 1964	Mouse	10.5	30	SL	Mortality: 2/10
Weir et al. 1961, 1964	Mouse	10.6	30	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	15.8	30	3	Mortality: 10/10
Weir et al. 1961, 1964	Mouse	7.3	60	SL	Mortality: 1/10
Weir et al. 1961, 1964	Mouse	7.8	60	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	11.6	60	3	Mortality: 10/10
Weir et al. 1964	Mouse	19.8	5	2	Convulsions; death after repeated exposures
Weir et al. 1964	Mouse	10.2	15	2	Convulsions; death after repeated exposures
Weir et al. 1964	Mouse	3.7	60	2	Convulsions; death after repeated exposures
Weeks et al. 1964	Mouse	401	0.5	SL	LC_{50}
Weeks et al. 1964	Mouse	133	2.0	SL	LC_{50}
Weeks et al. 1964	Mouse	53	5.0	SL	LC_{50}
Weeks et al. 1964	Mouse	19	15	SL	LC_{50}

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

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR PENTABORANE

Derivation Summary

AEGL-1 VALUES

AEGL-1 values for pentaborane are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)
Key reference: Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.				
Test species/Strain/Number: Dogs; beagle; unspecified sex; 3/concentration				
Exposure route/Concentrations/Durations: Inhalation; 1.4 ppm for 60 min; 5 consecutive days.				
Effects: No toxic signs or conditioned avoidance response (CAR) impairment occurred after the first 60-min exposure at 1.4 ppm. Dogs exposed a second time (the following day) began to exhibit CNS effects, including decreased activity, miosis, and CAR delays. Additional exposures at 1.4 ppm caused irritability and aggressiveness.				
End point/Concentration/Rationale: CNS toxicity; no-effect level of 1.4 ppm for a single 60-min exposure				
Uncertainty factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, similar effects (CNS toxicity) occurred in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species. Intraspecies: 3, the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.				
Modifying factor: None				
Animal-to-human dosimetric adjustment: Not applied				
Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear regression analysis of rat lethality data (Weir et al. 1961, 1964).				
Data adequacy: The data set on pentaborane was sufficient. The AEGL-2 values are supported by studies in monkeys exposed for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. The latter were not used because the exposure durations were too short, and the monkeys were not subjected to the CAR test.				

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

Key references:
(1) Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.
(2) Weir, F.W., D.W. Bath, and M.H. Weeks. 1961. Short-term Inhalation Exposures of Rodents to Pentaborane-9. ASD Technical Report 61-663. Aerospace Medical Laboratory, Wright-Patterson Air Force Base, OH. December 1961.

Test species/Strain/Number: Mice; white (strain not specified); male; 10/concentration

Exposure route/Concentrations/Durations: Inhalation; 6.9, 7.3, 6.9, 7.4, 7.5, and 11.6 ppm for 60 min

Effects: Tremors, ataxia, convulsions, red exudate around the mouth and nose, and death occurred within 24 h. The LC_{50} was 7.75 ppm, and the $BMCL_{05}$, and BMC_{01} values were 5.08 and 6.04 ppm, respectively.

End point/Concentration/Rationale: The $BMCL_{05}$ of 5.08 ppm was considered the threshold for lethality in mice.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, similar effects (CNS toxicity) occurred in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species.
Intraspecies: 3, the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear regression analysis of rat lethality data (Weir et al. 1961, 1964).

Data adequacy: The data set was adequate. LC_{50} values were available for four animal species, and had low variability among them. The AEGL-3 values are supported by lethality data in mice exposed for 4 h (Feinsilver et al. 1960), rats exposed for 60 min (Weir et al. 1961, 1964), and monkeys and dogs exposed for 2-15 min (Weeks et al. 1964), which would yield similar values.

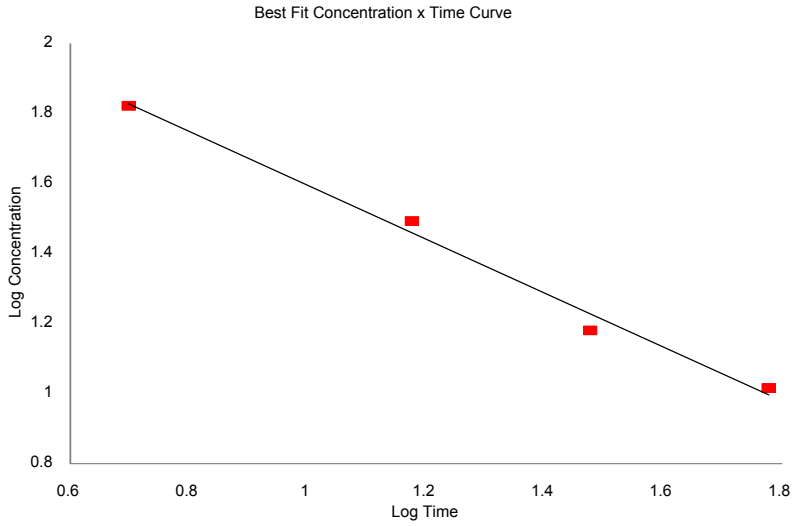
APPENDIX D

CONCENTRATION-EXPOSURE DURATION RELATIONSHIP FOR PENTABORANE

The 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 2.5 (ten Berge et al. 1986). For pentaborane, the value of n was determined using lethality data from studies in rats by Weir et al. (1961, 1964). Rat LD_{50} values (see Table D-1) were analyzed by linear regression to calculate a value of n = 1.3.

TABLE D-1 Pentaborane Lethality in Rats

Input Data					
Concentration	Log Concentration	Time (min)	Log Time	Regression Output	
66.6	1.8235	5	0.6990	Intercept	2.3670
31.2	1.4942	15	1.1761	Slope	-0.7702
15.2	1.1818	30	1.4771	R squared	0.9901
10.4	1.0170	60	1.7782	Correlation	-0.9951
n = 1.3				Degrees of freedom	2
k = 1,183.27				Observations	4



APPENDIX E

BENCHMARK DOSE CALCULATIONS (VERSION 2.4.0)

Probit Model. (Version: 3.3; Date: 2/28/2013)
Input Data File:
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Gnuplot Plotting File:
C:/USEPA/BMDS240/Data/Pentaborane/pro_pentaborane_60min_mouse_Prb-BMR05.plt
Thu Aug 29 13:13:50 2013

BMDS_Model_Run

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

Dependent variable = Effect
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
background = 0
intercept = -5.65795
slope = 0.663177

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

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Intercept	-10.5843	5.89507	-22.1384	0.969797
Slope	1.36615	0.813011	-0.227318	2.95963

Analysis of Deviance Table

Model	Log (likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-22.3996	6			
Fitted model	-26.072	2	7.3449	4	0.1187
Reduced model	-39.4295	1	34.0598	5	<.0001

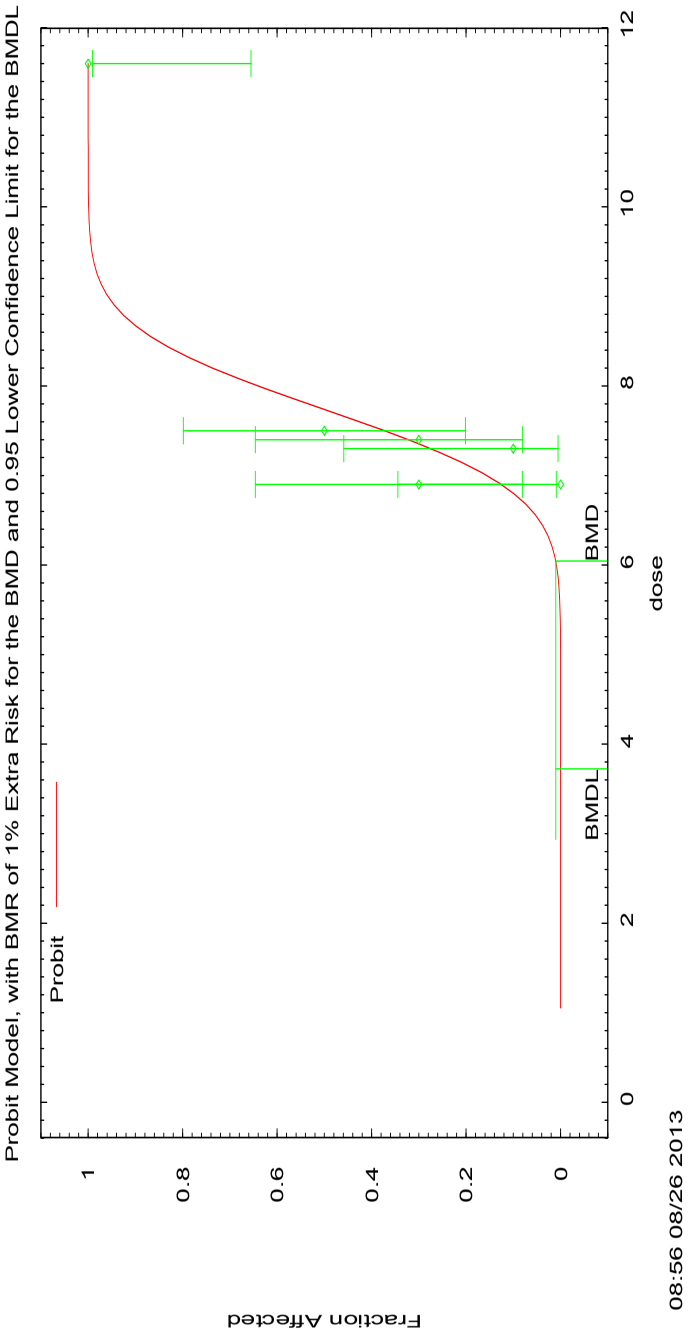
AIC: 56.1441

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
6.9000	0.1235	1.235	0.000	10	-1.187
7.3000	0.2705	2.705	1.000	10	-1.214
6.9000	0.1235	1.235	3.000	10	1.697
7.4000	0.3175	3.175	3.000	10	-0.119
7.5000	0.3676	3.676	5.000	10	0.868
11.6000	1.0000	10.000	10.000	10	0.001

Chi-square = 6.53 d.f. = 4 P-value = 0.1630

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 6.54353
BMDL = 5.08379



5

Tellurium Hexafluoride[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 Jennifer Rayner (Oak Ridge National Laboratory), 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).

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

Tellurium hexafluoride is a byproduct of ore refining. It is a colorless gas with a repulsive odor. It decomposes slowly in water to form hydrogen fluoride and tellurium ion. Tellurium hexafluoride is severely irritating and causes respiratory distress, pulmonary edema, and death in animals. In humans, it is reported to cause "garlic" breath, a metallic taste in the mouth, and fatigue. Inhalation of tellurium hexafluoride is expected to cause breathing difficulties in humans.

AEGL-1 values are not recommended for tellurium hexafluoride because of insufficient data. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 concentrations are without adverse effects.

Data were also inadequate for deriving AEGL-2 values. However, the standing operating procedures for determining AEGL values specifies that AEGL-2 values for chemicals with steep concentrations-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Lethality data on tellurium hexafluoride demonstrates a steep-concentration response curve. All rabbits, guinea pigs, rats, and mice exposed for 4 h to tellurium hexafluoride at concentrations of 5 ppm or higher died, and all mice exposed at 5 ppm for 1 h died. All animals exposed at 1 ppm for 1 or 4 h survived (Kimmerle 1960).

The point-of-departure for deriving AEGL-3 values was 1 ppm for 4 h, which was the highest concentration of tellurium hexafluoride at which no mortality occurred in rabbits, guinea pigs, rats, and mice (Kimmerle 1960). An interspecies uncertainty factor of 3 was applied because the four species appear to be

similarly sensitive to the acute effects of tellurium hexafluoride; however, that assessment is based on a small number of test animals (one to four animals per group). An intraspecies uncertainty factor of 3 was applied because tellurium hexafluoride is highly irritating and corrosive, and much of its toxicity is probably caused by a direct chemical effect on tissues; that type of portal-of-entry effect is not expected to vary greatly among individuals. A modifying factor of 10 also was applied to account for the sparse database on tellurium hexafluoride and for the potential effects of tellurium. Time scaling of the values were performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of data on tellurium hexafluoride to determine an empirical value for n, default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used.

The AEGL values for tellurium hexafluoride are presented in Table 5-1.

1. INTRODUCTION

Tellurium hexafluoride is a colorless gas created by the direct fluorination of tellurium metal (HSDB 2008). It is a byproduct of ore refining, and there are no known uses for it (ACGIH 2001; HSDB 2008). Production data were not found. Tellurium hexafluoride hydrolyzes slowly in water to hydrogen fluoride and telluric acid. Its chemical and physical properties are presented in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human data on the acute lethality of tellurium hexafluoride were found.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Odor Awareness

Tellurium hexafluoride has a repulsive odor (ACGIH 2001).

2.2.2. Case Reports

Blackadder and Manderson (1975) reported a case of tellurium hexafluoride exposure. Two men, 24 and 26 years old, were exposed when 50 g of tellurium hexafluoride gas leaked from a cylinder while they were doing research. The first man experienced tiredness, a metallic taste in the mouth, and sour garlic odor in his breath, sweat, and urine. He was admitted to the hospital for observation and developed a rash on the hands, arms, and neck after the second

day of observation. He also developed bluish-black patches between the fingers and on the neck and face, which took several weeks to fade. The second man experienced garlic odor of the breath and bluish-black patches on the skin. Liver-function tests, renal-function tests, urinalysis, chest radiographs, blood electrolytes, and blood indices were all normal. The men were not treated and both completely recovered; the garlic odor of the breath and blue-black patches on the skin took several weeks to clear. The skin discoloration was thought to be the result of dermal absorption of tellurium.

TABLE 5-1 AEGL Values for Tellurium Hexafluoride

Classification	10 min	30 min	1 h	4h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	0.0097 ppm (0.096 mg/m^3)	0.0067 ppm (0.066 mg/m^3)	0.0053 ppm (0.052 mg/m^3)	0.0033 ppm (0.033 mg/m^3)	0.0017 ppm (0.017 mg/m^3)	One-third of the AEGL-3 values (NRC 2001).
AEGL-3 (lethal)	0.029 ppm (0.28 mg/m^3)	0.020 ppm (0.20 mg/m^3)	0.016 ppm (0.16 mg/m^3)	0.010 ppm (0.10 mg/m^3)	0.0050 ppm (0.049 mg/m^3)	Highest concentration causing no mortality in rabbits, guinea pig, rats, and mice (Kimmerle 1960).

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

TABLE 5-2 Chemical and Physical Properties of Tellurium Hexafluoride

Parameter	Value	References
Synonyms	Tellurium fluoride (TEF6), (OC-6-11)-; tellurium fluoride (TEF)	HSDB 2008
CAS registry no.	7783-80-4	HSDB 2008
Chemical formula	TeF_6	HSDB 2008
Molecular weight	241.61	HSDB 2008
Physical state	Colorless gas	HSDB 2008
Melting point	-37.6ºC	ACGIH 2001
Boiling point	-38.9ºC	ACGIH 2001
Vapor density (air = 1)	8.3	HSDB 2008
Solubility in water	Decomposes slowly in water to telluric acid	ACGIH 2001
Vapor pressure	>760 torr at 20°C	ACGIH 2001
Flammability limits	Nonflammable gas	NIOSH 2011
Conversion factors	1 ppm = 9.88 mg/m^3 1 mg/m^3 = 0.10 ppm	NIOSH 2011

2.2.3. Occupational Exposure

Steinberg et al. (1942) examined 49 workers exposed to fumes of tellurium and its oxides for 15 or 22 months. The most commonly reported subjective symptoms were garlic odor of the breath, mouth dryness, metallic taste, somnolence, and garlic odor of the sweat. A small number of subjects occasionally reported loss of appetite and nausea. Somnolence was observed only in the workers with the highest urinary concentrations of tellurium. No alterations in hematologic or urinalysis parameters were observed.

2.3. Neurotoxicity

No human data on the neurotoxicity of tellurium hexafluoride were found.

2.4. Developmental and Reproductive Toxicity

No human data on the developmental or reproductive toxicity of tellurium hexafluoride were found.

2.5. Genotoxicity

No human data on the genotoxicity of tellurium hexafluoride were found.

2.6. Carcinogenicity

No human data on the carcinogenicity of tellurium hexafluoride were found.

2.7. Summary

Human exposure to tellurium hexafluoride or fumes of tellurium oxides caused metallic taste in the mouth; tiredness; sour garlic odor of the breath, sweat, and urine; and bluish-black patches on the skin. Tellurium hexafluoride is a respiratory irritant and humans may experience breathing difficulties after inhaling it (NIOSH 1978; OSHA 1996).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Kimmerle (1960) exposed one rabbit, one guinea pig, two male white rats, and four male white mice per group to tellurium hexafluoride for 1 or 4 h. Exposures were carried out in a 2-m^3 chamber. Tellurium hexafluoride was intro-

duced into the chamber through a glass burette and mixed with air by a propeller. The animals were exposed at 1 or 5 ppm (nominal concentrations) for 1 h and 1, 5, 10, 25, 50 or 100 ppm (nominal concentrations) for 4 h. The results are shown in Table 5-3. At 5 ppm for 1 h, severe damage was observed in the respiratory organs of the animals, and all mice died between 24 and 36 h. All animals survived 1-h exposures at 1 ppm. Exposure to tellurium hexafluoride at 1 ppm for 4 h caused respiratory dysfunction in all animals. All animals died from pulmonary edema after exposure at 5 ppm or higher for 4 h.

TABLE 5-3 Results of Acute Toxicity Studies of Tellurium Hexafluoride by Kimmerle (1960)

Species	Concentration (ppm)	Duration (h)	Effect
Rabbit	1	4	Respiratory dysfunction, pulmonary edema.
(1/group)	5		Death after 8 h.
	10		Death after 140 min.
	25		Death after 80 min.
	50		Death after 60 min.
	100		Death after 15 min
Rabbit	1	1	Significantly increased respiratory frequency.
(1/group)	5		Severe damage to respiratory organs.
Guinea pig	1	4	Respiratory dysfunction, pulmonary edema.
(1/group)	5		Death after 6 h.
	10		Death after 120 min.
	25		Death after 100 min.
	50		Death after 70 min.
	100		Death after 30 min.
Guinea pig	1	1	Significantly increased respiratory frequency.
(1/group)	5		Severe damage to respiratory organs.
Rat	1	4	Respiratory dysfunction, pulmonary edema.
(2/group)	5		Death after 6 and 24 h.
	10		Death after 100 and 115 min.
	25		Death after 60 and 85 min.
	50		Death after 55 and 70 min.
	100		Death after 20 and 25 min.
Rat	1	1	Significantly increased respiratory frequency.
(2/group)	5		Severe damage to respiratory organs.
Mouse	1	4	Respiratory dysfunction, pulmonary edema.
(4/group)	5		Death within 4-24 h.
	10		Death within 110-130 min.
	25		Death within 75-110 min.
	50		Death within 45-70 min.
	100		Death within 10-30 min.
Mouse	1	1	Significantly increased respiratory frequency.
(4/group)	5		Death between 24-36 h, severe damage to respiratory organs.

3.2. Nonlethal Toxicity

Kimmerle (1960) exposed one rabbit, one guinea pig, two male white rats, and four male white mice per group to tellurium hexafluoride at 1 or 5 ppm for 1 or 4 h, as described in Section 3.1. Significantly increased respiratory frequency (hyperpnea) was observed in all animals exposed at 1 ppm for 1 h. At 5 ppm for 1 h, severe damage was observed in the respiratory organs of the animals; the rabbit, guinea pigs, and rats survived the exposure but recovered very slowly. Exposure to tellurium hexafluoride at 1 ppm for 4 h caused respiratory dysfunction in all animals. The investigator also exposed the same species to tellurium hexafluoride at 1 ppm for 1 h each day for 5 days and found no visible effects in the animals. In the rabbit, liver-function tests were carried out after the end of the repeat-exposure test and again one week later. No hepatic damage was observed.

There are few data on other tellurium compounds. One study reported that one of four guinea pigs died 24 h after a single injection of tellurium oxide. The remaining guinea pigs survived the 1-week observation period (Amdur 1958). No histologic alterations were observed in the livers or kidneys of the surviving animals.

3.3. Developmental and Reproductive Toxicity

No animal data on the developmental or reproductive toxicity of tellurium hexafluoride were found, but a few studies on tellurium and tellurium pulveratum were available.

Oral exposure studies have found that the developing nervous system is sensitive to the toxicity of tellurium. Highly synchronous primary demyelination of peripheral nerves followed by remyelination was observed in developing rats exposed to 1.1% tellurium in the diet (Malczewska-Toth 2012). The demyelination was due to tellurium-induced inhibition of squalene epoxidase activity. Duckett (1970) reported that there were no differences in the size or appearance of the fetuses of dams exposed to tellurium at 3,000 ppm in their diet. Although no anomalies were found by light microscopy of the brains, electron microscopic examination revealed morphologic anomalies in the ependymal layer of tellurium-exposed fetuses; no microvilli were detected in the ventricular plasmalemma and the number of mitochondria was greatly diminished.

In weanling rats (17 days old) fed a diet containing 1% tellurium pulveratum for at least 3 days, partial or complete paralysis of the hind limbs was observed (Lampert et al. 1970). A gradual recovery started on the tenth day of exposure, and weakness of the hind limbs was only occasionally observed after 20-25 days of exposure. The investigators also noted severe wasting in the animals by the tenth exposure day. Consistent with the clinical signs, increased cellularity and demyelination was observed in the lumbar roots and sciatic nerves, with peak damage occurring after 4 days of exposure; remeylination was observed after 10 days of exposure. The investigators suggested that tellurium-induced

neuropathy was age-specific, as evidenced by remyelination despite continuing exposure. No histologic alterations were observed in the brain or spinal cord and demyelinated axons were occasionally observed in the brachial plexus of some animals; in general, no alterations were observed in the liver.

3.4. Genotoxicity

No data on the genotoxicity of tellurium hexafluoride were found.

3.5. Chronic Toxicity and Carcinogenicity

No data on the chronic toxicity or carcinogenicity of tellurium hexafluoride were found.

3.5. Summary

Only one study of tellurium hexafluoride toxicity in animal models was found. In that study, all rabbits, guinea pigs, rats, and mice exposed to tellurium hexafluoride at 5, 10, 25, 50, or 100 ppm for 4 h died (Kimmerle 1960). All mice exposed at 5 ppm for 1 h died, whereas animals exposed at 1 ppm for 1 h survived. Repeated exposure to tellurium hexafluoride at 1 ppm for 1 h per day for 5 days resulted in no clinical signs or mortality in any species tested. Clinical signs (respiratory distress) and post-mortem findings (pulmonary edema) were consistent with severe irritation in all animals except those exposed at 1 ppm for 1 h, which exhibited only hyperpnea. A limitation of this study is that only a small number of animals were tested. No data on the developmental or reproductive toxicity, genotoxicity, or chronic toxicity or carcinogenicity following inhalation exposure to tellurium hexafluoride were found. Studies of related chemicals (tellurium and tellurium pulveratum) have reported demyelination in peripheral nerves and morphologic alterations in the brain of developing animals after oral exposure (Duckett 1970; Lampert et al. 1970; Malczewska-Toth 2012).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Little information on the metabolism and disposition of tellurium hexafluoride were found. Tellurium hexafluoride may be hydrolyzed in the moist respiratory tract to hydrogen fluoride and the tellurium ion or telluric acid (HSDB 2008). Tellurium is distributed through the body with higher concentrations found in the kidneys, liver, bone, brain, and testes (IPCS 1998). In the liver, hepatic metabolism creates dimethyl telluride, which is exhaled and has a garlic

odor (IPCS 1998). Tellurium is mainly excreted in the urine with small amounts exhaled as dimethyl telluride (IPCS 1998).

4.2. Mechanism of Toxicity

In the moist respiratory tract, tellurium hexafluoride slowly hydrolyzes into hydrogen fluoride and tellurium ion or telluric acid. Kimmerle (1960) has shown that the toxic effects of inhaled tellurium hexafluoride are consistent with severe irritation and corrosion. Hydrogen fluoride is a severe irritant to the skin, eyes, and respiratory tract. The AEGL values for hydrogen fluoride, however, are orders of magnitude higher than the AEGL values for tellurium hexafluoride, which may indicate that hydrogen fluoride does not play a major role in its toxicity. Penetration of hydrogen fluoride to the lungs produces pulmonary hemorrhage and edema and may result in death (NRC 2004a). The mechanism of toxicity of tellurium is unknown. It has been shown that tellurium inhibits squalene epoxidase, which might interfere with neurotransmission through demyelination. Demyelination has been observed in young animals but not in humans (Anthony et al. 2001).

4.3. Structure-Activity Relationships

Because one mole of tellurium hexafluoride may decompose in moist atmospheres to form up to six moles of hydrogen fluoride, it might be assumed that tellurium hexafluoride may be approximately six times more toxic than hydrogen fluoride on a molar basis. However, the small data set on tellurium hexafluoride suggests that it is much more than six times as toxic as hydrogen fluoride.

The 1-h LC_{50} values for hydrogen fluoride for the mouse range from 342 to 501 ppm (NRC 2004a). If the acute inhalation toxicity of tellurium hexafluoride was due only to hydrogen fluoride, then 1-h LC_{50} values for tellurium hexafluoride should have a range of 57-84 ppm for mice. However, 100% mortality occurred in mice exposed to tellurium hexafluoride at 5 ppm for 1 h (Kimmerle 1960). The greater relative toxicity of tellurium hexafluoride might be due to the tellurium moiety and/or the slow hydrolysis rate of tellurium hexafluoride. If the slow hydrolysis rate resulted in more hydrogen fluoride being released in the lung than in the upper respiratory tract, it would result in greater pulmonary damage and likely be more lethal. Mortality in rats exposed to hydrogen fluoride at 1,300 ppm for 30 min by cannulation (to simulate mouth breathing) was 25%, whereas no mortality occurred in rats similarly exposed by nasal breathing (Stavert et al. 1991).

Few toxicity studies are available on other metal hexafluorides, such as uranium hexafluoride and selenium hexafluoride. The relevance of those compounds to tellurium hexafluoride has not been established. Tellurium hexafluoride is analogous to selenium hexafluoride in molecular structure and noble gas

configuration. Both are irritating gases that cause pulmonary edema and death. Tellurium hexafluoride was found to be more toxic in laboratory animals than selenium hexafluoride (Kimmerle 1960); although this comparison is limited by the small number of animals tested for both compounds (one rabbit, one guinea pig, two rats, and four mice). All rabbits, guinea pigs, rats, and mice exposed to selenium hexafluoride at 10 ppm for 4 h died, but survived exposure at 5 or 1 ppm. Animals exposed at 5 ppm exhibited difficulty breathing and pulmonary edema, which resolved during the follow-up period. No effects were observed in animals exposed selenium hexafluoride at 1 ppm. All rabbits, guinea pigs, rats, and mice exposed to tellurium hexafluoride at 5 ppm for 4 h died, but survived exposure at 1 ppm. Animals exposed at 1 ppm exhibited difficulty breathing and pulmonary edema, which resolved during the follow-up period. Unlike tellurium hexafluoride, uranium hexafluoride rapidly hydrolyzes to form hydrogen fluoride and uranyl fluoride (NRC 2004b); thus, the site of toxicity might be different from that of tellurium hexafluoride. Acute inhalation exposure to uranium hexafluoride results in renal damage caused by the uranium moiety (NRC 2004b). However, no evidence that the kidney is a sensitive target of tellurium hexafluoride or other tellurium compounds was found. No histologic alterations were observed in the kidneys of guinea pigs administered a single injection of tellurium oxide and no alterations in urinary glucose or albumin concentrations or urine specific gravity were observed in workers exposed to tellurium and its oxides (Steinberg et al. 1942).

4.4. Other Relevant Information

Although the data on the toxicity of tellurium are sparse, they suggest that it is a neurotoxicant. Somnolence was reported following accidental acute exposure to tellurium hexafluoride (Blackadder and Manderson 1975) and in workers exposed to tellurium and its oxides (Steinberg et al. 1942). Additionally, demyelination of peripheral nerves and morphologic alterations in the brain were observed in developing animals (Duckett 1970; Lampert et al. 1970; Malczewska-Toth 2012).

4.4.1. Species Variability

The study by Kimmerle (1960) suggests that the acute toxicity of tellurium hexafluoride is similar between rabbits, guinea pigs, rats, and mice. Mice might be slightly more sensitive, as they died from exposure to tellurium hexafluoride that the other species survived (5 ppm for 1 h). Although this sensitivity would be expected for a corrosive and severely irritating chemical, a major limitation of the study is that it tested a small number of animals.

4.4.2. Susceptible Populations

The effects of tellurium hexafluoride might be exacerbated in individuals with impaired pulmonary function due to the chemical's irritant properties (NIOSH 1978). However, no information on the susceptibility of such individuals to tellurium hexafluoride relative to normal individuals was found.

Mortality data on tellurium hexafluoride suggest a steep concentration-response curve, which implies little intraspecies variability. Mortality was 100% in rabbits, guinea pigs, rats, and mice exposed to tellurium hexafluoride at 5 ppm or higher for 4 h. All mice exposed at 5 ppm for 1 h died, but survived exposure at 1 ppm for 1 h (Kimmerle 1960).

4.4.3. Concentration-Exposure Duration Relationship

The 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). In the absence of data on tellurium hexafluoride from which to derive 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).

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues relevant to tellurium hexafluoride were found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to developing AEGL-1 values for tellurium hexafluoride were identified.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to developing AEGL-1 values for tellurium hexafluoride were identified.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended for tellurium hexafluoride because of insufficient data. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 concentrations are without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to developing AEGL-2 values for tellurium hexafluoride were identified.

6.2. Animal Data Relevant to AEGL-2

Kimmerle (1960) exposed one rabbit, one guinea pig, two male white rats, and four male white mice per group to tellurium hexafluoride at 1 or 5 ppm for 1 or 4 h. Hyperpnea was observed in all animals exposed at 1 ppm for 1 h. At 5 ppm for 1 h, severe damage in the respiratory organs of the animals was found; the rabbit, guinea pigs, and rats survived the exposure but recovered very slowly. All of the mice died. Exposure to tellurium hexafluoride at 1 ppm for 4 h caused respiratory dysfunction in all animals.

In a study of the chemical tellurium, morphologic alterations of the brain were found in the fetuses of rats fed tellurium (Duckett 1970). Extrapolating the results of this study to derive AEGL values for tellurium hexafluoride was considered inappropriate.

6.3. Derivation of AEGL-2 Values

Data on tellurium hexafluoride are not consistent with AEGL-2 severity effects. Animals experienced hyperpnea after exposure to tellurium hexafluoride at 1 ppm for 1 h. The standing operating procedures for determining AEGL values specifies that AEGL-2 values for chemicals with steep concentrations-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Lethality data on tellurium hexafluoride demonstrates a steep-concentration response curve. All rabbits, guinea pigs, rats, and mice exposed at concentrations of 5, 10, 25, 50, or 100 ppm for 4 h died, and all mice exposed at 5 ppm for 1 h died. All animals exposed at 1 ppm for 1 or 4 h survived (Kimmerle 1960).

AEGL-2 values for tellurium hexafluoride are presented in Table 5-4, and the calculations are presented in Appendix A.

TABLE 5-4 AEGL-2 Values for Tellurium Hexafluoride

10 min	30 min	1 h	4 h	8 h
0.0097 ppm (0.096 mg/m^3)	0.0067 ppm (0.066 mg/m^3)	0.0053 ppm (0.052 mg/m^3)	0.0033 ppm (0.033 mg/m^3)	0.0017 ppm (0.017 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to deriving AEGL-3 values for tellurium hexafluoride were identified.

7.2. Animal Data Relevant to AEGL-3

Mortality was 100% in rabbits, guinea pigs, rats, and mice exposed for 4 h to tellurium hexafluoride at 5 ppm or higher (Kimmerle 1960); at 1 ppm, the animals survived but experienced pulmonary edema and respiratory dysfunction. For a 1-h exposure, all mice exposed at 5 ppm died; the other species survived that exposure and recovered slowly from severe damage to the respiratory organs. Animals exposed at 1 ppm for 1 h experienced hyperpnea.

7.3. Derivation of AEGL-3 Values

The highest concentration of tellurium hexafluoride causing no mortality in rabbits, guinea pigs, rats, and mice (1 ppm for 4 h) was used to derive AEGL-3 values (Kimmerle 1960). An interspecies uncertainty factor of 3 was applied because the four test species appeared to similarly sensitive to the acute effects of tellurium hexafluoride (Kimmerle 1960); however, that assessment is based on a small number of test animals (one to four per group). An intraspecies uncertainty factor of 3 was applied because tellurium hexafluoride is highly irritating and corrosive, and much of its toxicity is likely caused by a direct chemical effect on the tissue; that type of portal-of-entry effect is not expected to vary greatly among individuals. The steep concentration-response curve for tellurium hexafluoride implies little intraindividual variability. A modifying factor of 10 also was applied to account for the sparse database on tellurium hexafluoride and for the potential effects of tellurium. Thus, the total adjustment was 100. The concentration-exposure 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 tellurium hexafluoride were inadequate for determining an empirical value for n, so default values of n = 3 when extrapolating to shorter durations (10, 30, and 60 min) and n = 1 when extrapolating to longer durations (8 h) were used. The AEGL-3 values for tellurium hexafluoride are presented in Table 5-5, and the calculations are presented in Appendix A.

TABLE 5-5 AEGL-3 Values for Tellurium Hexafluoride

10 min	30 min	1 h	4 h	8 h
0.029 ppm (0.28 mg/m^3)	0.020 ppm (0.20 mg/m^3)	0.016 ppm (0.16 mg/m^3)	0.010 ppm (0.10 mg/m^3)	0.0050 ppm (0.049 mg/m^3)

Because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min AEGL value, the 30-min AEGL-3 value is typically adopted as the 10-min value. For tellurium hexafluoride, however, this approach was not used and the 10-min value was calculated from the Kimmerle (1960) data. Several laboratory animal species were exposed to tellurium hexafluoride at 1 ppm for 1 h, and only hyperpnea, a nonlife-threatening end point, was observed in those animals.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for tellurium hexafluoride are presented in Table 5-6. AEGL-1 values are not recommended because of insufficient data. Data were also insufficient for deriving AEGL-2 values. Because tellurium hexafluoride has been shown to have a steep concentration-response curve, AEGL-2 values were estimated by dividing the AEGL-3 values by 3. AEGL-3 values were based on the highest concentration of tellurium hexafluoride causing no deaths in laboratory animals (Kimmerle 1960).

8.2. Other Standards and Guidelines

AEGL values for tellurium hexafluoride are compared with other guidelines and standards for this chemical in Table 5-7. The time-weighted average exposure concentration for workers is 0.02 ppm (29 CFR Part 1910 [2006]; NIOSH 2011; ACGIH 2013). The American Conference of Governmental Industrial Hygienists established a threshold limit value – time-weighted average of 0.02 ppm (measured as tellurium) on the basis that tellurium hexafluoride is approximately 2.5 times as acutely toxic as ozone and to protect against respiratory effects (ACGIH 2001). The immediately dangerous to life or health value (NIOSH 1994) is based on the acute inhalation toxicity data from the studies by Kimmerle (1960).

TABLE 5-6 AEGL Values for Tellurium Hexafluoride

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)	0.0097 ppm (0.096 mg/m^3)	0.0067 ppm (0.066 mg/m^3)	0.0053 ppm (0.052 mg/m^3)	0.0033 ppm (0.033 mg/m^3)	0.0017 ppm (0.017 mg/m^3)
AEGL-3 (lethal)	0.029 ppm (0.28 mg/m^3)	0.020 ppm (0.20 mg/m^3)	0.016 ppm (0.16 mg/m^3)	0.010 ppm (0.10 mg/m^3)	0.0050 ppm (0.049 mg/m^3)

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

TABLE 5-7 Standards and Guidelines for Tellurium Hexafluoride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.0097 ppm	0.0067 ppm	0.0053 ppm	0.0033 ppm	0.0017 ppm
AEGL-3	0.029 ppm	0.020 ppm	0.016 ppm	0.010 ppm	0.0050 ppm
IDLH (NIOSH)[a]	–	1 ppm	–	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	0.02 ppm as Te
PEL-TWA (OSHA)[c]	–	–	–	–	0.02 ppm as Te
REL-TWA (NIOSH)[d]	–	–	–	–	0.02 ppm as Te
MAC (The Netherlands)[e]	–	–	–	–	0.02 ppm

[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]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2013) 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.
[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29 CFR Part 1910 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/wk.
[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.
[e]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration – peak category]) (Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands (MSZW 2007) is defined analogous to the to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research

No quantitative human data on tellurium hexafluoride are available, and only a few animal studies have been conducted. A single study of the acute toxicity of tellurium hexafluoride in rabbits, guinea pigs, rats, and mice is available (Kimmerle 1960), but only a few animals were tested and some potentially relevant end points were not evaluated. For example, humans acutely or repeatedly exposed to tellurium compounds frequently report somnolence, but the Kimmerle (1960) study did not examine that end point. A few studies of the related chemicals tellurium and tellurium pulveratum (Duckett 1970; Lampert et al. 1970; Malczewska-Toth 2012) found morphologic alterations in fetuses and demyelination in weanling rats after oral exposure; it is unknown whether reproductive and developmental toxicity would also occur following acute inhala-

tion exposure to tellurium hexafluoride. In the moist respiratory tract, tellurium hexafluoride slowly breaks down into hydrogen fluoride and tellurium; however, the contribution of the hydrolysis products to tellurium hexafluoride toxicity is unknown. No mechanistic data are available for other potential end points, including neurotoxicity and reproductive and developmental toxicity. Additional acute inhalation toxicity studies would help strengthen the basis of the AEGL values.

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APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values

AEGL-1 values are not recommended because of insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Derivation of AEGL-2 Values

Key study:	Kimmerle, G. 1960. Comparative studies on the inhalation toxicity of sulfur-, selenium-, and tellurium-hexafluoride [in German]. Arch. Toxikol. 18:140-144.
Toxicity end points:	Data were inadequate for deriving AEGL-2 values. However, the standing operating procedures for determining AEGL values specifies that AEGL-2 values for chemicals with steep concentrations-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Lethality data on tellurium hexafluoride demonstrates a steep-concentration response curve. All rabbits, guinea pigs, rats, and mice exposed at concentrations of 5, 10, 25, 50, or 100 ppm for 4 h died, and all mice exposed at 5 ppm for 1 h died. All animals exposed at 1 ppm for 1 or 4 h survived (Kimmerle 1960).
Calculations:	
10-min AEGL-2:	0.029 ppm ÷ 3 = 0.0097 ppm
30-min AEGL-2:	0.020 ppm ÷ 3 = 0.0067 ppm
1-h AEGL-2:	0.016 ppm÷ 3 = 0.0053 ppm
4-h AEGL-2:	0.010 ppm÷ 3 = 0.0033 ppm
8-h AEGL-2:	0.005 ppm÷ 3 = 0.0017 ppm

Derivation of AEGL-3 Values

Key studies:	Kimmerle, G. 1960. Comparative studies on the inhalation toxicity of sulfur-, selenium-, and tellurium-hexafluoride [in German]. Arch. Toxikol. 18:140-144.

Toxicity end point:	Highest concentration causing no mortality in the guinea pig, rabbit, rat, and mouse (1 ppm for 4 h)
Uncertainty factors:	Interspecies: 3, because the guinea pig, rabbit, rat, and mouse appear to be similarly sensitive to the acute effects of tellurium hexafluoride; however, this assessment is based on a small number of animals. Intraspecies: 3, because tellurium hexafluoride is highly irritating and corrosive and much of the toxicity is likely caused by a direct chemical effect on the tissues; that type of portal-of-entry effect is not expected to vary greatly among individuals.
Modifying factor:	10, because of the sparse database on tellurium hexafluoride and the potential effects of tellurium
Time scaling:	$C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001) 1 ppm ÷ 100 (total uncertainty factor) = 0.01 ppm $(0.01 \text{ ppm})^3 \times 240 \text{ min} = 0.00024 \text{ ppm-min}$ $(0.01 \text{ ppm})^1 \times 240 \text{ min} = 2.4 \text{ ppm-min}$
10-min AEGL-3:	$C^3 \times 10 \text{ min} = 0.00024 \text{ ppm-min}$ C = 0.029 ppm
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 0.00024 \text{ ppm-min}$ C = 0.020 ppm
1-h AEGL-3:	$C^3 \times 30 \text{ min} = 0.00024 \text{ ppm-min}$ C = 0.016 ppm
4-h AEGL-3:	$C^1 \times 240 \text{ min} = 2.4 \text{ ppm-min}$ C = 0.010 ppm
8-h AEGL-3:	$C^1 \times 480 \text{ min} = 2.4 \text{ ppm-min}$ C = 0.0050 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR TELLURIUM HEXAFLUORIDE

Derivation Summary

AEGL-1 VALUES

No AEGL-1 values were derived for tellurium hexafluoride because of insufficient data. Absence of AEGL-1 values does not imply that exposure below the AEGL concentrations are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.0097 ppm	0.0067 ppm	0.0053 ppm	0.0033 ppm	0.0017 ppm

Data adequacy: Data on tellurium hexafluoride were inadequate for deriving AEGL-2 values. However, the standing operating procedures for determining AEGL values specify that AEGL-2 values for chemicals with steep concentrations-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Lethality data on tellurium hexafluoride indicate a steep-concentration response curve. All rabbits, guinea pigs, rats, and mice exposed at concentrations of 5, 10, 25, 50, or 100 ppm for 4 h died, and all mice exposed at 5 ppm for 1 h died. All animals exposed at 1 ppm for 1 or 4 h survived (Kimmerle 1960).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.029 ppm	0.020 ppm	0.016 ppm	0.010 ppm	0.0050 ppm

Key reference: Kimmerle, G. 1960. Comparative study of the inhalation toxicity of sulfur, selenium, and tellurium hexafluorides [in German] Arch. Toxikol. 18:140-144.

Test species/Strain/Number: Unspecified strains of rabbits (n = 1), guinea pigs (n = 1), rats (n = 2), and mice (n = 4)

Exposure route/Concentrations/Durations: Inhalation ; 1, 5, 10, 25, 50, 100 ppm for 4 h

Effects:
1 ppm: respiratory dysfunction, pulmonary edema
5 ppm: death after 4-24 h
10 ppm: death after 100-140 min
25 ppm: death after 60-110 min
50 ppm: death after 45-70 min
100 ppm: death after 10-30 min

End point/Concentration/Rationale: Highest concentration causing no mortality (1 ppm for 4 h)

(Continued)

AEGL-3 VALUES Continued

Uncertainty factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, because the guinea pig, rabbit, rat, and mouse appear to be similarly sensitive to the acute effects of tellurium hexafluoride; however, this assessment is based on a small number of animals. Intraspecies: 3, because tellurium hexafluoride is highly irritating and corrosive and much of the toxicity is likely caused by a direct chemical effect on the tissues; that type of portal-of-entry effect is not expected to vary greatly among individuals.
Modifying factor: 10, because of the sparse database on tellurium hexafluoride and to account for potential effects of tellurium
Animal-to-human dosimetric adjustment: None
Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001).
Data adequacy: Tellurium hexafluoride has a sparse database consisting of one lethality study in laboratory animals.

APPENDIX C

CATEGORY PLOT FOR TELLURIUM HEXAFLUORIDE

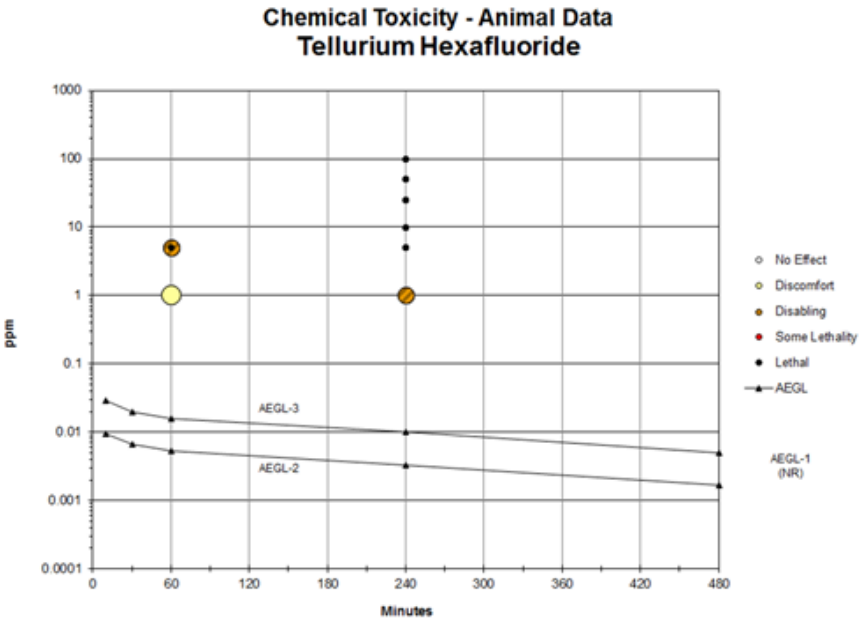

FIGURE C-1 Category plot of toxicity data and AEGL values for tellurium hexafluoride.

TABLE D-1 Data Used in the Category Plot for Tellurium Hexafluoride

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-2				0.0097	10	AEGL	
AEGL-2				0.0067	30	AEGL	
AEGL-2				0.0053	60	AEGL	
AEGL-2				0.0033	240	AEGL	
AEGL-2				0.0017	480	AEGL	
AEGL-3				0.029	10	AEGL	
AEGL-3				0.020	30	AEGL	
AEGL-3				0.016	60	AEGL	
AEGL-3				0.010	240	AEGL	
AEGL-3				0.0050	480	AEGL	
Kimmerle 1960	Rabbit	M	1	1	240	2	Respiratory dysfunction, pulmonary edema
Kimmerle 1960	Rabbit	M	1	5	240	3	Death after 8 h
Kimmerle 1960	Rabbit	M	1	10	240	3	Death after 140 min
Kimmerle 1960	Rabbit	M	1	25	240	3	Death after 80 min
Kimmerle 1960	Rabbit	M	1	50	240	3	Death after 60 min
Kimmerle 1960	Rabbit	M	1	100	240	3	Death after 15 min
Kimmerle 1960	Rabbit	M	1	1	60	1	Hyperpnea
Kimmerle 1960	Rabbit	M	1	5	60	2	Severe damage to respiratory organs
Kimmerle 1960	Guinea pig	M	1	1	240	2	Respiratory dysfunction, pulmonary edema
Kimmerle 1960	Guinea pig	M	1	5	240	3	Death after 8 h
Kimmerle 1960	Guinea pig	M	1	10	240	3	Death after 140 min

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
Kimmerle 1960	Guinea pig	M	1	25	240	3	Death after 80 min
Kimmerle 1960	Guinea pig	M	1	50	240	3	Death after 60 min
Kimmerle 1960	Guinea pig	M	1	100	240	3	Death after 15 min
Kimmerle 1960	Guinea pig	M	1	1	60	1	Hyperpnea
Kimmerle 1960	Guinea pig	M	1	5	60	2	Severe damage to respiratory organs
Kimmerle 1960	Rat	M	1	1	240	2	Respiratory dysfunction, pulmonary edema
Kimmerle 1960	Rat	M	1	5	240	3	Death after 8 h
Kimmerle 1960	Rat	M	1	10	240	3	Death after 140 min
Kimmerle 1960	Rat	M	1	25	240	3	Death after 80 min
Kimmerle 1960	Rat	M	1	50	240	3	Death after 60 min
Kimmerle 1960	Rat	M	1	100	240	3	Death after 15 min
Kimmerle 1960	Rat	M	1	1	60	1	Hyperpnea
Kimmerle 1960	Rat	M	1	5	60	2	Severe damage to respiratory organs
Kimmerle 1960	Mouse	M	1	1	240	2	Respiratory dysfunction, pulmonary edema
Kimmerle 1960	Mouse	M	1	5	240	3	Death after 8 h
Kimmerle 1960	Mouse	M	1	10	240	3	Death after 140 min
Kimmerle 1960	Mouse	M	1	25	240	3	Death after 80 min
Kimmerle 1960	Mouse	M	1	50	240	3	Death after 60 min
Kimmerle 1960	Mouse	M	1	100	240	3	Death abate 15 min
Kimmerle 1960	Mouse	M	1	1	60	1	Hyperpnea
Kimmerle 1960	Mouse	M	1	5	60	3	Death between 24-36 h

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethality.

6

Tetrafluoroethylene[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), Heather Carlson-Lynch (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

Tetrafluoroethylene is a colorless, odorless, and highly flammable gas. It is insoluble in water and in most organic solvents. Fluorocarbons as a class exhibit high chemical stability which might be responsible for their lack of biologic action in contrast with chlorocarbons. The primary end use of tetrafluoroethylene is for polymerization to produce Teflon®. Recent production data were not available.

No human data on exposure to tetrafluoroethylene were available. However, numerous laboratory studies of rodents exposed for durations up to 6 h were sufficient to derive AEGL values for tetrafluoroethylene. At lethal and near-lethal concentrations, animals died of pulmonary congestion. At nonlethal concentrations, tetrafluoroethylene was nephrotoxic in rodents. Nephrotoxicity is related to metabolism to a reactive intermediate via the hepatic glutathione *S*-transferases (GST). In the kidney, the glutathione conjugate is metabolized to the cysteine *S*-conjugate and is then bioactivated via renal ß-lyase to a reactive thiol. The resulting renal cell necrosis and regeneration is thought to be responsible for renal neoplasms in rats following chronic exposure. In all cases where recovery was evaluated, surviving animals had evidence of recovery from renal lesions.

The AEGL-1 values for tetrafluoroethylene are based on a no-observed-adverse-effect level (NOAEL) for reversible renal lesions observed in rats and

mice following a 6-h exposure to tetrafluoroethylene at 1,200 ppm (Keller et al. 2000). Renal toxicity results from a metabolite formed after a series of metabolic steps. No data comparing the toxicokinetics of tetrafluoroethylene in humans and rodents are available, but data from related compounds suggest that species differences in metabolism could be important. Thus, a default interspecies uncertainty factor of 10 was applied. A default intraspecies uncertainty factor of 10 also was applied because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds might modify susceptibility. The total uncertainty factor was 100. Time scaling was performed using the equation $C^n \times t = k$. Data on tetrafluoroethylene were insufficient for determining an empirical value for the exponent n, so default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 6-h point-of-departure to a 10-min value, the 10-min AEGL-1 value was set equal to the 30-min AEGL-1 value.

The AEGL-2 values for tetrafluoroethylene are based on reversible renal effects observed in rat studies. Dilley et al. (1974) found reversible renal lesions following a 30-min exposure to tetrafluoroethylene at 3,500 ppm, and Odum and Green (1984) found minor changes in urinary clinical chemistry parameters following a 6-h exposure at 3,000 ppm (increases in urinary glucose and enzyme activity were not statistically significant). These effects meet the definition of the AEGL-2. A 4-h exposure at 3,700 ppm resulted in renal tubule necrosis (Haskell Laboratory 1977), an irreversible effect (exceeds the definition of the AEGL-2). Although histopathologic examinations were not performed after a 6-h exposure at 4,000 ppm (Odum and Green 1984), it is likely that irreversible effects also took place. At 6,000 ppm for 6 h, renal-cell necrosis was observed.

The 6-h exposure to tetrafluoroethylene at 3,000 ppm (Odum and Green 1984) was considered a NOAEL for irreversible effects, and was used as the point-of-departure for calculating AEGL-2 values. An interspecies uncertainty factor of 10 and an intraspecies uncertainty factor of 10 were applied for the same reasons described of the AEGL-1 values. Time scaling was also performed in the same manner as for the AEGL-1 values. Because of the uncertainty associated with time scaling a 6-h point-of-departure to a 10-min value, the 10-min AEGL-2 value was set equal to the 30-min AEGL-2 value.

AEGL-3 values for tetrafluoroethylene are based on a study in Syrian hamster. Mortality rates in hamsters exposed to tetrafluoroethylene at 10,200, 20,700, 25,000, 30,000, 40,100, or 78,700 ppm for 4 h were 0, 0, 10, 70, 100, and 100%, respectively. Those data were used to calculate a 4-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 20,822 ppm, which was used as the point-of-departure. The choice of that concentration is supported by the highest nonlethal concentration of 20,000 ppm in a 4-h study with rats (Haskell Laboratory 1959). An interspecies uncertainty factor of 10 and an intraspecies uncertainty factor of 10 were applied for the same reasons described of the AEGL-1 values. Time scaling was also performed

in the same manner as for the AEGL-1 values. Because of the uncertainty associated with time scaling a 4-h point-of-departure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value. The AEGL values for tetrafluoroethylene are presented in Table 6-1.

Tetrafluoroethylene has carcinogenic potential, but neither inhalation nor oral carcinogenicity slope factors are available. An assessment based on the carcinogenic potential of tetrafluoroethylene indicates that AEGL values for a theoretical excess lifetime cancer risk of 10^{-4} would be lower than the AEGL values developed on the basis of noncancer end points (see Appendix C). The tumorigenic response to tetrafluoroethylene is the result of repeated long-term exposure causing repetitive tissue damage. Because AEGLs are applicable to rare events or a single once-in-a-lifetime exposure and because of the uncertainty in assessing excess cancer risk following a single acute exposure of 8 h or less, the acute toxicity values were used to set AEGL levels.

1. INTRODUCTION

Tetrafluoroethylene is a colorless and odorless gas. It is insoluble in water and in most organic solvents. Tetrafluoroethylene is extremely flammable and unstable; therefore, it is shipped in cylinders that contain stabilizers (Haskell Laboratory 1959; Matheson 1980). It is easily ignited by heat, sparks, or flames (HSDB 2012). The lower explosive limit for tetrafluoroethylene is 100,000 ppm (DuPont 1988). Additional chemical and physical properties of tetrafluoroethylene are presented in Table 6-2.

Fluorocarbons as a class exhibit high chemical stability. The C-F bond is stable because of the short inter-atomic distance between the atoms (Clayton 1967). The bond affinity may explain the lack of biologic action of fluorocarbons in contrast with chlorocarbons.

TABLE 6-1 AEGL Values for Tetrafluoroethylene

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	27 ppm (110 mg/m^3)	27 ppm (110 mg/m^3)	22 ppm (89 mg/m^3)	14 ppm (56 mg/m^3)	9.0 ppm (37 mg/m^3)	NOAEL for reversible renal lesions in rats and mice (Keller et al. 2000).
AEGL-2 (disabling)	69 ppm (280 mg/m^3)	69 ppm (280 mg/m^3)	55 ppm (220 mg/m^3)	34 ppm (140 mg/m^3)	23 ppm (92 mg/m^3)	NOAEL for renal necrosis in rats (Odum and Green 1984).
AEGL-3 (lethal)	420 ppm (1,700 mg/m^3)	420 ppm (1,700 mg/m^3)	330 ppm (1,400 mg/m^3)	210 ppm (850 mg/m^3)	100 ppm (430 mg/m^3)	4-h $BMCL_{05}$ for lethality in hamsters (Haskell Laboratory 1980).

[a]Tetrafluoroethylene has no distinctive odor.

TABLE 6-2 Chemical and Physical Properties of Tetrafluoroethylene

Parameter	Value	References
Synonyms	Ethene, tetrafluoro; perfluoroethylene; FC-1114; Fluoroplast 4; TFE monomer	HSDB 2012
CAS registry no.	116-14-3	HSDB 2012
Chemical formula	$CF_2 = CF_2$	Matheson 1980
Molecular weight	100.02	HSDB 2012
Physical state	Colorless gas	HSDB 2012
Melting point	-131.15°C	HSDB 2012
Boiling point	-75.9°C	HSDB 2012
Solubility in water	159 mg/L at 25°C	HSDB 2012
Density/specific gravity	1.519 g/cm^3 at -76°C	HSDB 2012
Vapor density (air = 1)	3.87	HSDB 2012
Vapor pressure	2.45×10^4 mm Hg at 25°C	HSDB 2012
Flammability limits	14-43% Lower explosive limit: 100,000 ppm	Matheson 1980; DuPont 1988
Conversion factors	1 ppm = 4.09 mg/m^3 1 mg/m^3 = 0.244 ppm	AIHA 2004

Tetrafluoroethylene is manufactured in enclosed systems in a four-step process involving the production of hydrogen fluoride and chloroform from calcium difluoride, hydrogen sulfide, methane, and chlorine (Gangal 2004). Hydrogen fluoride and chloroform are subsequently reacted in the presence of antimony trifluoride to form chlorodifluoromethane. Chlorodifluoromethane is pyrolysed at 590-900°C to produce a yield of 95% tetrafluoroethylene. When tetrafluoroethylene is shipped, Terpene B (0.4%) or d-limonene is added to inhibit polymerization (Gangal 2004).

US production of tetrafluoroethylene was between 50 and 100 million pounds in 2006 (HSDB 2012). Approximately two-thirds of tetrafluoroethylene produced is polymerized to produce Teflon®. Tetrafluoroethylene is dimerized to produce octafluorocyclobutane propellant for food product aerosols. It is also used in refrigerants, foam blowing agents, solvents, fluoropolymers, and sterilant gas (HSDB 2012).

The toxicity of tetrafluoroethylene has been reviewed by Clayton (1967), Kennedy (1990), ACGIH (2001), ECETOC (2003), and AIHA (2004). A number of unpublished studies conducted for the DuPont Chemical Company were available for review. Studies have also been conducted on the toxicity of pyrolysis products of tetrafluoroethylene resins. Because numerous combustion products, including hydrogen fluoride, are formed when resins are burned, the results of the pyrolysis studies are not discussed in this document.

2. HUMAN TOXICITY DATA

No human studies on the toxicity of tetrafluoroethylene were found. Monitoring data from several plants that use tetrafluoroethylene in closed systems indicate that 7-h time-weighted-average concentrations are 6.5 ppm or lower (FIG 1982). Alarms in the plants are set at 20 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data from studies of animals exposed to tetrafluoroethylene by inhalation are summarized in Table 6-3 and briefly discussed below.

3.1.1. Rats

Groups of four male CD rats were exposed by inhalation to tetrafluoroethylene at nominal concentrations of 10,000, 20,000, 40,000, 80,000, or 800,000 ppm for 4 h (Haskell Laboratory1959). The method used to generate the test atmosphere was not described. Tetrafluoroethylene was scrubbed with H_2SO_4 to remove the Terpene B inhibitor. The mortality rate was 0/4 at 10,000 ppm, 0/4 at 20,000 ppm, 2/4 at 40,000 ppm, 4/4 at 80,000 ppm, and 4/4 at 800,000 ppm. Rats in the 800,000-ppm group died after 2.75 h of exposure. The LC_{50} (lethal concentration, 50% lethality) was approximately 40,000 ppm. Clinical signs included labored breathing during exposure (all concentrations), weight loss (≥40,000 ppm), inactivity, dark eyes, prostration, and convulsions. Gross necropsy revealed hepatic injury (≥40,000 ppm), renal damage (all concentrations), and pulmonary congestion and edema (≥80,000 ppm).

Sakharova and Tolgskaya (1977) exposed groups of male and female rats (number and strain not specified) to tetrafluoroethylene at unspecified concentrations for 4 h. LC_{50} values are presented in Table 6-3. At necropsy, lesions were observed in the liver, kidneys, and brain. Renal lesions included degeneration and necrosis of the convoluted tubules. No further details were reported by the investigators.

A study by Zhemerdei (1958) is not included in Table 6-3 because of insufficient details (Kennedy 1990). The study reported 100% mortality in rats exposed to tetrafluoroethylene at 25,000 ppm for 2 h. The lowest concentration causing mortality in rabbits was 40,000 ppm; the exposure duration was not specified.

3.1.2. Mice

Sakharova and Tolgskaya (1977) exposed male and female mice (strain not specified) to unspecified concentrations of tetrafluoroethylene for 4 h. The LC_{50} value was 35,000 ppm. Details of the study were not provided.

TABLE 6-3 Acute Lethality in Laboratory Animals Exposed to Tetrafluoroethylene

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	10,000	4 h	0% mortality	Haskell Laboratory 1959
	20,000		0% mortality	
	40,000		50% mortality	
	80,000		100% mortality	
	800,000		100% mortality	
Rat	31,000-32,000	4 h	LC_{50}	Sakharova and Tolgskaya 1977
Mouse	35,000	4 h	LC_{50}	Sakharova and Tolgskaya 1977
Guinea pig	28,000	4 h	LC_{50}	Sakharova and Tolgskaya 1977
Hamster	10,200	4 h	0% mortality	Haskell Laboratory 1980
	20,700	4 h	0% mortality	
	25,000	4 h	10% mortality	
	30,000	4 h	70% mortality	
	40,100	4 h	100% mortality	
	78,800	4 h	100% mortality	
	28,500	4 h	LC_{50} (calculated)	

3.1.3. Guinea Pigs

Sakharova and Tolgskaya (1977) exposed male and female guinea pigs (strain not specified) to unspecified concentrations of tetrafluoroethylene for 4 h. The LC_{50} value was 28,000 ppm. Details of the study were not provided.

3.1.4. Hamsters

Groups of 10 male Syrian hamsters were exposed by inhalation to tetrafluoroethylene at analytically-determined concentrations of 0, 10,200, 20,700, 25,000, 30,000, 40,100, or 78,700 ppm for 4 h (Haskell Laboratory 1980). All animals exposed at the two lowest concentrations survived the 14-day observation period. Mortality rates in the 25,000- and 30,000-ppm groups were 1/10 and 7/10, respectively; the deaths occurred over 1-10 days. All animals in the 40,100- and 78,700-ppm groups died. The calculated LC_{50} value was 28,500 ppm (95% confidence interval: 26,400-31,500 ppm). Clinical signs included salivation and lethargy at 40,100 ppm and clear discharge from the nose and reduced response to sound at 78,700 ppm. No obvious clinical signs were observed at concentrations of 30,000 ppm or lower. Following exposure, moderate weight loss, defined as 6-15 g/day, occurred at concentrations of 20,700 ppm and higher. Following exposure at 10,200 ppm, weight loss was slight for one day after exposure. No histopathologic examinations were performed.

3.2. Nonlethal Toxicity

All acute toxicity studies reporting nonlethal effects from tetrafluoroethylene were conducted with rats. Results from those studies are summarized in Table 6-4. Relevant information is also available from a repeat-exposure study that described effects in rats after the first exposure to tetrafluoroethylene (Keller et al. 2000; see Section 3.3).

A group of 15 adult male Sprague-Dawley rats were exposed by inhalation to tetrafluoroethylene at 3,500 ppm for 30 min (Dilley et al. 1974). Ten of the animals were maintained for 2 weeks for metabolism studies. Five of the rats were serially killed for pathologic examination. No deaths were reported. Exposure to tetrafluoroethylene produced an increase in urinary fluoride, potassium, and creatinine and diuresis. Gross examination of the tissues performed 3-4 days after exposure revealed marked hyperemia of the renal medulla and a pale band in the cortex near the corticomedullary junction. Small ischemic-appearing areas were found occasionally in the mid-cortical area. These grossly-observed renal changes were nearly absent after 2 weeks. No lesions were observed microscopically.

A group of 10 CD male rats was exposed to tetrafluoroethylene at an analytically-determined concentration of 3,700 ppm for 4 h (Haskell Laboratory 1977). Renal damage (degeneration of the epithelium of the tubules) was found immediately after exposure. After a 14-day recovery period, fibrosis of the renal tubules was present. There were no clinical signs during exposure.

Groups of four male Wistar-derived rats were exposed to tetrafluoroethylene at 0, 1,000, 2,000, 3,000, 4,000, or 6,000 ppm for 6 h (Odum and Green 1984). The method used to generate the test atmosphere was not described. Rats were killed 24 h after the start of the exposure. No deaths were reported. Kidneys from the control and 6,000-ppm groups were examined microscopically.

TABLE 6-4 Non-lethal Toxicity in Rats Exposed to Tetrafluoroethylene

Concentration (ppm)	Exposure Duration	Effect	Reference
3,500	30 min	Reversible renal changes.	Dilley et al. 1974
3,700	4 h	Renal tubule fibrosis.	Haskell Laboratory 1977
1,000	6 h	No effects.	Odum and Green 1984
2,000	6 h	NOAEL for renal effects.	
3,000	6 h	Increases in urinary glucose and enzyme activity were small, variable, and not statistically significant.	
4,000	6 h	Increases in urinary glucose and enzyme activity were statistically significant.	
6,000	6 h	Renal necrosis.	

Marked damage to the proximal tubule of the kidneys was found in treated animals. The damage was characterized by renal tubular necrosis involving the pars recta of the proximal tubule and by calcified intratubular deposits in the medulla. Evaluations of the 24-h urine collections found high concentrations of urinary glucose and marked increases in alkaline phosphatase and γ-glutamyltranspeptidase activity. Damage to the kidneys in the lower dose groups was assessed by urinary glucose and enzyme activity levels. Using those two parameters, the 6-h exposure at 2,000 ppm was a no-observed-effect level and the 6-h exposure at 3,000 ppm resulted in small and variable (but not statistically significant) effects on urinary glucose and alkaline phosphatase and γ-glutamyltranspeptidase activity. At 4,000 ppm, increases in urinary glucose and enzyme activity were statistically significant.

3.3. Repeat-Exposure Studies

3.3.1. Dogs

Two dogs were exposed to tetrafluoroethylene at 1,000 ppm for 4 h/day, 5 days/week for a total of 25 exposures (Haskell Laboratory 1946; Table 6-5). The blood pressure of one dog dropped as exposures continued, but the second dog did not show any significant trend in blood pressure measurements. No abnormal heart sounds were detected. Both dogs gained weight during the exposure period. The dogs were subsequently exposed to tetrafluoroethylene at 4,000 ppm for 4 h on one day and for 6 h on the following day. Both tolerated the exposures "quite well." In another experiment, a dog was exposed to several concentrations of tetrafluoroethylene a few weeks apart. A 4-h exposure at 500 ppm had no effect on blood pressure, but a "fairly marked" drop in blood pressure was reported in the dog after being exposed at 1,000 ppm or higher. A fourth dog was exposed twice to tetrafluoroethylene at 2,000 ppm for 1 h. Blood pressure was unaffected after the first exposure, but dropped "fairly sharply" 4 h after the second exposure. Blood pressure measurements were not provided. The third and fourth dogs were killed 1 month after the last exposure, and no gross or microscopic lesions of the heart, lungs, spleen, liver, kidneys, or adrenal glands were found.

3.3.2. Rats

Groups of 10 male CD rats were exposed to tetrafluoroethylene at 0, 100, 500, 1,000, or 2,500 ppm (analytic concentrations of 0, 101, 500, 991, or 2,490 ppm) for 6 h/day, 5 days/week for 2 weeks (Haskell Laboratory 1981). Half of the animals were evaluated at the end of exposure and the other half after a 14-day recovery period. No clinical signs of toxicity were observed during treatment. Increases in renal and hepatic weight, reductions in serum alkaline phosphatase and glutamic pyruvic transaminase activity, and renal lesions were observed. Renal

TABLE 6-5 Repeat-Exposure Studies of Tetrafluoroethylene

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Dog, unspecified breed	1,000	4 h/d, 5 d/wk, 25 exposures	Few observations; drop in blood pressure in 1/2 dogs.	Haskell Laboratory 1946
	4,000	4 and 6 h	Tolerated "quite well."	
CD rat, 10 males/group	0, 100, 500, 990, 2,490	5 h/d, 5 d/wk, 2 wk	No clinical signs at any concentration. No effect at 990 ppm. Reversible changes in clinical chemistry parameters and reversible renal lesions at 2,490 ppm.	Haskell Laboratory 1981
CD rat, 10 males/group	0, 1,100, 3,510	4 h/d, 5 d/wk, 2 wk; killed 0 and 14 d postexposure	Reversible renal lesions at 1,100 ppm. Incomplete recovery of renal lesions at 3,510 ppm.	Haskell Laboratory 1977
F344 rat, 25 females/group	0, 31, 300, 600, 1,200	6 h/d, 9 exposures over 12 d	No cell proliferation in the kidneys after one exposure at any concentration. Increase in renal cell proliferation in 1,200-ppm group after test day 5 (recovery by test day 12); microscopic renal lesions at 600 and 1,200 ppm; renal function unaffected; liver and spleen unaffected.	Keller et al. 2000
F344/N rat, 5/sex/group	0, 312, 621, 1,250, 2,500, 4,990	6 h/d, 5 d/wk, 12 exposures over 16 d	Reduced weight gain in males and females at 5,000 ppm. Increased renal weight in all males and in females exposed at ≥2,500 ppm. Renal tubule degeneration in males and females exposed at ≥625 ppm. No renal lesions at 312 ppm.	NTP 1997
CD rat, 15/sex/group	0, 203, 606, 1,990	6 h/d, 5 d/wk, 90 d	Body and organ weight changes at 1,990 ppm; tubular nephrosis at 606 and 1,990 ppm. No-effect level was 200 ppm.	Haskell Laboratory 1982

CD rat, 50/sex/group	0, 312, 625, 1,250, 2,500, 5,000	5 h/d, 5 d/wk, 90 d	No clinical signs; reduced body weight and weight gain at 5,000 ppm; increased renal and hepatic weight at ≥625 ppm in one or both sexes; anemia; renal tubule degeneration in males at ≥625 ppm and in females at ≥2,500 ppm.	NTP 1997
$B6C3F_1$ mouse, 25 females/group	0, 31, 300, 600, 1,200	6 h/d, 9 exposures over 12 d	No cell proliferation in the kidneys after one exposure at any concentration; increase in renal cell proliferation in 600- and 1,200-ppm groups after test day 5 (recovery by test day 12); microscopic renal lesions at 1,200 ppm; no decreased renal function; liver and spleen unaffected.	Keller et al. 2000
$B6C3F_1$ mouse, 5/sex/group	0, 312, 622, 1,260, 2,500, 4,990	6 h/d, 5 d/wk, 12 exposures over 16 d	No clinical findings; no effect on body weight or weight gain; some organ weight differences in females at ≥2,500 ppm; renal tubule epithelial cell karyomegaly in males at ≥1,250 ppm and in females at ≥ 2,500 ppm; no renal lesions at 312 or 612 ppm.	NTP 1997
$B6C3F_1$ mouse, 48/sex/group	0, 312, 625, 1,250, 2,500, 5,000	5 h/d, 5 d/wk, 90 d	No clinical signs; no effect on body weight and weight gain; no effect on organ weight; anemia in males at ≥2,500 ppm and in females at 5,000 ppm; polyuria at ≥2,500 ppm (both sexes); renal epithelial cell karyomegaly at ≥1,250 ppm in both sexes; no renal lesions at 312 or 625 ppm.	NTP 1997
Syrian hamster, 10 males/group	0, 101, 500, 991, 2,490	6 h/d, 5 d/wk, for 2 wk	No clinical signs; no renal lesions; testicular atrophy in 2,490-ppm group only after 14-day post-exposure period.	Haskell Laboratory 1981
Syrian hamster, 15/sex/group	0, 203, 606, 1,990	6 h/d, 5 d/wk, 90 d	No effect on body weight or body weight gain; increased renal weight in females at 1,990 ppm; testicular atrophy in males at 1,990 ppm.	Haskell Laboratory 1982

lesions were found in the 2,490-ppm group only, and consisted of swelling of the tubular epithelial cells, dilation of the tubular lumen, and sparse cellular degeneration in the juxtamedullary cortex. These effects were not apparent after the 14-day recovery period. Urinary fluoride concentrations remained elevated after 14 days.

Groups of 10 male CD rats were exposed to tetrafluoroethylene at analytically-determined concentrations of 1,100 or 3,510 ppm for 4 h/day, 5 days/week for 2 weeks (Haskell Laboratory1977). At the higher concentration, mild to moderate body weight loss (unspecified) during the test phase was reported, but recovery took place during the 2-week postexposure period. Five rats from each group were killed immediately after exposure, and examinations revealed degenerative changes in the kidneys. Following the 2-week postexposure period, recovery from renal lesions was almost complete in the 1,100-ppm group and was incomplete in the 3,510-ppm group.

Groups of 25 female F344 rats were exposed to tetrafluoroethylene at 0, 31, 300, 600, or 1,200 ppm for 6 h/day over 12 days (Keller et al. 2000). The regimen involved 5 days of consecutive exposure, 2 days of no exposures, and 4 days of consecutive exposure. Groups of rats were killed after the first, fifth, and ninth exposure for evaluation of cell proliferation in the liver, kidneys, and spleen. The organs also were examined microscopically after the ninth exposure. No biologically significant effects on cell proliferation were found after a single exposure. On test day 5, a statistically and biologically significant increase in cell proliferation (indicated by cell labeling following infusion with 5-bromo-3′deoxyuridine) in the kidney was observed in rats exposed at 1,200 ppm (ninefold increase over the control value). The effect on cell proliferation was transient as cell proliferation was absent or less evident by test day 12. After the ninth exposure, minimal lesions of the kidney were observed microscopically in rats exposed at 600 and 1,200 ppm. Cell proliferation and lesions were accompanied by increases in renal weight. No microscopic changes were found in the liver or spleen.

Groups of five male and five female F344/N rats were exposed to tetrafluoroethylene at analytically-determined concentrations of 0, 312, 621, 1,250, 2,500, or 4,990 ppm for 6 h/day, 5 days/week for 12 exposures over a 16-day period (NTP 1997). Animals were observed twice daily for clinical signs and weighed weekly. Blood samples were taken before the animals were killed to evaluate hematology parameters. Animals were killed the day after the last exposure. Selected organs were weighed and selected tissues were examined microscopically. All rats survived to the end of the study. In contrast with respective control groups, the final mean body weights of males and females exposed at 4,990 ppm were statistically significantly reduced by 14% ($p < 0.01$) and 10% ($p < 0.05$), respectively. No treatment-related differences in hematology parameters were found. Relative to body weight, hepatic weight was significantly greater in treated males than in the controls, but appeared unaffected in the treated females. Absolute and relative renal weight was increased in all treated males and in females exposed at 2,500 and 4,990 ppm. Renal tubule degeneration was observed in all males exposed at 625 ppm or higher and in all females exposed

at 1,250 ppm or higher. Renal tubule degeneration was observed in three of five females exposed at 625 ppm. The severity of the lesion increased with concentration.

Groups of 15 male and 15 female CD rats were exposed by inhalation to tetrafluoroethylene at 0, 203, 606, or 1,990 ppm, 6 h/day, 5 days/week for up to 90 days (Haskell Laboratory 1982). Five rats per sex were killed after 45 days for interim evaluation. Decreased final body weight and body weight gain were observed in both sexes exposed at 1,990 ppm. Absolute and relative hepatic weights were significantly increased in both sexes at the end of the study, as were the absolute and relative renal weights of male rats in the 1,990-ppm group. Urinary fluoride concentrations increased in a concentration-dependent manner. At both the interim and final evaluations, tubular nephrosis was seen in male and female rats exposed at 606 and 1,990 ppm; frequency increased with exposure duration.

Before performing a chronic toxicity and carcinogenicity study, NTP (1997) conducted a 13-week range-finding study with F344/N rats (see Section 3.8 for details). At the end of the study, minimal to mild lesions of the kidney were observed in 10/10 male rats exposed at 650 ppm or higher and in 9/10 and10/10 female rats exposed at 2,500 and 5,000 ppm, respectively.

3.3.3. Mice

Groups of 25 female $B6C3F_1$ mice were exposed to tetrafluoroethylene at 0, 31, 300, 600, or 1,200 ppm for 6 h/day over 12 days (Keller et al. 2000). The regimen involved 5 consecutive days of exposure, 2 days of no exposure, and 4 consecutive days of exposure. Groups of mice were killed after the first, fifth, and ninth exposure for evaluation of cell proliferation in the liver, kidneys, and spleen. The organs were examined microscopically after the ninth exposure. No biologically significant effects on cell proliferation were observed after a single exposure. On test day 5, a statistically and biologically significant increase in cell proliferation (indicated by cell labeling) in the kidney was observed in mice exposed at 600 and 1,200 ppm. The effect on cell proliferation was transient and was absent or less evident by test day 12. After the ninth exposure, minimal lesions of the kidney were observed microscopically in mice exposed at 1,200 ppm. Cell proliferation and lesions were accompanied by increases in renal weight. No microscopic changes were found in the liver or spleen.

Groups of five male and five female $B6C3F_1$ mice were exposed to tetrafluoroethylene at analytically determined concentrations of 0, 312, 622, 1,260, 2,500, or 4,990 ppm for 6 h/day, 5 days/week, for 12 exposures over a 16-day period (NTP 1997). Observations were the same as in the study with rats (Section 3.3.2). All mice survived to the end of the study. The final mean body weights of males and females were similar among the respective control and exposure groups. No treatment-related differences in hematology parameters were found. The absolute and relative hepatic weights of females in the 5,000-

ppm group were significantly greater (25% and 15%, respectively) than those of controls. The absolute hepatic weight of females in the 2,500-ppm group was also increased by 19% relative to that of the controls. The absolute renal weight of females in the 5,000-ppm group was increased by 17% relative to that of the controls. Renal tubule karyomegaly (enlargement of the cell nucleus) was observed in male mice exposed at 1,250 ppm or higher and in female mice exposed to 2,500 ppm or higher. One of five females in the 1,250-ppm group was also affected. The severity of this lesion increased with concentration.

3.3.4. Hamsters

Groups of 10 male Syrian hamsters were exposed to tetrafluoroethylene at analytically-determined concentrations of 0, 101, 500, 991, or 2,490 ppm for 6 h/day, 5 days/week for 2 weeks (Haskell Laboratory 1981). No clinical signs of toxicity were observed during exposure. The three deaths that occurred during the exposures were not concentration-related and could not be attributed tetrafluoroethylene. Urinary fluoride concentrations were elevated immediately following the exposures (991- and 2,490-ppm groups), but not after the 14-day recovery period. After the recovery period, serum albumin was reduced in the three highest exposure groups. No changes in renal or hepatic weights or histopathologic lesions of the kidney were observed in hamsters killed immediately after exposure or after 14 days. Testicular atrophy was observed in the 2,490-ppm group only after the 14-day recovery period. This effect was not significant at lower concentrations.

Groups of 15 male and 15 female Syrian hamsters were exposed to tetrafluoroethylene at 0, 203, 606, or 1,990 ppm, 6 h/day, 5 days/week for up to 90 days (Haskell Laboratory 1982). Six hamsters per sex were killed after 45 days for interim evaluation. At the end of the study, body weight and body-weight gain appeared unaffected. Organ weights were variable; a clear increase in organ weights over control values was found only for renal weight in females exposed at 1,990 ppm. Urinary fluoride concentrations appeared to increase in a concentration-dependent manner, but reduced urine production complicated collection of samples. Considerable variation was seen in testes weight and maturity among the exposed groups, making the evaluation of testicular atrophy problematic. However, atrophic changes were observed in the testes, regardless of maturity, of hamsters exposed at 1,990 ppm at both the interim evaluation (4/6 test animals vs 1/6 controls) and final evaluation (5/9 test animals vs 1/9 controls).

3.4. Neurotoxicity

Rats exposed to tetrafluoroethylene for 5-10 min at concentrations of 500,000-700,000 ppm showed no signs of narcosis Haskell Laboratory (1946). Because this study used concentrations anticipated to be in the lethal range, the results cannot be used to estimate risk to humans. Rats exposed to lethal and

near-lethal concentrations showed no typical signs of narcosis (Sakharova and Tolgskaya 1977).

3.5. Cardiac Sensitization

In a standard cardiac sensitization test, none of four dogs and neither of two cats were sensitized by after being exposed to tetrafluoroethylene at 250,000-500,000 ppm for durations of 5-15 min (Burgison et al. 1955). Because this study used concentrations anticipated to be in the lethal range, the results cannot be used to estimate risk to humans.

3.6. Developmental and Reproductive Toxicity

No information on the developmental or reproductive effects of tetrafluoroethylene in animals was found.

3.7. Genotoxicity

Tetrafluoroethylene vapor was evaluated for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation by S9 rat liver homogenate (Haskell Laboratory 1986a). Test atmospheres (headspace concentrations) were 0.5-5% (4,900-48,200 ppm). Tetrafluoroethylene was not mutagenic in any test strain. Cysteine conjugates of tetrafluoroethylene were not mutagenic in the *S. typhimurium* assay, with or without metabolic activation by S9 rat kidney homogenate (Green and Odum 1985). The structurally-similar chemical tetrachloroethylene was not mutagenic in the *S. typhimurium* test and failed to induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells (summarized in NTP 1997). Tetrachloroethylene produced equivocal results in the mouse lymphoma mutagenicity assay.

Tetrafluoroethylene did not induce gene mutations at the HPRT locus in cultured Chinese hamster ovary cells (Haskell Laboratory 1986b). Exposures were for 5 h with metabolic activation and for 18 h without metabolic activation. Nominal atmospheric concentrations were 20-100%. A retest also produced negative results (Stahl 1988).

Tetrafluoroethylene was tested for clastogenic (chromosome-damaging) activity in vitro in Chinese hamster ovary cells, with and without metabolic activation (Vlachos 1987). Measured atmospheres of tetrafluoroethylene were 30.4-100%. No significant increases in structural chromosomal aberrations were seen after exposure for 5 h without metabolic activation or for 2 h with metabolic activation.

In a 13-week study, male and female B6C3F_1 mice were exposed to tetrafluoroethylene at 0, 312, 625, 1,250, 2,500, or 5,000 ppm for 6 h/day, 5 days/week

(Sheldon et al. 1988; NTP 1997). No increase in the frequency of micronucleated erythrocytes in peripheral blood samples was found.

Hong et al. (1998) investigated the frequency of H- and K-*ras* mutations in hepatocellular tumors taken from $B6C3F_1$ mice in the NTP (1997) carcinogenicity study (see Section 3.8). The frequency of H-*ras* codon 61 mutations in all treatment groups was lower than in the study controls and lower than in historical controls. K-*ras* mutations at several codons and H-*ras* mutations at codon 117 were not detected in hepatocellular neoplasms. The investigators concluded that hepatocellular neoplasms caused by tetrafluoroethylene are developed via a *ras*-independent pathway.

3.8. Chronic Toxicity and Carcinogenicity

The National Toxicology Program (NTP 1997) evaluated the inhalation carcinogenicity of tetrafluoroethylene in F344/N rats and $B6C3F_1$ mice of both sexes. NTP concluded that there was *clear evidence of carcinogenic activity* of tetrafluoroethylene in male F344/N rats based on increased incidences of renal tubule neoplasms and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of renal tubule neoplasms, liver hemangiosarcomas, hepatocellular neoplasms, and mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* in male and female $B6C3F_1$ mice based on increased incidences of hepatic hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas. On the basis of these studies, the International Agency for Research on Cancer (IARC 1999) concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of tetrafluoroethylene. Tetrafluoroethylene is *possibly carcinogenic to humans (Group 2B)*. IARC reported that no epidemiologic data relevant to carcinogenicity in humans were available. The American Conference of Governmental Industrial Hygienists recommended a rating of *A3 – confirmed animal carcinogen with unknown relevance to humans* (ACGIH 2001, 2013). NTP's chronic toxicity and carcinogenicity studies are described below.

Groups of 60 male F344/N rats were exposed to tetrafluoroethylene at 156, 312, or 625 ppm and groups of 60 female F344/N rats were exposed at 312, 625, or 1,250 ppm for 6 h/day, 5 days/week for 104 weeks (NTP 1997). Groups of 10 animals per sex were evaluated after 15 months for organ weight changes and clinical pathology. Survival was reduced in males in the 625-ppm group (2%) compared with the control group (34%). Survival in females of all treatment groups was reduced (30-36%) compared with controls (56%), but the reductions were not concentration-related. The incidence of cataracts in females exposed at 1,250 ppm was greater than in the controls. The primary nonneoplastic tissue lesions were hyperplasia and degeneration of the renal tubules in some or all of the treated males and females and were concentration related. Correlated with these lesions were increased incidences of renal tubule neoplasms (primarily adenomas) in males exposed at 625 ppm and females exposed

at 1,250 ppm. In males, incidences of renal tubule adenoma or carcinoma were 3/50 in controls, 5/50 at 156 ppm, 9/50 at 312 ppm, and 13/50 at 625 ppm. The incidences in females were 0/50 in controls, 3/50 at 312 ppm, 3/50 at 625 ppm, and 10/50 at 1,250 ppm. Liver neoplasms (hemangiosarcomas and hepatocellular adenomas or carcinomas) were increased in both sexes of all treatment groups. Mononuclear cell leukemia was increased in a concentration-related manner in females of all the treatment groups.

In the same study (NTP 1997), groups of 58 male and 58 female $B6C3F_1$ mice were exposed to tetrafluoroethylene at 0, 312, 625, or 1,250 ppm for 95-96 weeks. Groups of 10 animals per sex were evaluated after 15 months for organ weight changes. There were no treatment-related clinical findings. Survival rates were severely reduced in both sexes of treated mice. Reduced survival was attributed to exposure-related hepatic neoplasms. Body weight was generally unaffected until the end of the study. Non-neoplastic effects included hepatic angiectasis (both sexes in all treatment groups), hematopoietic cell proliferation of the liver (females in all treatment groups), renal tubule dilation (males in all treatment groups), renal tubule karyomegaly (males in the 625- and 1,250-ppm groups and females in the 1,250-ppm group), hematopoietic cell proliferation of the spleen (both sexes in all treatment groups). Concentration-related neoplastic lesions in both sexes included hepatocellular adenomas or carcinomas, hepatic hemangiomas and hemangiosarcomas, and histiocytic sarcomas. The incidences of hepatocellular adenoma or carcinoma in male mice were 26/48 in controls, 34/48 at 312 ppm, 39/48 at 625 ppm, and 35/48 at 1,250 ppm. The incidences in female mice were 17/48, 33/48, 29/47, and 28/47, respectively. Renal neoplasms were not increased in treated mice.

3.9. Summary

Acute lethal concentrations (approximate 4-h LC_{50} values) of tetrafluoroethylene were 28,000-40,000 ppm (Sakharova and Tolgskaya 1977; Haskell Laboratory 1959; 1980). The highest nonlethal values were 20,000 ppm for the rat (Haskell Laboratory 1959) and 20,700 ppm for the hamster (Haskell Laboratory 1980). No significant interspecies differences in acute lethality were found. Pulmonary congestion was observed at lethal or near-lethal concentrations. At lower concentrations, the kidney was the primary target of tetrafluoroethylene; no effects were observed in the liver. Renal damage was characterized by high concentrations of urinary glucose and increases in the activity of several enzymes. A 6-h exposure to tetrafluoroethylene at 2,000 ppm was a NOAEL for renal effects and a 6-h exposure at 3,000 ppm produced minimal effects (Odum and Green 1984). A 6-h exposure at 6,000 ppm resulted in frank renal effects. A 4-h exposure at 3,700 ppm produced pathologic changes in the kidney that were not completely reversible (Haskell Laboratory 1977). A single 6-h exposure to tetrafluoroethylene at 1,200 ppm was a no-effect concentration for renal lesions as evidenced by a lack of cell proliferation (Keller et al. 2000).

In repeat-exposure studies, renal lesions were reversible in rats exposed to tetrafluoroethylene at 2,490 ppm for 5 h/day for 2 weeks (Haskell Laboratory 1981) but were not completely reversible at 3,510 ppm for 4 h/day for 2 weeks (Haskell Laboratory 1977). Renal lesions were also reversible in rats exposed at 1,200 ppm for 6 h/day for 12 days (Keller et al. 2000).

Tetrafluoroethylene was not mutagenic or genotoxic in several assays. Chronic exposure resulted in carcinogenic effects in rats and mice of both sexes (NTP 1997). The kidneys, liver, and blood were targets of carcinogenicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No human studies on the absorption, distribution, metabolism, or excretion of tetrafluoroethylene were found.

Absorption of tetrafluoroethylene by the lungs is low, reflecting low solubility. Ding et al. (1980) exposed rabbits to tetrafluoroethylene at 1,000 ppm for 60 min via a face mask. Alveolar absorption was 6.8%.

The nephrotoxic effects of tetrafluoroethylene are attributable to a reactive metabolite formed in the kidney after a series of preliminary metabolic steps. The metabolism of tetrafluoroethylene was reviewed by Schnellmann (2008). CYP-450 oxidation, a pathway common to many haloalkenes, does not appear to be involved in the metabolism of tetrafluoroethylene. Tetrafluoroethylene is metabolized in the liver by glutathione (GSH)–*S*-transferases (GST) to *S*-(1,1,2,2-tetrafluoroethyl)glutathione. In the small intestine and bile, the GSH conjugate is degraded by the loss of glutamic acid and glycine to the cysteine *S*-conjugate. Mercapturic acid conjugates may also be formed in the small intestines. The cysteine *S*-conjugate is reabsorbed into the blood and transported to renal cells. Metabolism of the GSH conjugate to the cysteine conjugate, via the activity of γ-glutamyl transferase and a dipeptidase, may also occur in the kidney (Schnellmann 2008). Finally, the cysteine conjugate is metabolized by renal β–lyase to ammonia, pyruvate, and a reactive thiol that is capable of binding to macromolecules (Schnellmann 2008). This activation pathway has been observed in vitro in human proximal tubular renal cells (Chen et al. 1990).

Some tetrafluoroethylene may be metabolized further as evidenced by increased excretion of urinary fluoride after single or repeat exposure (Dilley et al. 1974; Kennedy 1990; Keller et al. 2000). Only a small amount of F^- ion was detected in the urine of rats exposed to tetrafluoroethylene at 3,700 ppm for 30 min (Dilley et al. 1974).

4.2. Mechanism of Toxicity

At high concentrations, death from tetrafluoroethylene may be due to pulmonary congestion. Nephrotoxic effects of tetrafluoroethylene are attributa-

ble to a reactive metabolite in the kidney; there is a correlation between the covalent binding of the reactive thiol of the cysteine conjugate with renal proteins and nephrotoxicity (reviewed by Schnellmann 2001). In addition, administration of the cysteine *S*-conjugate of tetrafluoroethylene (precursor of the reactive metabolite) by intraperitoneal injection (Lock and Ishmael 1998) or oral gavage (Keller et al. 2000) resulted in nephrotoxicity similar to that observed with the parent compound in inhalation studies. In animal models, the toxicity of tetrafluoroethylene is characterized by proximal tubular necrosis and is observed clinically as increases in urinary glucose and protein, cellular enzyme activity, and blood urea nitrogen. The mitochondrion might be the ultimate target of the reactive metabolite, as decreases in cellular respiration are observed before cell death. No hepatocellular toxicity was observed from tetrafluoroethylene by any route of administration.

The mechanism of action that leads to tumor formation may be renal tubule damage via the processing of the glutathione conjugate. Cell necrosis followed by chronic regeneration of the epithelium in the kidney (increased cell proliferation) results in greater opportunity for error in DNA synthesis and mutation (Cohen and Ellwein 1990; Cohen 1998).

4.3. Structure-Activity Relationships

C-F containing compounds are generally less toxic than their chlorinated counterparts because of the stability of the C-F bond (Odum and Green 1984). For three fluoroethylenes—dichlorodifluoroethylene, chlorotrifluoroethylene, and tetrafluoroethylene—toxicity decreased as the number of fluorine atoms increased (Sakharova and Tolgskaya 1977). Using rat 4-h LC_{50} values for comparison, dichlorodifluoroethylene and chlorotrifluoroethylene were approximately 240 and 18 times more toxic, respectively, than tetrafluoroethylene.

For halogenated methanes, ethanes, and ethylenes, fluorine substituents decrease tissue solubility (Gargas et al. 1988). Therefore, uptake of fluoroethylenes is lower than that of chloroethylenes.

4.4. Other Relevant Information

4.4.1. Species Variability

Species differences in toxicity among rats, mice, and guinea pigs exposed to tetrafluoroethylene were not obvious (see Tables 6-3, 6-4, and 6-5).

Data comparing uptake or metabolism of tetrafluoroethylene by rodents and humans are not available. However, data on compounds with similar metabolic pathways suggest species differences in metabolism that may also apply to tetrafluoroethylene. For example, physiologically-based pharmacokinetic modeling of the related compound tetrachloroethylene (which, unlike tetrafluoroethylene, is also metabolized via CYP450 oxidation) suggested that blood concen-

trations of the parent compound were comparable in mice, rats, and humans exposed via inhalation (Chiu and Ginsberg 2011). However, predictions of the oxidative- and conjugative-metabolite concentrations were very different among the three species, with lower predicted concentrations of oxidative metabolites and higher (10-fold or greater) predicted concentrations of conjugative metabolites in humans (Chiu and Ginsberg 2011). Although the prediction of higher concentrations of conjugative metabolites in humans had significant uncertainty associated with it (because of sparse data) and might be partly explained by lower relative oxidative metabolism (a pathway not relevant to tetrafluoroethylene), the model results suggest the possibility of important interspecies differences in metabolism that might affect susceptibility to tetrafluoroethylene.

4.4.2. Susceptible Populations

No data on the variability in human susceptibility to tetrafluoroethylene toxicity was available. As noted above, metabolism of tetrafluoroethylene to the penultimate nephrotoxic metabolite involves several steps and enzymes, including glutathione-*S*-transferase, γ-glutamyl transferase, and the cysteine-*S*-conjugate β-lyase. Polymorphisms in any of these enzymes may increase or decrease susceptibility to tetrafluoroethylene nephrotoxicity by an unknown amount. For example, Moore et al. (2010) observed differential risks of renal cancer (believed to occur through a similar metabolic activation pathway) in people occupationally exposed to the related compound trichloroethylene, depending on their GST and cysteine β-lyase genotypes. In addition, sex-dependent differences may exist in the human metabolism of tetrafluoroethylene (although obvious sex differences in tetrafluoroethylene toxicity in laboratory animals were not discernable; see Table 6-5). In vitro studies using rodent renal cells suggest sex differences in the metabolism of the related compound tetrachloroethylene to its nephrotoxic metabolite (occurring through a similar metabolic pathway) (Lash et al. 2002).

4.4.3. Concentration-Exposure Duration Relationship

Tetrafluoroethylene has low solubility in biologic fluids. Although blood concentrations of halogenated hydrocarbons reach equilibrium rapidly and do not increase greatly with exposure duration (NRC 1996; Bakshi 1998), metabolism and resulting damage to the kidneys may have a time component. No empirical data on the relationship between concentration and exposure duration for a single end point were found. When such data are lacking, time scaling is performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). 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).

4.4.4. Concurrent-Exposure Issues

No concurrent exposure issues relevant to tetrafluoroethylene were found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human studies on tetrafluoroethylene were available for deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Only a few acute studies of tetrafluoroethylene assessed effects that meet the definition of the AEGL-1. After a single 6-h exposure of female rats or mice to tetrafluoroethylene at 1,200 ppm, there was no increase in cell proliferation in the kidney (the target organ) (Keller et al. 2000). Cell proliferation would indicate cell necrosis followed by replacement. Groups of four male Wistar-derived rats had no damage to the kidneys immediately following a 6-h exposure to tetrafluoroethylene at 2,000 ppm, and minimal damage was found after a 6-h exposure at 3,000 ppm (Odum and Green 1984). Damage was assessed via clinical chemistry parameters.

5.3. Derivation of AEGL-1 Values

The AEGL-1 values for tetrafluoroethylene are based on a NOAEL of 1,200 ppm for reversible renal lesions in rodents. Renal cell proliferation was not observed in rats or mice following a 6-h exposure to tetrafluoroethylene at 1,200 ppm in the well-conducted study by Keller et al. (2000). Renal toxicity from tetrafluoroethylene results from a metabolite formed after a series of metabolic steps. No data comparing the toxicokinetics of tetrafluoroethylene in humans and rodents are available, but data from related compounds suggest that species differences in metabolism may be important (see Section 4.4.1). Thus, a default interspecies uncertainty factor of 10 was applied. A default intraspecies uncertainty factor of 10 also was applied because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence of polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds that might modify susceptibility (see Section 4.4.2). The total uncertainty factor was 100. Time scaling was performed using the equation $C^n \times t = k$. Data on tetrafluoroethylene were insufficient for determining an empirical value for the exponent n, so default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time-scaling a 6-h

point-of-departure to a 10-min value, the 10-min AEGL-1 value was set equal to the 30-min AEGL-1 value. Table 6-6 presents the AEGL-1 values for tetrafluoroethylene. The calculations are presented in Appendix A, and a category plot of the AEGL values in relation to the toxicity data on tetrafluoroethylene is presented in Appendix B.

Repeat-exposure studies showing minimal effects from tetrafluoroethylene support the AEGL-1 values. When the exposures in the key study with rats and mice (Keller et al. 2000) were repeated for up to 12 days, cell proliferation occurred in both species after five exposures at 1,200 ppm, but was less evident or absent after nine exposures. Nine exposures over 12 days produced occasional degeneration or necrosis of renal tubule epithelial cells at 600 ppm (rats) and 1,200 ppm (rats and mice). The investigators considered the renal effects to be minimal in rats at both 600 and 1,200 ppm. In rats and hamsters exposed to tetrafluoroethylene at concentrations of 203, 606, or 1,990 ppm over 90 days, 203 ppm was the no-observed adverse effect concentration for both species (Haskell Laboratory 1982). No renal lesions were found in rats or mice exposed to tetrafluoroethylene at 312 ppm for 90 days (NTP 1997).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human studies on tetrafluoroethylene were available for deriving AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Several acute exposure studies of tetrafluoroethylene reported effects meeting the definition of the AEGL-2. Rats exposed at 3,500 ppm for 30 min exhibited gross changes of the kidney, but no renal lesions were observed microscopically 14 days after exposure (Dilley et al. 1974). Exposure at a slightly higher concentration of 3,700 ppm for a longer duration (4 h) resulted in irreversible effects (Haskell Laboratory 1977). In that study, fibrosis of the renal tubules was observed after a 14-day recovery period. Although microscopic examinations of the kidneys were not performed, clinical chemistry values indicated that a 6-h exposure of rats to tetrafluoroethylene at 2,000 ppm was a no-effect concentration for renal damage (Odum and Green 1984). A concentration of 3,000 ppm can be considered the threshold for renal lesions as clinical chemistry

TABLE 6-6 AEGL-1 Values for Tetrafluoroethylene

10 min	30 min	1 h	4 h	8 h
27 ppm (110 mg/m^3)	27 ppm (110 mg/m^3)	22 ppm (89 mg/m^3)	14 ppm (56 mg/m^3)	9 ppm (37 mg/m^3)

parameters were only slightly affected (effects on urinary glucose concentrations and activity of several enzymes were small, variable, and not statistically significant). At 4,000 ppm, increases in urinary glucose and enzyme activity were statistically significant and, on the basis of the Haskell Laboratory (1977) study, renal fibrosis likely resulted.

6.3. Derivation of AEGL-2 Values

Renal effects in two acute exposure studies of tetrafluoroethylene in rats meet the definition of the AEGL-2. Reversible renal lesions were reported by Dilley et al. (1974) and changes in clinical chemistry parameters indicating reversible renal effects were found by Odum and Green (1984). The 30-min exposure of rats to tetrafluoroethylene at 3,500 ppm (Dilley et al. 1974) was not used because time scaling would result in concentrations incompatible with the AEGL-1 values. A 6-h exposure of rats to tetrafluoroethylene at 3,000 ppm resulted in increases in urinary glucose concentrations and enzyme activity levels that were small, variable, and not statistically significant (Odum and Green 1984). Thus, 3,000 ppm was considered a NOAEL for irreversible renal lesions and was used as the point-of-departure for calculating the AEGL-2 values.

For the same reasons described above for the AEGL-1 values, a total uncertainty factor of 100 was applied; a factor of 10 for interspecies differences and a factor of 10 for intraspecies differences. Time scaling was performed as described for the AEGL-1 values. Because of the uncertainty associated with time-scaling a 6-h point-of-departure to a 10-min value, the 10-min AEGL-2 value was set equal to the 30-min AEGL-2 value. Table 6-7 presents the AEGL-2 values for tetrafluoroethylene. The calculations are presented in Appendix A, and a category plot of the AEGL values in relation to the toxicity data on tetrafluoroethylene is presented in Appendix B.

Repeat-exposure studies of tetrafluoroethylene that result in reversible effects support the choice of the key study. In the rat, renal lesions consisting of cellular degeneration in the juxtamedullary cortex were reversible after exposure to tetrafluoroethylene at 2,490 ppm for 6 h/day, 5 days/week for 2 weeks (Haskell Laboratory 1981). No pathologic lesions were found in the kidneys of dogs exposed at 4,000 ppm for 4 h on one day and 6 h on the following day (Haskell Laboratory 1946). Although the study is old, the results are consistent with other studies.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human studies on tetrafluoroethylene were available for deriving AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Lethality studies of tetrafluoroethylene in several species are available. The highest 4-h nonlethal concentrations were 20,000 ppm in the rat (Haskell Laboratory 1959) and 20,700 ppm in the hamster (Haskell Laboratory 1980). In the latter study, groups of 10 male Syrian hamsters were exposed by inhalation to tetrafluoroethylene at concentrations (analytically determined) of 0, 10,200, 20,700, 25,000, 30,000, 40,100, or 78,700 ppm for 4 h (Haskell Laboratory 1980). All animals in the two lowest exposure groups survived the 14-day observation period. Mortality rates in the 25,000, and 30,000 ppm groups were 1/10 and 7/10, respectively; the deaths occurred over 1-10 days. All animals in the 40,100- and 78,700-ppm groups died. The calculated LC_{50} was 28,500 ppm (95% confidence interval: 26,400-31,500 ppm). Clinical signs included salivation and lethargy at 40,100 ppm and clear discharge from the nose and reduced response to sound at 78,700 ppm. No obvious clinical signs were observed at concentrations of 30,000 ppm or lower.

7.3. Derivation of AEGL-3 Values

Using data from the 4-h study of tetrafluoroethylene in hamsters (Haskell Laboratory 1980), a benchmark concentration approach was used to derive AEGL-3 values (NRC 2001). The 4-h $BMCL_{05}$ of 20,822 ppm was used as the point-of-departure. The choice of $BMCL_{05}$ is supported by the highest 4-h nonlethal concentration of 20,000 ppm in a study of rats (Haskell Laboratory 1959).

For the same reasons described above for the AEGL-1 values, a total uncertainty factor of 100 was applied; a factor of 10 for interspecies differences and a factor of 10 for intraspecies differences. Time scaling was performed as described for the AEGL-1 values. Because of the uncertainty associated with time-scaling a 4-h point-of-departure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value. Table 6-8 presents the AEGL-3 values for tetrafluoroethylene. The calculations are presented in Appendix A, and a category plot of the AEGL values in relation to the toxicity data on tetrafluoroethylene is presented in Appendix B.

TABLE 6-7 AEGL-2 Values for Tetrafluoroethylene

10 min	30 min	1 h	4 h	8 h
69 ppm (280 mg/m^3)	69 ppm (280 mg/m^3)	55 ppm (220 mg/m^3)	34 ppm (140 mg/m^3)	23 ppm (92 mg/m^3)

TABLE 6-8 AEGL-3 Values for Tetrafluoroethylene

10 min	30 min	1 h	4 h	8 h
420 ppm (1,700 mg/m^3)	420 ppm (1,700 mg/m^3)	330 ppm (1,400 mg/m^3)	210 ppm (850 mg/m^3)	100 ppm (430 mg/m^3)

The 4- and 8-h values of 210 ppm and 100 ppm, respectively, are supported by repeat-dose studies in which dogs tolerated tetrafluoroethylene at 4,000 ppm for 4 or 6 h for 2 days without overt toxicity (Haskell Laboratory 1946) and rats tolerated 2,490 ppm for 5 h/day for 2 weeks (Haskell Laboratory 1981), 3,510 ppm for 4 h/day for 2 weeks, and 4,990 ppm for 6 h/day, 5 days/week for up to 90 days (NTP 1997) without overt signs of toxicity.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for tetrafluoroethylene are presented in Table 6-9. Laboratory studies in rodents were sufficient to derive AEGL values for most of the exposure durations. At lethal and near-lethal concentrations, animals died of pulmonary congestion. At nonlethal concentrations, tetrafluoroethylene was nephrotoxic in rodents. Nephrotoxicity is related to metabolism of tetrafluoroethylene to a reactive intermediate via the hepatic glutathione *S*-transferases. In the kidney, the glutathione conjugate is metabolized to the cysteine *S*-conjugate and then bioactivated via renal ß-lyase to a reactive metabolite. The resulting renal cell necrosis and regeneration is thought to be responsible for renal neoplasms in rats after chronic exposure to tetrafluoroethylene.

The AEGL-1 values are based on a NOAEL for reversible renal effects in rats and mice, and the AEGL-2 values are based on renal necrosis in the rat. AEGL-3 values are based on an estimated lethality threshold in hamsters, which is supported by a study in rats.

An estimation of AEGL values based on the carcinogenic potential of tetrafluoroethylene resulting from a single, short-term exposure was made (see Appendix C). The assessment shows that AEGLs derived on the basis of carcinogenic effects would be lower than all of the AEGL values. The carcinogenicity assessment was based on a long-term exposure study showing tumorigenic responses in several organs and tissues of rats and mice. The tumorigenic response in the kidneys is believed to be secondary to repeated tissue injury. In other organs, no precancerous lesions were observed in either species following subchronic exposure. With the exception of lesions of the kidneys, there are no acute exposure data demonstrating a tumorigenic response. Because of the uncertainties inherent in assessing excess cancer risk following a single acute exposure at durations of 8 h or less, the acute toxicity values were used to set the AEGL values.

8.2. Other Standards and Guidelines

Tetrafluoroethylene has been cleared by the U.S. Food and Drug Administration under 21 CFR 177.1550 for food-related uses in perfluorocarbon resins made by polymerizing or copolymerizing the chemical.

Current standards and guidelines for tetrafluoroethylene are presented in Table 6-10. The emergency response planning guidelines (ERPGs) of the American Industrial Hygiene Association (AIHA 2004, 2013) are higher than the AEGL values. The ERPG-1 value is based on urinary fluoride concentrations (an indicator of mild transient health effects) in rats and hamsters exposed to tetrafluoroethylene at 200 ppm for 90 days (Haskell Laboratory 1982). For the ERPG-2, a 30-min exposure to tetrafluoroethylene at 3,500 ppm that resulted in grossly observable changes in the kidneys of rats (Dilley et al. 1974) and the repeated daily 6-h exposure at 500 ppm ((Haskell Laboratory 1981) were considered. The potential for cancer from a single 1-h exposure was considered small. The 1-h ERPG-3 was based on a judgment that the LC_{50} values for most species were around 30,000 ppm for a 4-h exposure and no adverse clinical effects were found in rats or mice exposed at 5,000 ppm for 6 h/day, 5 days/week for 13 weeks (NTP 1997).

The American Conference of Governmental Industrial Hygienists established a threshold limit value for tetrafluoroethylene of 2 ppm (ACGIH 2001, 2013) to minimize the potential for renal toxicity and hepatic and renal cancers based on a 2-year bioassay in rodents (NTP 1997).

TABLE 6-9 AEGL Values for Tetrafluoroethylene

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	27 ppm	27 ppm	22 ppm	14 ppm	9.0 ppm
AEGL-2 (disabling)	69 ppm	69 ppm	55 ppm	34 ppm	23 ppm
AEGL-3 (lethal)	420 ppm	420 ppm	330 ppm	210 ppm	100 ppm

TABLE 6-10 Standards and Guidelines for Tetrafluoroethylene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	27 ppm	27 ppm	22 ppm	14 ppm	9.0 ppm
AEGL-2	69 ppm	69 ppm	55 ppm	34 ppm	23 ppm
AEGL-3	420 ppm	420 ppm	330 ppm	210 ppm	100 ppm
ERPG-1 (AIHA)[a]	–	–	200 ppm	–	–
ERPG-2 (AIHA)[a]	–	–	1,000 ppm	–	–
ERPG-3 (AIHA)[a]	–	–	10,000 ppm	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	2 ppm

[a]ERPG (emergency response planning guideline, American Industrial Hygiene Association) (AIHA 2004, 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]TLV -TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2013) is the time-weighted average concentration for a normal 8-h work day and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

8.3. Data Adequacy and Research

No human data on tetrafluoroethylene are available. Data from studies with rodents were adequate for deriving AEGL values for several exposure durations. Although some of the data were old, more recent and well-conducted repeat-exposure studies were available.

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APPENDIX A

DERIVATION AEGL VALUES FOR TETRAFLUOROETHYLENE

Derivation of AEGL-1 Values

Key study:	Keller, D.A., G.L. Kennedy, Jr., P.E. Ross, D.P. Kelly, and G.S. Elliott. 2000. Toxicity of tetrafluoroethylene and S-(1,1,2,2-tetrafluoroethyl)-L-cysteine in rats and mice. Toxicol. Sci. 56(2):414-423.
Toxicity end point:	NOAEL for reversible renal lesions in rats and mice (1,200 ppm for 6 h)
Uncertainty factors:	Total uncertainty factor: 100 Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility
Modifying factor:	None
Time scaling:	$C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The 10-min AEGL-1 value was set equal to the 30-min AEGL-1 value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value. $(1{,}200 \text{ ppm} \div 100)^3 \times 360 \text{ min} = 622{,}080 \text{ ppm-min}$ $(12 \text{ ppm} \div 100)^1 \times 360 \text{ min} = 4{,}320 \text{ ppm-min}$
Calculations:	
10-min AEGL-1:	Set equal to the 30-min AEGL-1 value of 27 ppm
30-min AEGL-1:	$C^3 \times 30 \text{ min} = 622{,}080 \text{ ppm-min}$ C = 27 ppm
1-h AEGL-1:	$C^3 \times 60 \text{ min} = 622{,}080 \text{ ppm-min}$ C = 22 ppm
4-h AEGL-1:	$C^3 \times 240 \text{ min} = 622{,}080 \text{ ppm-min}$ C = 14 ppm

8-h AEGL-1:	$C^1 \times 480$ min = 4,320 ppm-min C = 9.0 ppm

Derivation of AEGL-2 Values

Key study:	Odum, J., and T. Green. 1984. The metabolism and nephrotoxicity of tetrafluoroethylene in the rat. Toxicol. Appl. Pharmacol. 76(2):306-318.
Toxicity end point:	NOAEL for irreversible renal lesions (3,000 ppm for 6 h)
Uncertainty factors:	Total uncertainty factor: 100 Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility
Modifying factor:	None
Time scaling:	$C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The 10-min AEGL-2 value was set equal to the 30-min AEGL-2 value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value. $(3{,}000 \text{ ppm} \div 100)^3 \times 360$ min 9.72×10^6 ppm-min $(30 \text{ ppm} \div 100)^1 \times 360$ min = 10,800 ppm-min
Calculations:	
10-min AEGL-2:	Set equal to the 30-min value of 69 ppm
30-min AEGL-2:	$C^3 \times 30$ min = 9.72×10^6 ppm-min C = 69 ppm
1-h AEGL-2:	$C^3 \times 60$ min = 9.72×10^6 ppm-min C = 55 ppm
4-h AEGL-2:	C^3 x 240 min = 9.72×10^6 ppm-min C = 34 ppm
8-h AEGL-2:	$C^1 \times 480$ min = 10,800 ppm-min C = 23 ppm

Derivation of AEGL-3 Values

Key study:	Haskell Laboratory. 1980. Inhalation Median Lethal Concentration (LC_{50}) in Hamsters. Haskell Laboratory Report No. 809-80. DuPont Co., Haskell Laboratory, Newark, DE.
Toxicity end point:	Estimated lethality threshold in the hamster (4-h $BMCL_{05}$ of 20,822 ppm)
Uncertainty factors:	Total uncertainty factor: 100 Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility
Modifying factor:	None
Time scaling:	$C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with extrapolating a 4-h point-of-departure to a 10-min value. $(20{,}822 \text{ ppm} \div 100)^3 \times 240 \text{ min} = 2.166 \times 10^9$ ppm-min $(20{,}822 \text{ ppm} \div 100)^1 \times 240 \text{ min} = 49{,}968$ ppm-min
Calculations:	
10-min AEGL-3:	Set equal to the 30-min value of 420 ppm
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 2.166 \times 10^9$ ppm-min C = 420 ppm
1-h AEGL-3:	$C^3 \times 60 \text{ min} = 2.166 \times 10^9$ ppm-min C = 330 ppm
4-h AEGL-3:	20,822 ppm ÷ 100 = 208 ppm (rounded to 210 ppm)
8-h AEGL-3:	$C^1 \times 480 \text{ min} = 49{,}968$ ppm-min C = 100 ppm

APPENDIX B

CATEGORY PLOT FOR TETRAFLUOROETHYLENE

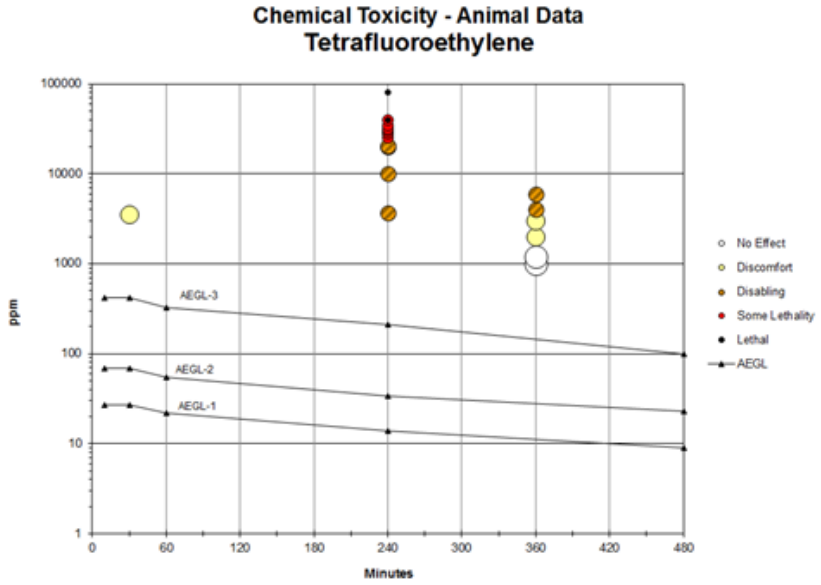

FIGURE B-1 Category plot of toxicity data and AEGL values for tetrafluoroethylene.

TABLE B-1 Data Used in Category Plot for Tetrafluoroethylene

Source	Species	ppm	Minutes	Category
AEGL-1		27	10	AEGL
AEGL-1		27	30	AEGL
AEGL-1		22	60	AEGL
AEGL-1		14	240	AEGL
AEGL-1		9	480	AEGL
AEGL-2		69	10	AEGL
AEGL-2		69	30	AEGL
AEGL-2		55	60	AEGL
AEGL-2		34	240	AEGL
AEGL-2		23	480	AEGL
AEGL-3		420	10	AEGL
AEGL-3		420	30	AEGL
AEGL-3		330	60	AEGL

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category
AEGL-3		100	480	AEGL
AEGL-3		210	240	AEGL
Dilley et al. 1974	Rat	3,500	30	1, reversible renal changes
Haskell Laboratory 1977	Rat	3,700	240	2, renal tubule fibrosis
Haskell Laboratory 1959	Rat	10,000	240	2, no mortality
Haskell Laboratory 1959	Rat	20,000	240	2, no mortality
Haskell Laboratory 1980	Hamster	20,700	240	2, no mortality
Haskell Laboratory 1980	Hamster	25,000	240	SL, 10% mortality
Sakharova and Tolgskaya 1977	Guinea pig	28,000	240	SL, 50% mortality
Haskell Laboratory 1980	Hamster	28,500	240	SL, 50% mortality
Haskell Laboratory 1980	Hamster	30,000	240	SL, 70% mortality
Sakharova and Tolgskaya 1977	Rat	31,500	240	SL, 50% mortality
Sakharova and Tolgskaya 1977	Mouse	35,000	240	SL, 50% mortality
Haskell Laboratory 1959	Rat	40,000	240	SL, 50% mortality
Haskell Laboratory 1980	Hamster	40,100	240	3, 100% mortality
Haskell Laboratory 1959	Rat	80,000	240	3, 100% mortality
Odum and Green 1984	Rat	1,000	360	0, no effects
Keller et al. 2000	Rat and mouse	1,200	360	0, no renal cell proliferation
Odum and Green 1984	Rat	2,000	360	1, no renal effects
Odum and Green 1984	Rat	3,000	360	1, nonsignificant clinical chemistry changes
Odum and Green 1984	Rat	4,000	360	2, significant clinical chemistry changes
Odum and Green 1984	Rat	6,000	360	2, renal necrosis

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

APPENDIX C

CANCER ASSESSMENT OF TETRAFLUOROETHYLENE

The US Environmental Protection Agency (EPA) has not conducted a cancer assessment of tetrafluoroethylene. NTP (1997) has conducted cancer bioassays for this chemical in F344 rats and $B6C3F_1$ mice. There was clear evidence of carcinogenicity in male and female rats and male and female mice.

Groups of 60 male F344/N rats were exposed to tetrafluoroethylene at 0, 156, 312, or 625 ppm for 6 h/day, 5 days/week for 104 weeks (NTP 1997). A statistically significant increase in hepatocellular adenomas or carcinomas (4/50, 7/50, 15/50, and 8/50) and renal tubule adenoma or carcinoma (single sections 1/50, 0/50, 6/50, and 3/50; single and step sections 3/50, 5/50, 9/50, and 13/50) were found. The incidence of any of these tumors in male rats was 5/50, 7/50, 16/50, and 11/50 with increasing concentration.

Groups of 60 female rats were exposed to tetrafluoroethylene at 0, 312, 625, or 1,250 ppm for 6 h/day, 5 days/week for 104 weeks (NTP 1997). A statistically significant increase in hepatocellular adenoma or carcinoma (0/50, 7/50, 12/50, and 8/50), hepatic hemangiosarcoma (0/50, 0/50, 5/50, and 1/50), renal tubule adenoma or carcinoma (single sections 0/50, 3/50, 1/50, and 5/50; single and step sections 0/50, 3/50, 3/50, and 10/50), and mononuclear cell leukemia (16/50, 31/50, 23/50, and 36/50) was found. The incidence of any of these tumors in female rats was 16/50, 33/50, 32/50, and 41/50 with increasing concentration.

In the same study (NTP 1997), groups of 58 male and 58 female $B6C3F_1$ mice were exposed to tetrafluoroethylene at 0, 312, 625, or 1,250 ppm for 95-96 weeks. In male mice, a statistically significant increase in the incidences of hepatic hemangioma or hemangiosarcoma (0/48, 26/48, 30/48, and 38/48), hepatocellular adenoma or carcinoma (26/48, 34/48, 39/48, and 35/48), and histiocytic sarcoma in all organs (0/48, 12/48, 7/48, and 7/48) was found. The incidence of any of these tumors in male mice was 24/48, 35/48, 47/48, and 44/48 with increasing concentration. In female mice, a statistically significant increase in the incidences of hepatic hemangioma or hemangiosarcoma (0/48, 31/48, 28/47, and 35/47), hepatocellular adenoma or carcinoma (17/48, 33/48, 29/47, and 28/47), and histiocytic sarcoma in all organs (1/48, 21/48, 19/47, and 18/48) was found. The incidence of any of these tumors in female mice was 17/48, 45/48, 45/48, and 44/48 with increasing concentration.

These data were used to derive an inhalation unit risk for tetrafluoroethylene using procedures consistent with EPA (1994, 2005) guidelines. The total cancer risk of any tumor is the value of interest; therefore, the data on the incidence of any tumor that was statistically significant was used. The derivation of the inhalation unit risk was calculated after conversion to continuous exposure (24 h/day and 7 days/week) as described in EPA (1994). Exposure in the bioassay in ppm was multiplied by 6 h/24 h and 5 days/7 days. The multi-stage model was used to calculate the lower 95% confidence limit for a 10% tumor response ($BMCL_{10}$). If data from all concentrations did not provide an adequate fit, the highest concentration was omitted. The inhalation unit risk was calculated by dividing 0.1 by the $BMCL_{10}$. The calculated inhalation unit risks from the individual bioassays were 0.00598 $(ppm)^{-1}$ for male rats, 0.00798 $(ppm)^{-1}$ for

female rats, 0.0149 $(ppm)^{-1}$ for male mice, and 0.0413 $(ppm)^{-1}$ for female mice. The geometric mean of these values (0.013 $[ppm]^{-1}$ or 5.32×10^{-2} $[mg/m^3]^{-1}$) was used in the calculation of the carcinogenicity assessment as described in NRC (2001).

Calculations to estimate a concentration of tetrafluoroethylene that would cause a theoretical excess cancer risk of 10^{-4} are presented below:

$$\text{Risk of } 1 \times 10^{-4}\text{: } (1 \times 10^{-4} \text{ risk}) \div (5.32 \times 10^{-2} \text{ mg/m}^3)^{-1} = 1.88 \times 10^{-3} \text{ mg/m}^3$$

To convert 1.88×10^{-3} mg/m^3 for a 70-year exposure (25,600 h) to a 24-h exposure:

$$\begin{aligned} \text{24-h exposure} &= \text{dose} \times 25{,}600 \text{ h} \\ &= (1.88 \times 10^{-3} \text{ mg/m}^3) \times 25{,}600 \\ &= 48.15 \text{ mg/m}^3 \end{aligned}$$

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

$$(48.15 \text{ mg/m}^3) \div 6 = 8.0 \text{ mg/m}^3 \text{ (2.0 ppm)}$$

Therefore, on the basis of potential carcinogenicity of tetrafluoroethylene, an acceptable 24-h exposure would be 8 mg/m^3 (2.0 ppm). If the exposure is limited to a fraction of a 24-h period, the fractional exposure becomes 1/fraction × 24 h (NRC 1985).

$$\begin{aligned} \text{24-h exposure} &= 8.0 \text{ mg/m}^3 \text{ (2.0 ppm)} \\ \text{8-h exposure} &= 24 \text{ mg/m}^3 \text{ (5.9 ppm)} \\ \text{4-h exposure} &= 48 \text{ mg/m}^3 \text{ (12 ppm)} \\ \text{1-h exposure} &= 192 \text{ mg/m}^3 \text{ (47 ppm)} \\ \text{0.5-h exposure} &= 385 \text{ mg/m}^3 \text{ (94 ppm)} \end{aligned}$$

For 10^{-5} or 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold. The mechanism of action that leads to renal tumor formation may be attributed to renal tubule damage via the processing of the glutathione conjugate. Cell necrosis followed by constant regeneration of the epithelium in the kidney (increased cell proliferation) results in greater opportunity for error in DNA synthesis and mutation. The mechanism of action leading to neoplasms in the liver and other organs is unclear. No treatment-related lesions of the liver in rats or mice of either sex were found after 16-day or 13-week exposures to tetrafluoroethylene at 5,000 ppm for 6 h/day, 5 days/week, although hepatic weights were increased (NTP 1997). Because of the uncertainties inherent in assessing excess cancer risk following a single acute exposure of 8 h or less duration, the acute toxicity values were used to set the AEGL values for tetrafluoroethylene.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR TETRAFLUOROETHYLENE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
27 ppm	27 ppm	22 ppm	14 ppm	9 ppm

Key reference: Keller, D.A., G.L. Kennedy, Jr., P.E. Ross, D.P. Kelly, and G.S. Elliott. 2000. Toxicity of tetrafluoroethylene and S-(1,1,2,2-tetrafluoroethyl)-L-cysteine in rats and mice. Toxicol. Sci. 56(2):414-423.

Test species/Strain/Number: Rat, F344, 25 females/group. Mice; $B6C3F_1$, 24 females/group.

Exposure route/Concentrations/Durations: Inhalation; 0, 31, 300, 600, or 1,200 ppm for 6 h

Effects: No biologically significant effect on cell proliferation at any concentration

End point/Concentration/Rationale: NOAEL for reversible renal effects (1,200 ppm for 6 h)

Uncertainty factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking
Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 6-h point-of-departure to a 10-min value, the 10-min AEGL-1 value was set equal to the 30-min AEGL-1 value.

Data adequacy: The key study was well-conducted. Additional animal studies conducted at higher concentrations show a continuum of renal toxicity.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
69 ppm	69 ppm	55 ppm	34 ppm	23 ppm

Key reference: Odum, J., and T. Green. 1984. The metabolism and nephrotoxicity of tetrafluoroethylene in the rat. Toxicol. Appl. Pharmacol. 76(2):306-318.

Test species/Strain/Number: Rat; Wistar-derived; 4 males/group

(Continued)

AEGL-2 VALUES Continued

Exposure route/Concentrations/Durations: Inhalation; 0, 1,000, 2,000, 3,000, 4,000, or 6,000 ppm for 6 h

Effects:
1,000 ppm: no observed effects
2,000 ppm: NOAEL for renal effects
3,000 ppm: threshold for urinary glucose and enzyme changes
4,000 ppm: significant increases in urinary glucose and enzyme activities (no histologic examination)
6,000 ppm: renal necrosis (histologic examination)

End point/Concentration/Rationale: NOAEL for renal necrosis (3,000 ppm for 6 h)

Uncertainty factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking
Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 6 h point-of-departure to a 10-min value, the 10-min AEGL-2 value was set equal to the 30-min AEGL-2 value.

Data adequacy: The key study was well-conducted. That study and other animal studies of tetrafluoroethylene at other concentrations showed a continuum of renal toxicity.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
420 ppm	420 ppm	330 ppm	210 ppm	100 ppm

Key reference: Haskell Laboratory. 1980. Inhalation Median Lethal Concentration (LC_{50}) in Hamsters. Haskell Laboratory Report No. 809-80. DuPont Co., Haskell Laboratory, Newark, DE.

Test species/Strain/Number: Hamster; Syrian; 10 males/group

Exposure route/Concentrations/Durations: Inhalation; 10,200, 20,700, 25,000, 30,000, 40,100, or 78,700 ppm for 4 h

Effects:
10,200 ppm: 0% mortality
20,700 ppm: 0% mortality
25,000 ppm: 10% mortality
30,000 ppm: 70% mortality
40,100 ppm: 100% mortality
78,700 ppm: 100% mortality

(Continued)

AEGL-3 VALUES Continued

End point/Concentration/Rationale: 4-h $BMCL_{05}$ of 20,822 ppm
Uncertainty factors/Rationale: Total uncertainty factor: 100 Interspecies: 10, because data on interspecies differences in the toxicokinetics of tetrafluoroethylene are lacking Intraspecies: 10, because data on variability in the toxicokinetics of tetrafluoroethylene in humans are lacking and because of evidence that polymorphisms in several of the enzymes in the bioactivation pathway for this and related compounds may modify susceptibility
Modifying factor: None
Animal-to-human dosimetric adjustment: Not applied
Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 4-h point-of-departure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value.
Data adequacy: The results of the key study are supported by a similar mortality pattern in rats (Haskell Laboratory 1959).