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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 13

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

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

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

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

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the thirteenth volume in that series. AEGL documents for boron trifluoride, bromoacetone, chloroacetone, hexa-

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

fluoroacetone, perchloryl fluoride, piperidine, propargyl alcohol, trimethoxysilane and tetramethoxysilane, and trimethylbenzenes are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

The six interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for boron trifluoride (interim reports 8 and 15), bromoacetone (interim report 20a), chloroacetone (interim reports 16, 19a, and 20a), hexafluoroacetone (interim reports 16 and 19a), perchloryl fluoride (interim report 20a), piperidine (interim reports 18 and 20a), propargyl alcohol (interim reports 16 and 19a), trimethoxysilane and tetramethoxysilane (interim reports 19a and 20a), and trimethylbenzenes (interim reports 16, 18, and 19a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), Florence Kinoshita (Hercules Incorporated [retired]), James McDougal (Wright State University [retired]), Kenneth Poirier (Kendle International, Inc.), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), 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 interim report 8 was overseen by David Moore (Battelle

Memorial Institute), and the reviews of interim reports 15, 16, 18, 19a, and 20a by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 13

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

This report is the thirteenth 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 Syracuse Research Corporation. 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 for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared twelve 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). This report is the thirteenth volume in that series. AEGL documents for boron trifluoride, bromoacetone, chloroacetone, hexafluoroacetone, perchloryl fluoride, piperidine, propargyl alcohol, trimethoxysilane and tetramethoxysilane, and trimethylbenzenes are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

Boron Trifluoride[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 Claudia Troxel (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

Boron trifluoride-dimethyl ether is one of several different complexes that can be formed with boron trifluoride. The complexes are generally formed for ease of handling boron trifluoride. The ether complexes consist of a 1:1 molar ratio of boron trifluoride and the dimethyl or diethyl ether and can dissociate under the proper temperature and pressure conditions. A single study was found that addressed the toxicity of boron trifluoride-dimethyl ether, but it reported only nominal concentrations. Because the complex can dissociate to form boron trifluoride, the AEGL values are based on this one chemical species.

Boron trifluoride is a colorless gas with an odor described both as pungent and suffocating and as pleasant. Although the gas is stable in dry air, it immediately forms a dense white mist or cloud when exposed to moist air. Boron trifluoride reacts with moisture (even at low concentrations) to form the dihydrate, $BF_3 \cdot 2H_2O$. Boron trifluoride dihydrate is strongly corrosive to the eyes and skin of rabbits. Boron trifluoride is an excellent catalyst, and has fire retardant and antioxidant properties, nuclear applications, and insecticidal properties.

No definitive data were available on the toxicity of inhaled boron trifluoride in humans. One study reported that a worker could detect the odor of boron trifluoride at a concentration of 4.1 mg/m^3 (1.5 ppm) (Torkelson et al. 1961). Acute toxicity studies with dogs, rats, mice, and guinea pigs were available, but exposure concentrations were generally expressed only in terms of nominal concentrations. Studies that measured exposure concentrations and compared them with nominal concentrations found that actual concentrations

ranged from 2.7-56% of nominal concentrations (Torkelson et al. 1961; Rusch et al. 1986; Bowden 2005). Studies identifying end points other than mortality were few. No data were available to evaluate the potential for boron trifluoride to cause developmental or reproductive toxicity or carcinogenicity in animals. Boron trifluoride was not mutagenic in several stains of *Salmonella typhimurium*.

AEGL-1 values are based on a no-effect level for irritation. A group of 10 rats exposed for 4 h to measured concentrations of boron trifluoride at 25 mg/m^3 had no abnormal findings, whereas rats exposed to the next higher concentration of 74 mg/m^3 had histopathologic changes in the larynx and tracheal bifurcation indicative of irritation (Bowden 2005). The concentration of 25 mg/m^3 was selected as the point of departure for calculating AEGL-1 values. The irritant effects seen at 74 mg/m^3 are more severe than the threshold effects for the AEGL-1values. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was applied because irritation is a direct contact effect and is not expected to vary greatly among species. An intraspecies uncertainty factor of 3 was applied because the mechanism of irritation is not expected to vary greatly in subpopulations. The same AEGL value was applied to all AEGL durations because the point of departure is a no-effect level for mild irritation.

Relevant data for deriving AEGL-2 values were not available. Therefore, the AEGL-3 values were divided by 3 to obtain reasonable estimates of the AEGL-2 values. Dividing AEGL-3 values by 3 is supported by the steep dose-response curve (Rusch et al. 1986).

The derivation of AEGL-3 values was based on the threshold for lethality. Rusch et al. (1986) calculated a 4-h LC_{50} (lethal concentration 50% lethality) of 1,210 mg/m^3 (exposures were to liquid aerosols of boron trifluoride dihydrate; concentrations reported are based on boron trifluoride). Using individual mortality data, a 4-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) was calculated by a log-probit analysis using EPA Benchmark Dose Software version 1.4.1c [2007] (EPA 2012). The resulting 4-h $BMCL_{05}$ of 554 mg/m^3 was used to derive the AEGL-3 values. An interspecies uncertainty factor of 3 was applied because boron trifluoride is a corrosive irritant, and the mechanism of action is not expected to vary greatly among species. An intraspecies uncertainty factor of 3 was chosen, because the mechanism of irritation is not expected to vary greatly among subpopulations. An intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve for lethality (3/10 rats died at 1,010 mg/m^3, while 9/10 rats died at 1,540 mg/m^3), which indicates little variability in the response within a population. The Rusch et al. (1986) study is supported by the Kasparov and Kiriĭ (1972) study that reported a 4-h LC_{50} of 1,180 mg/m^3 in rats. Time scaling was performed using the concentration-time relationship equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n could not be determined because of inadequate data, so the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from

longer to shorter exposure periods. The 10-min value was set equal to the 30-min value because of the uncertainty associated with extrapolating data from a 4-h exposure duration to a 10-min AEGL value.

The AEGL values for boron trifluoride are presented in Table 1-1. Although the gas is stable in dry air, boron trifluoride reacts to form the dihydrate when exposed to even low levels of moisture in the air (NIOSH 1976; Hoffman, 1981). Therefore, all AEGL values are reported only in mg/m^3.

1. INTRODUCTION

Boron trifluoride-dimethyl ether is one of several different complexes that can be formed with boron trifluoride. The complexes are generally formed for ease of handling of boron trifluoride (NIOSH 1976). Other complexes that can be formed include boron trifluoride with monoethylamine, water, phenol, phosphoric acid, piperidine, dimethyl aniline, methanol, or diethyl ether (NIOSH 1976). A summary table of acute toxicity studies with some of the boron trifluoride complexes can be found in Appendix E. The ether complexes consist of a 1:1 molar ratio of boron trifluoride and either the dimethyl or diethyl ether, and can dissociate under the proper temperature and pressure conditions. A single study was found that evaluated the toxicity of boron trifluoride-dimethyl ether, but it reported only nominal concentrations. Because the complex can dissociate to form boron trifluoride, the AEGL derivations are based on this one chemical species.

Boron trifluoride is a colorless gas with an odor that has been described both as pungent and suffocating (Budavari et al. 1996) and as a "rather pleasant acidic" odor (Torkelson et al. 1961). Chemical and physical data for boron trifluoride and boron trifluoride-dimethyl ether (when available) are listed in Table 1-2. Although the gas is stable in dry air, it immediately forms a dense white mist or cloud when exposed to moist air (NIOSH 1976). Hoffman (1981) reported that when exposed to moisture in the air, even at low levels, boron trifluoride reacts to form the dihydrate, $BF_3.2H_2O$. In water, boron trifluoride is believed to form the following products: fluoboric acid (HBF_4), monohydroxyfluoboric acid (HBF_3OH), dihydroxyfluoboric acid ($HBF_2(OH)_2$), trihydroxyfluroboric acid ($HBF(OH)_3$), and boric acid (H_3BO_3) (NIOSH 1976). Boron trifluoride probably reacts slowly with water to form hydrogen fluoride. It has been suggested that if hydrogen fluoride is formed, it is almost immediately complexed with other species (NIOSH 1976). Dunn (1980) demonstrated that boron trifluoride dihydrate is strongly corrosive to the eyes and skin of rabbits. Topical administration of undiluted boron trifluoride dihydrate (0.1 mL) to the eye caused complete corneal opacity and necrosis of the conjunctivae, nictating membrane, and upper and lower eyelids. The corrosive action was not alleviated by irrigation of the eye with tap water. Topical application of undiluted boron trifluoride dihydrate (0.5 mL) to the skin under a semi-occlusive patch for 24 h resulted in total corrosion of the skin.

TABLE 1-1 Summary of AEGL Values for Boron Trifluoride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	No-effect level for irritation at 25 mg/m^3 for 4 h (Bowden 2005).
AEGL-2 (disabling)	37 mg/m^3	37 mg/m^3	29 mg/m^3	18 mg/m^3	9.3 mg/m^3	One-third AEGL-3 values
AEGL-3 (lethal)	110 mg/m^3	110 mg/m^3	88 mg/m^3	55 mg/m^3	28 mg/m^3	4-h $BMCL_{05}$ in rats of 554 mg/m^3 (Rusch et al. 1986).

TABLE 1-2 Chemical and Physical Data for Boron Trifluoride

Parameter	Value[a]	Reference
Synonyms	Trifluoroborane; boron trifluoride-dimethyl ether (1:1); boron trifluoride-dimethyl etherate; fluoride bority-diemthylether (1:1)	NIOSH 2011 Lewis 1996
CAS registry no.	7637-07-2 353-42-4 (BF_3-dimethyl ether)	
Chemical formula	BF_3 $C_2H_60•BF_3$ (BF_3-dimethyl ether)	
Molecular weight	67.81 g 113.89 g (BF_3-dimethyl ether)	Budavari et al. 1996 Lewis 1996
Physical state	Gas Liquid (BF_3-dimethyl ether)	Budavari et al. 1996
Color	Colorless	Budavari et al. 1996
Melting point	-128.37°C -14°C (BF_3-dimethyl ether)	AIHA 1999 Lewis 1996
Boiling point (760 mm Hg)	-100.4°C	Budavari et al. 1996
Vapor density (air =1)	3.077 g/L	Budavari et al. 1996
Solubility in water	332 g/100 g at 0°C	Budavari et al. 1996
Vapor pressure	>1 Torr at 20°C	ACGIH 1991
Conversion factors	1 ppm = 2.76 mg/m^3 1 mg/m^3 = 0.36 ppm (v/v) 1 ppm = 4.65 mg/m^3 (BF_3-dimethyl ether)	AIHA 1999 Calculated

[a]Data are for boron trifluoride unless specified otherwise.

Boron trifluoride is a strong Lewis acid and is, therefore, an excellent catalyst that is used in polymerizations, esterifications, and alkylations (NIOSH 1976). Its fire retardant and antioxidant properties are used by the magnesium

industry for protecting molten magnesium and its alloys from oxidation (NIOSH 1976; Budavari et al. 1996), and its nuclear applications include use in neutron detection instruments, boron-10 enrichment, and in the production of neutron-absorbing salts for molten-salt breeder reactors (NIOSH 1976). Boron trifluoride also has insecticidal properties (NIOSH 1976; Budavari et al. 1996).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on lethality in humans following acute inhalation exposure to boron trifluoride were found.

2.2. Nonlethal Toxicity

In the description of animal studies by Torkelson et al. (1961) discussed in Section 3 below, it was mentioned that a worker noted that boron trifluoride had a rather pleasant acidic odor a concentration of 4.1 mg/m^3 (1.5 ppm).

Stewart and Waisberg (1988) reported the only documented case of boron trifluoride poisoning found in the literature. A part-time scrap merchant knocked a valve off a gas cylinder containing boron trifluoride in his garage. A choking white gas was released, quickly overcoming him, his infant son, and his pregnant wife. Upon admission to the hospital, hypoxemia with minimal acidosis was noted. The three patients were treated with ventilation and oxygen. The father and son recovered within 48 h, while the pregnant mother remained unconscious for 36 h and recovered slowly. Urinary concentrations of fluoride were not increased in the 24-h urine samples collected from the subject. The authors stated that all three patients recovered uneventfully. No other details, such as the pregnancy outcome, were provided.

2.3. Developmental and Reproductive Toxicity

No data on the developmental or reproductive toxicity of boron trifluoride in humans were found.

2.4. Genotoxicity

No data on the genotoxicity of boron trifluoride in humans were found.

2.5. Carcinogenicity

No data on the carcinogenicity of boron trifluoride in humans were found.

2.6. Summary

No definitive data on the toxicity of boron trifluoride in humans were found. One paper reported that three individuals (an adult male, an infant, and a pregnant woman) survived exposure to an unknown but debilitating concentration of boron trifluoride. A worker exposed to approximately 4.1 mg/m^3 (1.5 ppm) boron trifluoride reported the odor to be rather pleasant and acidic.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Vernot et al. (1977) determined 1-h LC_{50} values for boron trifluoride in rats. Groups of five male and five female Sprague-Dawley rats were exposed at various concentrations of boron trifluoride (individual concentrations not specified; not clear whether values were measured or nominal concentrations) for 1 h in either a bell jar or large desiccator (not stated which). The 1-h LC_{50} values, calculated by probit analysis, were 1,100 mg/m^3 (95% CI [confidence interval]: 883-1,289 mg/m^3) (equivalent to 387 ppm (95% CI: 320-467 ppm) for male rats, and 1,000 mg/m^3 (95% CI: 809-1,294 mg/m^3) (equivalent to 371 ppm; 95% CI: 293-469 ppm) for female rats. No other experimental details were provided.

A series of experiments in rats investigated the acute toxicity of inhaled boron trifluoride (DuPont Company 1948); most of these tests are described below in Section 3.2.2. In one experiment, a group of six rats was exposed for 4 h to boron trifluoride at a nominal concentration of 3,900 mg/m^3 (1,400 ppm). One rat died after 148 min of exposure, and another died within 24 h of exposure. Necropsy of the rat that died during the exposure revealed general cyanosis, acute inflammatory reaction of the larynx and upper trachea, and slightly edematous lungs with moderate congestion of alveolar walls. The other rat had consolidation of the upper part of all the lobes of the lung, pus in the bronchi, desquamated mucosa, and areas of emphysema. The four surviving rats were observed for 4 days, and were observed to only experience weight loss. Necropsy of the animals revealed areas of the lungs with thickened alveolar walls as a result of swelling of the lining cells.

Groups of 10 rats, 10 mice, and 10 guinea pigs were exposed to nominal concentrations of boron trifluoride (Stokinger and Spiegl 1953). Rats were exposed at 2,100 mg/m^3 (750 ppm) for 5.5 h or 370 mg/m^3 (135 ppm) for 10.9 h. The actual exposure concentrations may have been much less since only nominal concentrations were reported. Exposures were conducted in a dynamic exposure chamber measuring 28 ×12 × 6 inches, with plastic sides and a removable plastic top. Three screens were placed inside the chamber to separate the three

species that were exposed simultaneously. Gaseous boron trifluoride was diluted with nitrogen, and continuously metered by a flow meter through copper lines into one end of the chamber with removal at the opposite end of the chamber using a small, motor driven compressor (approximately 1 air change/min). Animals were observed for 14 days following the exposure. The chemical purity was unknown, and the age, sex, and strain of the animals were not specified. At 2,100 mg/m^3 for 5.5 h, 1/10 rats died, whereas no rats died at 370 mg/m^3 for 10.9 h. Animals surviving the exposure did not exhibit any weight loss during the postexposure observation period.

Kasparov and Kiriĭ (1972) reported a 4-h LC_{50} of 1,180 mg/m^3 for 50 albino rats exposed to boron trifluoride. It was not stated if animals were exposed to nominal or measured concentrations. Necropsy of exposed animals revealed cyanosis of mucous membranes and hemorrhage of internal organs, including the lungs. Lung weights were increased, and pulmonary examination revealed edema, alveolar duct destruction, and vascular dilation. Hyperemia and edema were observed in the kidneys, spleen, and brain. The mucous membranes of the eyes showed evidence of irritation.

F344 rats were exposed by inhalation to boron trifluoride dihydrate for 4 h, 9 days, or 13 weeks (Rusch et al. 1986). The stable dihydrate of boron trifluoride was used to avoid the secondary reaction of dihydrate formation that would occur in the inhalation chamber because of the hygroscopic nature of boron trifluoride gas. A nebulizer was used to generate the aerosol, and the concentration was controlled by regulating the airflow of the compressed, breathing-grade air through the nebulizer. Exposure concentrations were measured hourly by trapping a known volume of test atmosphere, dissolving the aerosol in distilled water, and analyzing the sample using an ion-selective electrode technique. Particle size was measured hourly during the acute exposure, three times per week during the 9-day exposure, and twice per week during the subchronic exposure. The mean particle size ranged from 1.5-2.2 microns; more than 97% of the particles were smaller than 10 microns.

For the acute study, groups of five male and five female 9-week-old F344 rats were exposed for 4 h to liquid aerosols of boron trifluoride dihydrate at mean measured concentrations of 0, 1,010, 1,220, 1,320, or 1,540 mg/m^3 (animals were exposed to boron trifluoride dihydrate, but the concentrations are based on boron trifluoride) (Hoffman 1981; Rusch et al. 1986). Nominal concentrations ranged from 4,100 mg/m^3 for the low-concentration group to 6,200 mg/m^3 for the high-concentration group. Loss of the chemical was attributed to losses associated with high aerosol generation. Rats were observed during the exposure and daily for 14 days postexposure. Body weight was recorded prior to exposure (day 0) and on days 1, 2, 4, 7, and 14 postexposure. Gross necropsy was conducted on all animals. Mortality was observed in all exposure groups (see Table 1-3). A 4-h LC_{50} of 1,210 mg/m^3 (95% CI: 1,080-1,350 mg/m^3) was calculated using the method of Litchfield and Wilcoxon (1949). Clinical signs observed during exposure included reduced activity, closed eyes, excessive

TABLE 1-3 Mortality in Rats Exposed to Boron Trifluoride Aerosol for 4 Hours

Concentration (mg/m^3)	Mortality (%) [day of death]
0	0/10 (0)
1,010	3/10 (30) [0, 3, 6]
1,220	2/10 (20) [0, 3]
1,320	8/10 (80) [1, 1, 2, 3, 3, 3, 4, 5]
1,540	9/10 (90) [0, 0, 0, 1, 2, 3, 4, 5, 5]

Source: Rusch et al. 1986.

lacrimation, and excessive oral and nasal discharge. The high-concentration group also exhibited gasping. Clinical signs of respiratory distress (dry rales, moist rales, gasping) and/or irritation (excessive oral and nasal discharge and lacrimation) were noted 4 hours after exposure in most of the exposed animals. Two rats (one each from the 1,320- and 1,540-mg/m^3 groups) had corneal opacities when removed from the chamber and later died. Most clinical signs in surviving rats were no longer present by day 6. All rats lost weight following exposure, but the control rats lost less (4-11 g) than the exposed rats (19-56 g). All rats gained weight by day 14, indicating reversibility of toxicity. Necropsy of exposed animals revealed red discoloration of the lungs in all exposure groups. Discoloration of the thymus, kidney, and liver were reported in animals dying spontaneously in all groups, but it was unclear whether these changes were an effect of treatment. Slight increases in liver and lung weight were observed in exposed females (lung weight was 2-5% greater than controls; liver weight was 13-15% greater than controls).

In the subacute study, groups of five male and five female F344 rats were exposed to liquid aerosols of boron trifluoride dihydrate for 6 h/day, 5 days/week for 9 days, at mean measured concentrations of 0, 24, 66, or 180 mg/m^3 (animals were exposed to boron trifluoride dihydrate, but concentrations given are based on boron trifluoride) (Hoffman and Rusch 1982b; Rusch et al. 1986). Nominal concentrations were 48, 117, and 390 mg/m^3, respectively. The differences between nominal and measured concentrations were attributed to absorption by the chamber wall. Animals were observed twice daily, clinical signs were recorded twice a week (exposure days 2, 5, 9, and 11), and body weight was recorded weekly. At study termination, the brains, gonads, kidneys, liver, lungs, spleen, and thymus were weighed, and the lungs, trachea, turbinates, liver, kidneys, stomach, duodenum, testis, and epididymis were examined microscopically. All 10 rats from the high-concentration group died before the sixth exposure. Clinical signs after two days included mucoid and/or red nasal discharge, dry or moist rales, dried red material around nose or mouth, lacrimation, and yellow anal-genital staining, whereas three control females exhibited mucoid nasal discharge and one control male had mucoid nasal discharge and dry rales (see Table 1-4). Clinical signs did not appear to be related to concen-

tration at day 2. Clinical signs were increased in incidence and severity after 5 days of exposure. Mean body weight and body weight gain were statistically decreased in males of all exposure groups and in females of the mid- and high-concentration groups. Concentration-related increases in absolute and relative lung weights were observed in both sexes of the low- and mid-concentration groups (increased by 12% and 21%, respectively, compared with controls), while absolute and relative liver weights were decreased in the mid-concentration groups (approximately 79% of controls). The only treatment-related histopathologic finding was necrosis and pyknosis of the proximal tubular epithelium in the kidneys from animals exposed at 180 mg/m^3.

TABLE 1-4 Clinical Signs in Rats Exposed to Boron Trifluoride for Nine Days

Observation	0 mg/m^3	24 mg/m^3	66 mg/m^3	180 mg/m^3
Exposure day 2				
Number examined	10	10	10	10
Number affected	4	7	7	7
No signs	6	3	3	3
Mucoid nasal discharge	4	5	4	5
Red nasal discharge, dried red material around nose or mouth	0	2	2	1
Dry rales	1	2	2	1
Moist rales	0	1	0	2
Lacrimation	0	0	0	1
Stained anal-genital area	0	2	1	1
Exposure day 5				
Number examined	10	10	10	10
Number affected	0	6	10	10
No signs	10	4	0	0
Dead	0	0	0	3
Mucoid nasal discharge	0	0	9	2
Red nasal discharge, dried red material around nose or mouth	0	6	6	4
Dry rales	0	0	3	0
Moist rales	0	2	7	1
Lacrimation	0	0	0	7
Stained anal-genital area	0	1	5	5
Gasping, shallow or labored breathing	0	0	0	3
Poor condition	0	0	0	8

Source: Adapted from Hoffman and Rusch 1982b; Rusch et al. 1986.

In the subchronic study, groups of 20 male and 20 female F344 rats were exposed to liquid aerosols of boron trifluoride dihydrate for 6 h/day, 5 days/week for 13 weeks, at mean measured concentrations of 0, 2.0, 6.0, or 17 mg/m^3 (animals were exposed to boron trifluoride dihydrate, but the concentrations given are based on boron trifluoride) (Hoffman and Rusch 1982a; Rusch et al. 1986). Nominal concentrations were 6.4, 24, and 54 mg/m^3, respectively. Differences between nominal and measured concentrations were again attributed to absorption by the chamber wall. Animals were observed twice daily, a detailed clinical assessment was performed on all animals weekly, and body weight was recorded weekly. Hematology and clinical chemistry analysis, urinalysis, and urinary ionic and total fluoride and serum total fluoride amounts were determined after 1 month of exposure (5 rats/sex/dose), during the final week of exposure (15 rats/sex/dose), or 2 weeks after the last exposure (retained group of 5 rats/sex/dose). In addition, urine ionic and total fluoride measurements were taken after 2 months of exposure, and bone fluoride analysis was conducted on all animals. All rats were subjected to gross necropsy, and the brain, lungs, heart, liver, spleen, kidneys, and gonads were weighed. Tissues from the control and high-concentration groups were examined for histopathologic changes, and sections of the kidneys, nasal turbinates, lungs, and liver were examined from all animals.

One male rat from the high-concentration group died during week 12 (Hoffman and Rusch 1982a; Rusch et al. 1986). Clinical signs in exposed animals included an increased incidence of dried red material around the nose, dried material around the mouth, excessive lacrimation, and dry rales, primarily in the high-concentration group. In the low-concentration groups, irritation in the form of excessive lacrimation was observed in 5 rats of the 2 mg/m^3 group (1-2 times starting at week 10), and in 16 rats of the 6-mg/m^3 group (1-2 times starting at week 2). No differences in body weight, ophthalmologic findings, hematology analysis, organ weight, or gross necropsy findings were observed in exposed animals compared with controls. Urinalysis revealed a concentration-related decrease in urinary calcium and concentration-related increase in urinary fluoride. Clinical chemistry analysis revealed concentration-related decreases in serum protein and globulin concentrations, and one male rat with elevated blood urea nitrogen (BUN) concentration. A concentration-related increase in fluoride concentration in the femurs of exposed animals was observed. The concentrations persisted during the recovery period, suggesting either slow release from the bone or irreversible binding. Histopathologic examination of the male rat in the high-concentration group that died had findings consistent with toxic renal tubular necrosis, and the rat with elevated BUN concentrations exhibited mild renal lesions that probably would not have affected its survival.

3.1.2. Mice

Groups of 10 mice, 10 rats, and 10 guinea pigs were exposed to nominal concentrations of boron trifluoride (Stokinger and Spiegl 1953). Mice were ex-

posed at 2,100 mg/m^3 (750 ppm) for 5.5 h or 370 mg/m^3 (135 ppm) for 10.9 h. Actual exposure concentrations may have been less since only nominal concentrations were reported. Exposures were conducted in a dynamic exposure chamber measuring 28 × 12 × 6 inches, with plastic sides and a removable top. Three screens were placed inside the chamber to separate the different species that were exposed simultaneously. Gaseous boron trifluoride was diluted with nitrogen, and continuously metered by a flow meter through copper lines into one end of the chamber with removal at the opposite end of the chamber using a small, motor driven compressor (approximately 1 air change/min). Animals were observed for 14 days after the exposure. The chemical purity was unknown, and the age, sex, and strain of the animals used was not specified. One of 10 mice exposed at 2,100 mg/m^3 for 5.5 h died, whereas no deaths occurred in mice exposed at 370 mg/m^3 for 10.9 h. Mice that survived did not to exhibit any weight loss during the postexposure observation period.

Kasparov and Kiriĭ (1972) reported a 2-h LC_{50} of 3,460 mg/m^3 for 70 albino mice exposed to boron trifluoride. It was not stated if animals were exposed to nominal or measured concentrations. Necropsy of exposed animals revealed cyanosis of mucous membranes and hemorrhage of internal organs, including the lungs. Lung weight was increased, and examination revealed edema, alveolar duct destruction, and vascular dilation. Hyperemia and edema were observed in the kidneys, spleen, and brain. The mucous membranes of the eyes showed evidence of irritation.

3.1.3. Guinea Pigs

A series of experiments was carried out in guinea pigs to investigate the acute toxicity of inhaled boron trifluoride (DuPont Company 1948). Most of the experimental details were not provided, including the chemical purity, sex and strain of animals, description of exposure chamber, and generation of test material aerosol. In the first experiment, two guinea pigs exposed to boron trifluoride at approximately 2,760 mg/m^3 (1,000 ppm) died during the first 5 min of exposure. Necropsy revealed pale and distended lungs, and histopathologic examination found emphysema with partially detached bronchial epithelium. No edema was observed. In the next experiment, two guinea pigs were exposed for 3 h at a nominal concentration of 720 mg/m^3 (260 ppm). Guinea pigs exhibited signs of respiratory distress within a few minutes of exposure, and had labored breathing throughout the first hour of exposure. One guinea pig died 90 min into the exposure, and necropsy revealed distended lungs and pulmonary edema. The other guinea pig survived the 3-h exposure and was sacrificed the next day. Examination of the lungs revealed thickening of the pleura, atelectasis of some portions of the lungs, and areas of emphysema. Pretreatment with pyribenzamine or adrenaline (20 mg/kg or 0.1 mg, respectively, injected subcutaneously 15 min before exposure to boron trifluoride) did not modify the response of guinea pigs when they were subsequently exposed to boron trifluoride at 2,760 mg/m^3 (1,000 ppm) or 280-550 mg/m^3 (100-200 ppm).

Groups of 10 rats, 10 mice, and 10 guinea pigs were exposed to nominal concentrations of boron trifluoride (Stokinger and Spiegl 1953). Guinea pigs were exposed at 2,100 mg/m^3 (750 ppm) for 5.5 h, 970 mg/m^3 (350 ppm) for 1.4 h, or 370 mg/m^3 (135 ppm) for 10.9 h. Actual exposure concentrations may have been less since only nominal concentrations were reported. Exposures were conducted in a dynamic exposure chamber measuring 28 × 12 × 6 inches, with plastic sides and a removable top. Three screens were placed inside the chamber to separate the different species that were exposed simultaneously. Gaseous boron trifluoride was diluted with nitrogen, and continuously metered by a flow meter through copper lines into one end of the chamber with removal at the opposite end of the chamber using a small, motor driven compressor (approximately 1 air change/min). Animals were observed for 14 days after the exposure. The chemical purity was unknown, and the age, sex, and strain of the animals used were not specified. A summary of the mortality data is presented in Table 1-5. Surviving animals did not exhibit any weight loss during the postexposure observation period.

Kasparov and Kiriĭ (1972) reported a 4-h LC_{50} of 109 mg/m^3 in 42 guinea pigs exposed to boron trifluoride. It was not stated if animals were exposed to nominal or measured concentrations. Necropsy of exposed animals revealed cyanosis of mucous membranes and hemorrhage of internal organs, including the lungs. Lung weight was increased, and examination revealed edema, alveolar duct destruction, and vascular dilation. Hyperemia and edema were observed in the kidneys, spleen, and brain. The mucous membranes of the eyes showed evidence of irritation.

Torkelson et al. (1961) conducted a number of repeated exposure studies in which guinea pigs were exposed to nominal concentrations of boron trifluoride at 8, 21, or 35 mg/m^3 (3, 7.7, or 12.8 ppm) for 7 h/day, 5 days/week for various durations. Measured concentrations of the 8 and 21 mg/m^3 exposures were 4 mg/m^3 and 8-11 mg/m^3, respectively. The exposure chamber used for the 21- and 35-mg/m^3 exposures was a 160-L cubical chamber, whereas the 8-mg/m^3 exposures occurred in a 3,700-L rectangular, vault-type chamber. The chemical purity was not determined. Dry boron trifluoride gas was metered into the exposure chamber with a stream of nitrogen to prevent loss of the chemical. To determine actual exposure concentrations, air samples were taken from the chamber by drawing chamber air through a fritted glass scrubber containing distilled water. Samples also were taken from several areas within the chambers to ensure reasonable distribution of the boron trifluoride. A carbamic acid technique was used to determine the concentration of total boron, and the equivalent concentration of boron trifluoride was calculated.

In the first experiment, 10 male guinea pigs were exposed to boron trifluoride at a nominal concentration of 35 mg/m^3 for 7 h/day, 5 days/week, for up to 42-45 exposures in 62-65 days (Torkelson et al. 1961). The exposed animals had obvious difficulty breathing and appeared asthmatic. Death from respiratory irritation and asphyxia occurred in 7/10 guinea pigs starting after the nineteenth exposure. Lung weight was increased, and gross examination of the lungs

revealed pneumonitis primarily in the hilar regions. Microscopic examination of the lungs revealed vessels in the alveolar walls distended with red-blood cells, erythrocytes on the alveoli, phagocytic cells containing a yellow material, thickened alveolar walls separated from the vascular epithelium, and areas of collapse and emphysema. In a second experiment, 10 male guinea pigs were exposed to boron trifluoride at a nominal concentration of 21 mg/m^3 (average measured concentration of 8-11 mg/m^3) for 7 h/day, 5 days/week for up to 29 exposures. Four guinea pigs developed what appeared to be asthmatic attacks and died; one animal died during the second, fifth, sixth, and eleventh exposure. Six guinea pigs survived 28 exposures, but had difficulty breathing and exhibited signs discomfort. They were accidentally killed after exposure to high concentrations of boron trifluoride and nitrogen on the twenty-ninth exposure day. In a third experiment, a group of 10 male and 10 female guinea pigs were exposed to boron trifluoride at a nominal concentration of 8 mg/m^3 (average measured concentration of 4 mg/m^3) for 7 h/day, 5 days/week for 127-128 exposures. All animals were killed after the last exposure and subjected to gross necropsy. The heart, lungs, liver, kidneys, spleen, and testes were weighed; these organs plus the adrenal glands and pancreas were also examined microscopically. No exposure-related deaths were observed, and no changes in growth rate, appearance, organ weights, or gross findings were noted in exposed animals compared with unexposed controls. Exposed guinea pigs had a slightly higher incidence of pneumonitis than controls.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Two dogs were exposed to boron trifluoride at a concentration estimated to be between 1,380-2,760 mg/m^3 (500-1,000 ppm) for 30 min (one dog) or 2 h (one dog) (DuPont Company 1948). Most of the experimental details were not provided, including the chemical purity, sex and strain of animals, description of exposure chamber, generation of test material aerosol, and method used for determining the concentration. The dog exposed for 30 min gagged, wheezed, and spit up frothy mucous during the exposure, but recovered after the exposure ended. The dog exposed for 2 h exhibited similar clinical signs during the exposure. For 40 min after exposure ended, the dog breathed slowly with a prolonged expiratory phase, breath sounds were noisy and bronchial, and musical rales

TABLE 1-5 Mortality of Guinea Pigs Exposed to Boron Trifluoride

Concentration	Duration	Mortality
750 ppm (2,100 mg/m^3)	5.5 h	10/10 (100%)
350 ppm (970 mg/m^3)	1.4 h	7/10 (70%)
135 ppm (370 mg/m^3)	10.9 h	1/10 (10%)

Source: Adapted from Stokinger and Spiegl 1953.

were heard over all areas of the chest. Noisy breath sounds and moist rales were still present after 160 min. The dog coughed frequently and blood pressure and body temperature became elevated. By 24 h postexposure, respiration was slow but not labored, moist rales were heard on inspiration, and a cough was still present. By 48-h postexposure, the dog's chest sounded clear; the dog was killed and necropsied. Findings included acute inflammation of the epiglottic and laryngeal tissues above the cords and slightly congested trachea and bronchi. Microscopic examination revealed marked edema of the larynx with surface necrosis, desquamation, and polymorphonuclear exudate; emphysema in the lung with areas of congestion and edema; mucopurulent exudate in the bronchi; and renal capsular spaces and convoluted tubules distended with albuminous fluid.

3.2.2. Rats

Groups of 10 male and 10 female Sprague-Dawley rats received whole body exposures to boron trifluoride hydrate vapor and aerosol (99.8% purity) at measured concentrations of 9, 25, or 74 mg/m^3 (nominal concentrations of 319, 734, and 982 mg/m^3, respectively) for 4 h (Bowden 2005). The droplet sizes at the three concentrations had mass median aerodynamic diameters of 0.7, 2.3, and 3.3 µm, respectively; 99, 89, and 79% of the droplets, respectively, were less than 7 µm. A control group was exposed to clean air. The control group and 25-mg/m^3 group were exposed on February 17, 2004; the 74-mg/m^3 group was exposed on April 21, 2004; and the 9-mg/m^3 group was exposed on September 21, 2004. Animals were from the same source and generally of the same age. Five male and five female rats/group were killed 24-h postexposure (subgroup 1), while the remaining five male and five female rats/group were observed for 14-days postexposure before termination (subgroup 2). Clinical signs in all animals were recorded are various times, including at the end of chamber equilibration; 15 min, 30 min, and 1 h into the exposure; hourly intervals during the exposure; immediately after exposure ended; and 1- and 2-h postexposure. Clinical signs were also recorded twice daily during the observation period (subgroup 2). Body weight was recorded prior to exposure (day 0), daily during the observation period (subgroup 2), and at necropsy. A visual inspection of water consumption was conducted daily. All animals were subjected to gross necropsy, and the lung and kidney weights were recorded. The respiratory tract and kidneys were fixed and examined by light microscopy. No exposure-related effects were noted on body weight, water consumption, lung or kidney weights, or macroscopic findings. Clinical signs were limited to the 25-mg/m^3 group, which exhibited no response to outside stimuli after 4 h of exposure, and one female in the 74-mg/m^3 group, which had brown staining around the snout and jaw immediately after exposure that persisted to 1-h postexposure. The clinical signs in the 25-mg/m^3 group were not considered an effect of treatment because they were not related to concentration, and there were no other supporting data that boron trifluoride is a neurotoxicant. Exposure-related histopathologic findings

were noted only in the 74-mg/m^3 group (see Table 1-6). Examination of the larynx 24-h postexposure revealed ventral cartilage necrosis (minimal to slight) in 4/5 males and 4/5 females and anterior ventral hemorrhage (minimal) in 2/5 males. These changes were not observed in the control or other exposure groups. Animals from the 74-mg/m^3 group also had an increase in the severity of ventral epithelial hyperplasia and ventral inflammatory cell infiltration in the larynx compared with control animals. Following a 2-week recovery period, ventral cartilage necrosis was still noted in one male and one female. Histopathologic findings in the trachea included an increased incidence cilia loss (minimal) at the point of tracheal bifurcation 24-h postexposure, particularly in the 74-mg/m^3 females. Incidences were comparable to controls after 2-weeks postexposure.

TABLE 1-6 Summary of Histopathologic Findings in Rats Exposed Boron Trifluoride for Four Hours

		Number of males Concentration (mg/m^3)				Number of females Concentration (mg/m^3)			
Finding	Severity	0	9	25	74	0	9	25	74
Number examined		5	5	5	5	5	5	5	5
Larynx (24-h postexposure)									
Cartilage necrosis	Total	0	0	0	4	0	0	0	4
	Minimal	0	0	0	1	0	0	0	2
	Slight	0	0	0	3	0	0	0	2
Anterior ventral hemorrhage	Minimal	0	0	0	2	0	0	0	0
Ventral epithelial hyperplasia	Total	2	1	3	4	2	0	1	5
	Minimal	1	1	3	1	2	0	1	3
	Slight	1	0	0	3	0	0	0	2
Ventral inflammatory-cell infiltration	Total	3	3	3	5	2	1	4	5
	Minimal	2	2	2	2	2	1	4	2
	Slight	1	1	1	3	0	0	0	3
Larynx (2-wk postexposure)									
Cartilage necrosis	Total	0	0	0	1	0	0	0	1
	Minimal	0	0	0	1	0	0	0	0
	Slight	0	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0	1
Anterior ventral hemorrhage	Minimal	0	0	0	0	0	0	0	0
Ventral epithelial hyperplasia	Total	0	2	1	0	0	1	0	0
	Minimal	0	2	0	0	0	1	0	0
	Slight	0	0	1	0	0	0	0	0
Ventral inflammatory-cell infiltration	Total	1	2	2	1	1	1	0	1
	Minimal	1	1	1	1	1	1	0	1
	Slight	0	1	1	0	0	0	0	0
Tracheal bifurcation (24-h postexposure)									
Loss of cilia	Minimal	0	3	2	2	1	3	2	5
Tracheal bifurcation (2-wk postexposure)									
Loss of cilia	Minimal	0	0	0	1	1	0	1	0

Source: Bowden 2005.

A series of experiments was carried out on rats to investigate the acute toxicity of inhaled boron trifluoride (DuPont Company 1948). Most of the experimental details were not provided, including chemical purity, sex and strain of animals, description of exposure chamber, generation of test material vapor, and whether exposure concentrations were nominal or analytic. In the first experiment, two rats were exposed to boron trifluoride at approximately 2,760 mg/m^3 (1,000 ppm) for 1 h. Both rats survived the exposure (no mention was made of clinical signs), and were killed and examined 24 h later. Abnormal lung findings included pulmonary congestion with swelling of the cells lining the alveoli. In the second experiment, two rats exposed for 3 h to a nominal concentration of 720 mg/m^3 (260 ppm) showed no clinical signs during exposure and no gross or microscopic changes in the lungs or other organs when killed and examined the following day. In the third experiment, a group of six rats was exposed for 4 h to a nominal concentration of boron trifluoride at 3,900 mg/m^3 (1,400 ppm). The results of this experiment are reported in Section 3.1.1 of this document because mortalities were reported.

Torkelson et al. (1961) conducted a number of repeated-exposure studies in which rats were exposed to boron trifluoride at nominal concentrations of 8, 21, or 35 mg/m^3 for 7 h/day, 5 days/week for various durations. Average measured concentrations for the 8- and 21-mg/m^3 exposures were 4 and 8-11 mg/m^3, respectively. The exposure chamber used for the 21- and 35-mg/m^3 exposures was a 160-L cubical chamber, whereas the 8-mg/m^3 exposures occurred in a 3,700-L rectangular, vault-type chamber. The chemical purity was not determined. Dry boron trifluoride gas was metered into the exposure chamber with a stream of nitrogen to prevent loss of the chemical. To determine actual exposure concentrations, air samples were taken from the chamber during exposure by drawing chamber air through a fritted glass scrubber containing distilled water. Samples were also taken from several areas within the chambers to ensure reasonable distribution of the boron trifluoride. A carbamic acid technique was used to determine the concentration of total boron, and the equivalent concentration of boron trifluoride was calculated.

In the first experiment, 14 female rats were exposed to nominal concentrations of boron trifluoride of 35 mg/m^3 for 7 h/day, 5 days/week for up to 60 exposures total (Torkelson et al. 1961). One rat died after 34 exposures, but the cause of death was not determined. Groups of four rats were killed for examination after 45 or 60 exposures. No changes in appearance, mortality, or organ weights were noted. Gross examination revealed changes in the lungs indicative of chemical irritation, with microscopic evaluation revealing pneumonitis. Five rats exposed for 60 exposures and allowed to recover for 1 month did not exhibit any changes in body weight or appearance. In a second experiment, five female rats were exposed at 21 mg/m^3 for 7 h/day, 5 days/week for 33 exposures in 51 days. No changes in appearance or body weight were observed. Fluorosis was not observed in the teeth, but the fluoride content in the bones and teeth was increased. In a third experiment, groups of 12 male and 12 female rats were exposed to boron trifluoride at a nominal concentration of 8 mg/m^3 for 7 h/day, 5

days/week for 127-128 times. All animals were killed after the last exposure and subjected to gross necropsy. The heart, lungs, liver, kidneys, spleen, and testes were weighed; these organs plus the adrenal glands and pancreas were also examined microscopically. The lower jaws were examined for fluorosis. All animals survived. No changes in growth rate, appearance, organ weights, or gross findings were observed in exposed animals compared with unexposed controls. Microscopic examination of the lungs revealed areas of pneumonitis, peribronchiole round cell infiltration, and areas of congestion of capillaries lining the alveolar walls. Fluorosis was not evident.

3.2.3. Rabbits

No changes in body weight, gross necropsy findings, organ weights (heart, lungs, liver, kidneys, spleen, and testes), or microscopic findings (adrenal glands and pancreas, in addition to the organs that were weighed) were observed in a group of three male and tree female rabbits exposed to boron trifluoride at a nominal concentration of 8 mg/m^3 (average measured concentration of 4 mg/m^3) for 7 h/day, 5 days/week for a total of 127-128 exposures (Torkelson et al. 1961).

3.3. Developmental and Reproductive Toxicity

No data were found regarding the potential for inhaled boron trifluoride to cause developmental or reproductive toxicity in laboratory animals.

3.4. Genotoxicity

Boron trifluoride at concentrations of 0.01-5 mg/plate was not mutagenic to *Salmonella typhimurium* strains TA-1535, TA-1537, TA-98, or TA-100 in the presence or absence of metabolic activation; however, it was toxic to all strains at the highest concentration (Wudl and Goode 1982).

3.5. Carcinogenicity

No data were found regarding the potential for boron trifluoride to cause cancer in laboratory animals.

3.6. Summary

A summary of lethal and nonlethal effects of boron trifluoride is presented in Tables 1-7 and 1-8. Unfortunately, exposure concentrations were not analyzed or clearly defined in most of the reports. Studies which actually measured the exposure concentrations and compared them with nominal concentrations found

TABLE 1-7 Summary of Acute Lethal Inhalation Data on Laboratory Animals

Concentration		Duration	Effect	Reference
mg/m^3	ppm[a]			
Rat				
1,100[b]	387	1 h	LC_{50} in male rats	Vernot et al. 1977
1,000[b]	371	1 h	LC_{50} in female rats	
1,210		4 h	LC_{50} in male and female rats	Rusch et al. 1986
1,180[b]		4 h	LC_{50}	Kasparov and Kiriĭ 1972
3,900[c]	1,400	4 h	2/6 died; one 148 min into exposure, the other within 24 h of exposure	DuPont Company 1948
2,100[c]	750	5.5 h	1/10 died	Stokinger and Spiegl 1953
Mouse				
3,460[b]		2 h	LC_{50}	Kasparov and Kiriĭ 1972
2,100[c]	750	5.5 h	1/10 died	Stokinger and Spiegl 1953
Guinea pig				
2,760[c]	1,000	5 min	2/2 died	DuPont Company 1948
720[c]	260	3 h	1/2 died	
109[b]		4 h	LC_{50}	Kasparov and Kiriĭ 1972
210[c]	750	5.5 h	10/10 died	Stokinger and Spiegl 1953
970[c]	350	1.4 h	7/10 died	
370[c]	135	10.9 h	1/10 died	

[a]Concentration provided in ppm only if the study authors reported concentrations in those units.
[b]Not known if nominal or measured concentrations.
[c]Nominal concentration.

TABLE 1-8 Summary of Nonlethal Inhalation Data on Laboratory Animals

Concentration		Duration[b]	Effect	Reference
mg/m^3	ppm[a]			
Dog				
1,380-2,760[c]	500-1,000	30 min	1 dog; gagged, wheezed, spit up frothy mucous during exposure; recovered after exposure.	DuPont Company 1948
		2 h	1 dog; similar clinical signs, necropsy 48-h postexposure revealed edema of larynx, emphysema in lungs, exudate in bronchi, renal capsular spaces, convoluted tubules distended with fluid.	
Rat				
2,760[c]	1,000	1 h	2/2 rats survived; pulmonary congestion.	DuPont Company 1948
720[c]	260	3 h	No clinical signs, no gross or microscopic changes.	
370[c]	135	10.9 h	10/10 rats survived.	Stokinger and Spiegl 1953
9		4 h	No effects.	Bowden 2005
25			No effects.	
74			Histopathologic changes in larynx and tracheal bifurcation indicative of irritation.	
24		6 h/d, 5 d/wk for 9 d	10/10 survived; clinical signs included oral and nasal discharge, lacrimation, dry and moist rales, gasping, poor condition; increased lung weight.	Rusch et al. 1986
66			10/10 survived; same clinical signs; decreased body weights; increased lung weight.	

35[c]	12.8[c]	7 h/d, 5 d/wk up to 60 exposures	14 rats; no changes in appearance or organ weights; gross/microscopic changes in lungs, pneumonitis.	Torkelson et al. 1961
8-11	3-4	7 h/d, 5 d/wk for 33 exposures	5 rats; no changes in appearance or body weight.	
4	1.5	7 h/d, 5 d/wk for 127-128 exposures	12 males, 12 females; no changes in appearance, body or organ weights, or gross necropsy findings.	
Mouse				
370[c]	135	10.9 h	10/10 survived.	Stokinger and Spiegl 1953
Guinea pig				
4	1.5	7 h/d, 5 d/wk for 127-128 exposures	10 males, 10 females; no changes in appearance, body or organ weights, increased incidence of pneumonitis.	Torkelson et al. 1961
Rabbit				
4	1.5	7 h/d, 5 d/wk for 127-128 exposures	3 males, 3 females; no changes in appearance, body or organ weights, or gross or microscopic findings.	Torkelson et al. 1961

[a]Concentration provided in ppm only if the study authors reported the exposure concentrations in those units.
[b]Some repeated-exposure studies are included in the table if the data were deemed relevant.
[c]Nominal concentration.

that actual concentrations ranged from 2.7-56% of nominal concentrations (Torkelson et al. 1961; Rusch et al. 1986; Bowden 2005). This is, therefore, an important consideration when analyzing studies based on nominal exposure concentrations.

Several LC_{50} values were reported. Rusch et al. (1986) calculated a 4-h LC_{50} of 1,210 mg/m^3 in male and female rats based on exposure to measured concentrations of boron trifluoride. Vernot et al. (1977) reported 1-h LC_{50} values of 1,100 and 1,000 mg/m^3 for male and female rats, respectively (unknown whether the concentrations were nominal or measured). Kasparov and Kiriĭ (1972) reported a 2-h LC_{50} of 3,460 mg/m^3 in mice, a 4-h LC_{50} of 1,180 mg/m^3 in rats, and a 4-h LC_{50} of 109 mg/m^3 in guinea pigs (unknown whether exposure concentrations were nominal or measured). Stokinger and Spiegl (1953) reported no mortality in mice and rats exposed at 370 mg/m^3 (nominal) for 10.9 h, whereas 1/10 guinea pigs died under the same exposure conditions.

Acute toxicity studies identifying end points other than those of mortality were few. Exposure of dogs to boron trifluoride at 1,380-2,760 mg/m^3 (nominal) for 30 min or 2 h resulted in gagging, wheezing, and frothy mucous production, with pulmonary and renal effects evident at microscopic examination in the dog exposed for 2 h (DuPont Company 1948). Pulmonary congestion was found in rats exposed to boron trifluoride at 2,760 mg/m^3 (nominal) for 1 h, but no effects were found in rats exposed at 720 mg/m^3 (nominal) for 3 h, or in rats and mice exposed at 370 mg/m^3 (nominal) for 10.9 h (DuPont Company 1948; Stokinger and Spiegl 1953).

Repeated-exposure studies reporting measured exposure concentrations were included in the discussion of the toxicity of boron trifluoride to provide a complete description of the chemical's toxicity at quantified levels of exposure. Studies by Torkelson et al. (1961) found no adverse effects in rats exposed at 8-11 mg/m^3 for 7 h/day, 5 days/week for 33 exposures, or in rats and rabbits exposed at 4 mg/m^3 for 7 h/day, 5 days/week for 127-128 exposures. Four guinea pigs exposed at 8-11 mg/m^3 for 7 h/day, 5 days/week died by the eleventh exposure. A slightly higher incidence of pneumonitis was the only effect observed in guinea pigs exposed at 4 mg/m^3 for 7 h/day, 5 days/week for 127-128 exposures. In a nine-day exposure study by Rusch et al. (1986), mortality from renal toxicity was observed in all rats of the high-concentration group (180 mg/m^3), whereas all rats survived exposure at 24 or 66 mg/m^3. Clinical signs were recorded on exposure days 2, 5, 9, and 11. Signs of irritation were observed in exposed groups, but were not related to concentration on exposure day 2. However, clinical signs worsened with increasing concentration and with continued exposure. A subchronic study was conducted by Rusch et al. (1986), in which groups of rats were exposed to boron trifluoride at 2, 6, or 17 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. One rat died in the high-concentration group at week 12, but all rats from the 2- and 6-mg/m^3 group survived. Excessive lacrimation was observed in five rats of the 2-mg/m^3 group (1-2 times starting at week 10), and in 16 rats of the 6-mg/m^3 group in 16 (1-2 times starting at week 2).

No data were available to evaluate the potential for boron trifluoride to cause developmental or reproductive toxicity or carcinogenicity in animals. Boron trifluoride was not mutagenic in several strains of *S. typhimurium*.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Female rats exposed to boron trifluoride aerosol for approximately 6 weeks had elevated fluoride content in the bones and teeth (Torkelson et al. 1961). A subchronic inhalation study in rats reported a concentration-related decrease in urinary calcium and concentration-related increase in urinary ionic fluoride and fluorine amounts, and clinical chemistry analysis revealed concentration-related decreases in serum protein and globulin levels, concentration-related increase in serum fluorine, and one male rat with elevated BUN levels (Rusch et al. 1986). The study authors propose that the depression of urinary calcium may have been related to increased calcium utilization as a consequence of the higher body amounts of fluoride. A comparison of urinary fluoride amounts to total urinary fluorine indicated that less than half of the boron trifluoride dissociated to free fluoride while the remainder appeared to have been excreted as undissociated boron trifluoride. Elimination of boron trifluoride (undissociated) increased to a greater degree with increasing exposure concentration compared to urinary ionic fluoride. A concentration-related increase in fluoride levels in the bones of exposed animals was also observed. The bone concentration of fluoride continued to increase even after the final exposure. It was assumed that the continued deposition in the bone occurred as a consequence of the serum fluoride source. This increase is consistent with a pattern of deposition of free fluoride from the blood.

4.2. Mechanism of Toxicity

Data specifically addressing the mechanism of inhaled boron trifluoride toxicity were not available. An examination of the toxicity data on inhaled boron trifluoride indicates that acute exposure to a lethal concentration results in effects related to the corrosive, irritant nature of this compound. Findings observed during necropsy of animals exposed once to a lethal concentration of boron trifluoride included:

- an acute inflammatory reaction of the larynx and upper trachea and slightly edematous lungs with moderate congestion of alveolar wall in one rat and consolidation of the upper part of the lobes of the lungs and pus in the bronchi in another rat (DuPont Company 1948);
- increased lung weight, pulmonary edema, and alveolar duct destruction in albino rats and guinea pigs (Kasparov and Kiriĭ 1972);

- distended lungs and pulmonary edema in one guinea pig and thickening of the pleura, atelectasis, and areas of emphysema in another guinea pig (DuPont Company 1948);
- marked edema of the larynx with surface necrosis, desquamation, and polymorphonuclear exudate, pulmonary emphysema with areas of congestion, and mucopurulent exudate in the bronchi of dogs (DuPont Company 1948); and
- renal capsular spaces and convoluted tubules distended with albuminous fluid in dogs (DuPont Company 1948).

The concentration-response for lethality resulting from an acute 4-h exposure is very steep; 3/10 rats died at 1,010 mg/m^3, while 9/10 rats died at 1,540 mg/m^3 (Rusch et al. 1986).

In contrast to the pulmonary effects observed from short inhalation exposures to high concentrations of boron trifluoride, repeated exposure at lower concentrations can result in fatal renal toxicity. When rats were exposed at 180 mg/m^3 for 6 h/day, 5 days/week for 9 days, all 10 died by the sixth exposure from renal toxicity (renal necrosis and pyknosis) (Rusch et al. 1986). When exposed at 17 mg/m^3 for 6 h/day for 13 weeks, one rat died during week 12 from renal toxicity (necrosis of the proximal tubule epithelium and tip of the renal papillae), while another exhibited renal lesions that were mild in severity (elevated BUN, hypertrophied tubule epithelial cells with karyomegaly, remnants of necrotic epithelial cells in the lumina of scattered tubules) and most likely would not have affected the survival of the animal (Rusch et al. 1986). The mechanism of action for the renal toxicity is not known, but appears to follow a steep concentration-response curve during a 9-day exposure, all rats exposed at 180 mg/m^3 died, whereas no rats died or exhibited any signs of renal toxicity at 66 mg/m^3.

4.3. Structure Activity Relationships

Boron trifluoride-dimethyl ether is one of several different complexes that can be formed with boron trifluoride. A single study was found that addressed the toxicity of boron trifluoride-dimethyl ether, but it reported only nominal concentrations. Because the complex can dissociate to form boron trifluoride, the AEGL values are based on this one chemical species alone.

4.4. Other Relevant Information

4.4.1. Species Variability

Guinea pigs were much more sensitive than other species to inhaled boron trifluoride. Guinea pigs are known to be much more sensitive to some respiratory irritants, sometimes demonstrating strong allergic anaphylactic lung responses. Sensitivity to histamine is a recognized phenomenon in guinea pigs,

and is one of the reasons it is a good model for pulmonary sensitivity (Karol 1992). Because of this sensitivity, the guinea pig data for boron trifluoride were not considered in the derivation of AEGL values.

4.4.2. Susceptible Subpopulations

Information on subpopulations susceptible to boron trifluoride was not available.

4.4.3. Concentration-Exposure Duration Relationship

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

4.4.4. Toxicity of Boron Trifluoride-Dimethyl Ether

The study by Stokinger and Spiegl (1953) is the only publication that addressed the toxicity of boron trifluoride-dimethyl ether. In a pilot study, groups of 2 or 3 guinea pigs, groups of 6 or 10 mice, and groups of 4 rats were exposed to various nominal concentrations of boron trifluoride-dimethyl ether for various durations and observed for 14 days for mortality. A summary of the mortality data is presented in Table 1-9. The authors reported that mortality occurred within 14 h in the rat and mouse, but after less than 4 h in the guinea pig.

In a repeated-exposure experiment, groups of dogs, rats, mice, guinea pigs, and rabbits were exposed to boron trifluoride at nominal concentrations of 74 or 138 mg/m^3 (27 or 50 ppm) for 6 h/day, 6 days/week for a total of 30 exposure days. A summary of the mortality can be found in Table 1-10. The authors noted that a few deaths occurred after only 5 h at 138 mg/m^3. Pathologic examination of the animals revealed mild pulmonary irritation and some degree of thyroid colloid depletion. No changes were observed in the liver, spleen, kidneys, intestines, lymph nodes, bone marrow, gonads, or adrenal glands. However, none of the dying animals were examined.

TABLE 1-9 Mortality in Laboratory Animals Exposed to Boron Trifluoride-Dimethyl Ether

Concentration (nominal)			
ppm	mg/m^3	Duration (h)	Mortality (%)
Rat			
4,580	21,000	6.5	4/4 (100)
3,450	16,000	9.5	4/4 (100)
2,580	12,000	3.5	2/4 (50)
1,290	6,000	14	1/4 (25)
850	4,000	14	3/4 (75)
550	2,600	14	1/4 (25)
485	2,300	14	1/4 (25)
345	1,600	14	0/4 (0)
265	1,200	14	0/4 (0)
Mouse			
880	4,100	5.6	3/6 (50)
380	1,800	7	10/10 (100)
225	1,000	14	3/10 (30)
155	720	14	0/10 (0)
100	470	14	0/10 (0)
Guinea pig			
3,135	15,000	0.8	2/2 (100)
2,000	9,300	0.3	2/2 (100)
1,105	5,100	0.3	2/2 (100)
695	3,200	2.8	3/3 (100)
570	2,700	0.9	2/2 (100)
405	1,900	0.3	2/2 (100)
225	1,000	0.8	2/2 (100)
110	510	2.3	1/2 (50)
50	230	3.8	1/2 (50)
38	180	14	0/2 (0)

Source: Stokinger and Spiegl 1953.

TABLE 1-10 Mortality in Laboratory Animals Exposed to Boron Trifluoride Dimethyl Ether for 30 Days

	Mortality (%)	
Species	27 ppm (130 mg/m^3)	50 ppm (230 mg/m^3)
Dog	0/5 (0)	0/5 (0)
Rat	6/100 (6)	18/99 (18)
Mouse	9/47 (19)	89/89 (100)
Guinea pig	2/30 (7)	23/30 (77)
Rabbit	0/12 (0)	0/12 (0)
Cat	0/6 (0)	2/6 (33)

Source: Stokinger and Spiegl 1953.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to deriving AEGL-1 values were available.

5.2. Summary of Animal Data Relevant to AEGL-1

Rats exposed for 4 h to a measured concentration of boron trifluoride at 25 mg/m^3 had no abnormal findings, whereas rats exposed at the next higher concentration of 74 mg/m^3 had histopathologic changes in the larynx and tracheal bifurcation indicative of irritation. The histopathologic changes in the larynx included minimal to slight ventral cartilage necrosis, minimal anterior ventral hemorrhage, and an increase in the severity of ventral epithelial hyperplasia and ventral inflammatory cell infiltration. Histopathologic changes in the trachea included an increased incidence of cilia loss (minimal) at the point of tracheal bifurcation. Following a two-week recovery period, only ventral cartilage necrosis was still noted (in one male and one female) (Bowden 2005).

5.3. Derivation of AEGL-1 Values

AEGL-1 values are based on a no-effect level for irritation in rats of 25 mg/m^3. (Irritant effects observed at 74.4 mg/m^3 were considered more severe than the threshold effects for AEGL-1 values.) A total uncertainty factor of 10 was applied. Because irritation is a direct contact effect, an interspecies uncertainty factor of 3 was applied because the mechanism of action is not expected to vary greatly among species (see NRC 2001, Section 2.5.3.2.3.), and an intraspecies uncertainty factor of 3 was applied because the mechanism of action is not expected to vary greatly in subpopulations (see NRC 2001; Section 2.5.3.4.4.). The 4-h value was set equal for all AEGL durations because the point of departure is a no-effect level for mild irritation.

AEGL-1 values are presented in Table 1-11. Although the gas is stable in dry air, boron trifluoride reacts to form the dihydrate upon exposure to even low levels of moisture in the air (NIOSH 1976; Hoffman 1981). Therefore, AEGL values are reported only in mg/m^3.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values were available.

TABLE 1-11 AEGL-1 Values for Boron Trifluoride

10 min	30 min	1 h	4 h	8 h
2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3

6.2. Summary of Animal Data Relevant to AEGL-2

Acute toxicity data from animal studies meeting the definition of AEGL-2 end points were not available. Histopathologic findings in rats exposed for 4 h to boron trifluoride at 74 mg/mg^3 were indicative of mild irritation (Bowden 2005), an effect less severe than that those defined by AEGL-2 values.

6.3. Derivation of AEGL-2 Values

In the absence of relevant data for deriving AEGL-2 values for boron trifluoride, the AEGL-3 values were divided by 3 to obtain a reasonable estimate. Dividing the AEGL-3 values by 3 is supported by the steep dose-response curve (Rusch et al. 1986).

AEGL-2 values are presented in Table 1-12. Although the gas is stable in dry air, boron trifluoride reacts to form the dihydrate upon exposure to even low levels of moisture in the air (NIOSH 1976; Hoffman 1981). Therefore, all AEGL values are reported only in mg/m^3.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Rusch et al. (1986) calculated a 4-h LC_{50} of 1,210 mg/m^3 for rats on the basis of measured concentrations of boron trifluoride dihydrate. A number of other studies also reported lethality end points: Vernot et al. (1977) reported a 1-h LC_{50} of 1,100 and 1,000 mg/m^3 for male and female rats, respectively (unknown whether concentrations were nominal or measured); Kasparov and Kiriĭ (1972) reported a 2-h LC_{50} of 3,460 mg/m^3 in mice, a 4-h LC_{50} of 1,180 mg/m^3 in rats, and a 4-h LC_{50} of 109 mg/m^3 in guinea pigs (unknown whether concentrations were nominal or measured); and Stokinger and Spiegl (1953) reported a no-effect level for death of 370 mg/m^3 (nominal) for 10.9 h in mice and rats. Studies that measured exposure concentrations and compared them with nominal concentrations found that actual concentrations ranged from 2.7-56% of nominal (Torkelson et al. 1961; Rusch et al. 1986; Bowden 2005); therefore, this difference should be considered when basing AEGL values on a nominal concentration.

TABLE 1-12 AEGL-2 Values For Boron Trifluoride

10 min	30 min	1 h	4 h	8 h
37 mg/m^3	37 mg/m^3	29 mg/m^3	18 mg/m^3	9.3 mg/m^3

7.3. Derivation of AEGL-3 Values

AEGL-3 values are based on the threshold for lethality found by Rusch et al. (1986). Using the individual mortality data from that study, a 4-h BMC_{01} (benchmark concentration with 1% response) of 736 mg/m^3 and $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 554 mg/m^3 were calculated by a log-probit analysis using EPA Benchmark Dose Software version 2.0 (2007) (see Appendix B). The 4-h $BMCL_{05}$ of 554 mg/m^3 was used to derive AEGL-3 values because it is the more conservative value. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was applied because boron trifluoride is a corrosive irritant and the mechanism of action is not expected to vary greatly among species. An intraspecies uncertainty factor of 3 was chosen because the mechanism of irritation is not expected to vary greatly among subpopulations. An intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve for lethality (3/10 rats died at 1,010 mg/m^3, while 9/10 rats died at 1,540 mg/m^3), which indicates there is not much variability in the response within a population. The Rusch et al. (1986) study is supported by the Kasparov and Kiriĭ (1972) study that reported a 2-h LC_{50} of 1,180 mg/m^3 in rats. Because the irritation occurring at the AEGL-3 level is severe irritation leading to death, the point of departure is not set equal across all AEGL time points. Instead, time-scaling was performed using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n could not be empirically derived because of inadequate data. Therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods, and n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-min value was set equal to the 30-min value because of the uncertainty in extrapolating from a 4-h exposure duration to a 10-min exposure duration.

AEGL-3 values for boron trifluoride are presented in Table 1-13. Although the gas is stable in dry air, boron trifluoride reacts to form the dihydrate upon exposure to even low levels of moisture in the air. Therefore, the values are reported only in mg/m^3.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for boron trifluoride are summarized in Table 1-14. AEGL-1 values are based on a no-effect level for irritation. Because relevant data for deriving AEGL-2 values were not available, the AEGL-3 values were divided by 3 to provide a reasonable estimate of AEGL-2 values. AEGL-3 values are based on a $BMCL_{05}$ derived measured concentrations in a rat mortality study. A limitation of the study was that mortality was observed at all exposure concen-

trations. AEGL values are reported in mg/m^3 because boron trifluoride gas becomes an aerosol upon contact with moisture in the air.

A useful way to evaluate the AEGL values in context of existing empirical data is presented in Figure 1-1. For this plot, the toxic response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: no effects, discomfort, disabling, and lethal and partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The concentrations often span a several orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 1-1 plots AEGL values for boron trifluoride along with the existing acute animal toxicity data in terms of the categories assigned to them (see data in Appendix C). This plot shows that the AEGL values are below exposure concentration in animals resulting in any effects, and should therefore be protective of human health.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for short-term exposures to boron trifluoride are presented in Table 1-15. The 1-h AEGL-1, AEGL-2, and AEGL-3 are comparable to the Emergency Response Planning Guidelines—ERPG-1, ERPG-2, and ERPG-3, respectively (AIHA 1999, 2008). The 8-h AEGL-1 is comparable to the 8-h Recommended Exposure Limits - Time-Weighted Average (NIOSH 2011) and Maximaal Aanvaaarde Concentratie (SDU Uitgevers 2000). The 30-min AEGL-3 value is almost twice that of the Immediately Dangerous to Life and Health value (NIOSH 1994).

TABLE 1-13 AEGL-3 Values For Boron Trifluoride

10 min	30 min	1 h	4 h	8 h
110 mg/m^3	110 mg/m^3	88 mg/m^3	55 mg/m^3	28 mg/m^3

TABLE 1-14 AEGL Values for Boron Trifluoride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3
AEGL-2 (disabling)	37 mg/m^3	37 mg/m^3	29 mg/m^3	18 mg/m^3	9.3 mg/m^3
AEGL-3 (lethal)	110 mg/m^3	110 mg/m^3	88 mg/m^3	55 mg/m^3	28 mg/m^3

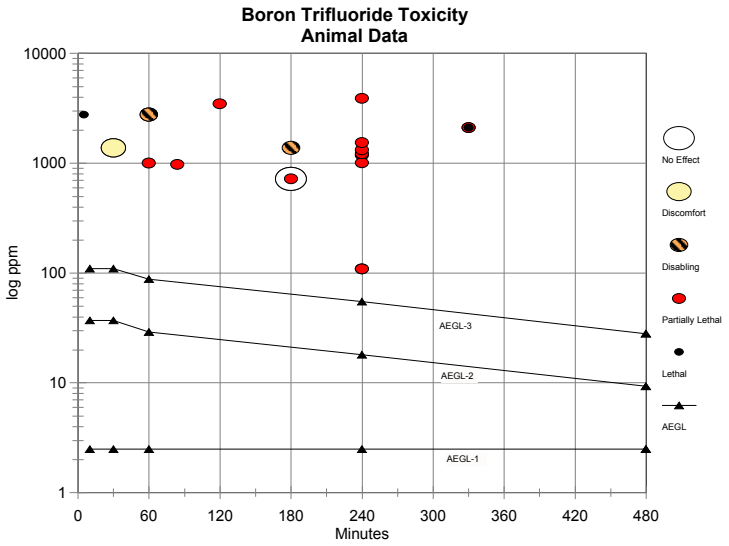

FIGURE 1-1 Category Plot of Animal Toxicity Data on Boron Trifluoride Compared with AEGL Values

TABLE 1-15 Extant Standards and Guidelines for Boron Trifluoride

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3
AEGL-2	37 mg/m^3	37 mg/m^3	29 mg/m^3	18 mg/m^3	9.3 mg/m^3
AEGL-3	110 mg/m^3	110 mg/m^3	88 mg/m^3	55 mg/m^3	28 mg/m^3
ERPG-1 (AIHA)[a]			2 mg/m^3		
ERPG-2 (AIHA)			30 mg/m^3		
ERPG-3 (AIHA)			100 mg/m^3		
IDLH (NIOSH)[b]		25 ppm [69 mg/m^3]			
TLV-STEL-Ceiling (ACGIH)[c]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]
PEL-Ceiling (OSHA)[d]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]
REL- Ceiling (NIOSH)[e]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]	1 ppm [3 mg/m^3]
MAC (The Netherlands)[f]					1 ppm [3 mg/m^3]

[a]ERPG (emergency response planning guidelines) (American Industrial Hygiene Association [AIHA 1999, 2008])

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 or developing health effects more severe than mild transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for boron trifluoride is based on the observation that while exposure to boron trifluoride at 6 mg/m^3 for 6 h/day, 5 days/week for 3 months produced slight signs of irritation (excessive lacrimation in 1-3 rats of 40 during 6 of 15 observation periods), exposure at 2 mg/m^3 for the same period did not.
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 boron trifluoride is based on the observations that all animals survived nine 6-h exposures at 66 mg/m^3 and showed no histopathologic lesions associated with the exposure; however, a 6-h exposure at 6 mg/m^3 and 17 mg/m^3 for 13 weeks produced transient signs of irritation. Acute exposure of dogs at 500-1,000 ppm (1,380-2,760 mg/m^3) resulted in marked irritation. Although these studies provided support for a level above 30 ppm, concern about impaired ability to escape because of the irritant effects of boron trifluoride suggested a lower value.
ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for boron trifluoride is based on animal studies. Two inhalation studies in rats determined a 4-h median lethal concentration of 1,200 mg/m^3, while one study indicated that even a 1-h exposure of rats at approximately 1,000 mg/m^3 could cause death. Furthermore, sensitivity to the respiratory irritant effects may be species dependent.
[b]IDLH (immediately dangerous to life or health) (National Institute for Occupational Safety and Health [NIOSH 1994]) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The IDLH for boron trifluoride is based on subchronic inhalation toxicity data in animals (Rusch et al. 1986).
[c]TLV-STEL-Ceiling (threshold limit value – short-term exposure limit - ceiling) (American Conference of Governmental Industrial Hygienists [ACGIH 2008]) is a 15-min TWA exposure that must not be exceeded during any part of the workday.
[d]PEL-Ceiling (permissible exposure limit – ceiling) (Occupational Health and Safety Administration [29CFR Part 1910.1000 [1996]) is a ceiling value that must not be exceeded during any part of the workday.
[e]REL-Ceiling (recommended exposure limit – ceiling) (National Institute for Occupational Safety and Health [NIOSH 2011) is a ceiling value that must not be exceeded during any part of the workday.
[f]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands, MSZW 2004) is defined analogous to the ACGIH TLV-TWA (a 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).

8.3. Data Quality and Research Needs

Inadequate data were available for deriving AEGL values for boron trifluoride-dimethyl ether. Therefore, the AEGLs were based on the dissociation

compounds boron trifluoride. No definitive toxicity data on boron trifluoride in humans was available, and animal studies generally relied on nominal exposure concentrations. Studies that measured the exposure concentrations and compared them with nominal concentrations found that actual concentrations ranged from 2.7-56% of nominal values. Therefore, nominal concentrations of boron trifluoride are unreliable.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR BORON TRIFLUORIDE

Derivation of AEGL-1 Values

Key study:	Bowden, A.M. 2005. Boron Trifluoride Dihydrate Acute (Four-H) Inhalation Irritation Threshold Study in Rats. Conducted by Huntingdon Life Sciences Ltd.: Cambridgeshire, England; Sponsored by Honeywell International, Inc., Morristown, NJ.
Toxicity end points:	No-effect level for irritation of 25 mg/m^3 for 4 h.
Time scaling	Values were set equal across all AEGL durations because the point of departure is a no-effect level for irritation.
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	Not applicable
10-min AEGL-1:	Set equal to 4-h AEGL-1 value of 2.5 mg/m^3
30-min AEGL-1:	Set equal to 4-h AEGL-1 value of 2.5 mg/m^3
1-h AEGL-1:	Set equal to 4-h AEGL-1 value of 2.5 mg/m^3
4-h AEGL-1:	25 $mg/m^3 \div 10 = 2.5$ mg/m^3
8-h AEGL-1:	Set equal to 4-h AEGL-1 value of 2.5 mg/m^3

Derivation of AEGL-2 Values

Calculations:	Because there were no relevant data for deriving AEGL-2 values, AEGL-3 values were divided by 3 to estimate AEGL-2 values

10-min AEGL-2:	110 mg/m^3 ÷ 3 = 37 mg/m^3
30-min AEGL-2:	110 mg/m^3 ÷ 3 = 37 mg/m^3
1-h AEGL-2:	88 mg/m^3 ÷ 3 = 29 mg/m^3
4-h AEGL-2:	55 mg/m^3 ÷ 3 = 18 mg/m^3
8-h AEGL-2:	28 mg/m^3 ÷ 3 = 9.3 mg/m^3

Derivation of AEGL-3 Values

Key study:	Rusch, G.M., G.M. Hoffman, R.F. McConnell, and W.E. Rinehart, W.E. 1986. Inhalation toxicity studies with boron trifluoride. Toxicol. Appl. Pharmacol. 83(1):69-78.
Toxicity end point:	4-h $BMCL_{05}$ in rats of 554 mg/m^3
Time scaling:	$C^n \times t = k$ (default of n = 3 for extrapolation from longer to shorter durations; default of n = 1 for extrapolation from shorter to longer durations) $[(554\ mg/m^3 \div 10)]^1 \times 4\ h = 221.6\ mg/m^3\text{-h}$ $[(554\ mg/m^3) \div 10]^3 \times 4\ h = 680{,}125.9\ mg/m^3\text{-h}$
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	Not applicable
10-min AEGL-3:	Set equal to the 30-min value of 110 mg/m^3 because of uncertainty with extrapolating from a 4-h exposure to 10 min.
30-min AEGL-3:	$C^3 \times 0.5\ h = 680{,}125.9\ mg/m^3\text{-h}$ $C^3 = 1{,}360{,}251.8\ mg/m^3$ $C = 110\ mg/m^3$
1-h AEGL-3:	$C^3 \times 1\ h = 680{,}125.9\ mg/m^3\text{-h}$ $C^3 = 680{,}125.9\ mg/m^3$ $C = 88\ mg/m^3$

4-h AEGL-3: $C^1 \times 4\ h = 221.6\ mg/m^3\text{-}h$
$C^1 = 55.4\ mg/m^3$
$C = 55\ mg/m^3$

8-h AEGL-3: $C^1 \times 8\ h = 221.6\ mg/m^3\text{-}h$
$C^1 = 27.7\ mg/m^3$
$C = 28\ mg/m^3$

APPENDIX B

BENCHMARK DOSE CALCULATIONS FOR BORON TRIFLUORIDE

Probit Model. (Version: 3.1; Date: 05/16/2008)
Input Data File: C:\USEPA\BMDS2\Data\LogBF3Set.(d)
Gnuplot Plotting File: C:\USEPA\BMDS2\Data\LogBF3Set.plt
Thu Aug 27 09:29:46 2009

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 = No._affected
Independent variable = DOSE
Slope parameter is restricted as slope > = 1

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -33.8553
Slope = 4.76995

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

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

Parameter Estimates

Variable	Estimate	Standard Error	95.0% Wald Confidence Interval	
			Lower Limit	Upper Limit
Background	0	NA		
Intercept	-32.9607	10.9082	-54.3404	-11.581
Slope	4.64094	1.53091	1.64041	7.64146

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

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance Test	DF	P-value
Full model	-19.3675	5			
Fitted model	-22.3	2	5.86491	3	0.1184
Reduced model	-34.2965	1	29.8579	4	<0.0001

AIC: 48.6

Goodness of Fit

		Scaled			
Dose	Estimated Probability	Expected	Observed	Size	Residual
0	0	0	0	10	0
1,010	0.196	1.96	3	10	0.829
1,220	0.5082	5.082	2	10	-1.95
1,320	0.6503	6.503	8	10	0.992
1,540	0.8647	8.647	9	10	0.326

Chi-square = 5.58; DF = 3 P-value = 0.1340

Benchmark Dose Computation

Specified effect = 0.01
Risk type = Extra risk
Confidence level = 0.95
BMD = 735.755
BMDL = 408.953

Benchmark Dose Computation

Specified effect = 0.05
Risk type = Extra risk
Confidence level = 0.95
BMD = 852.132
BMDL = 554.475

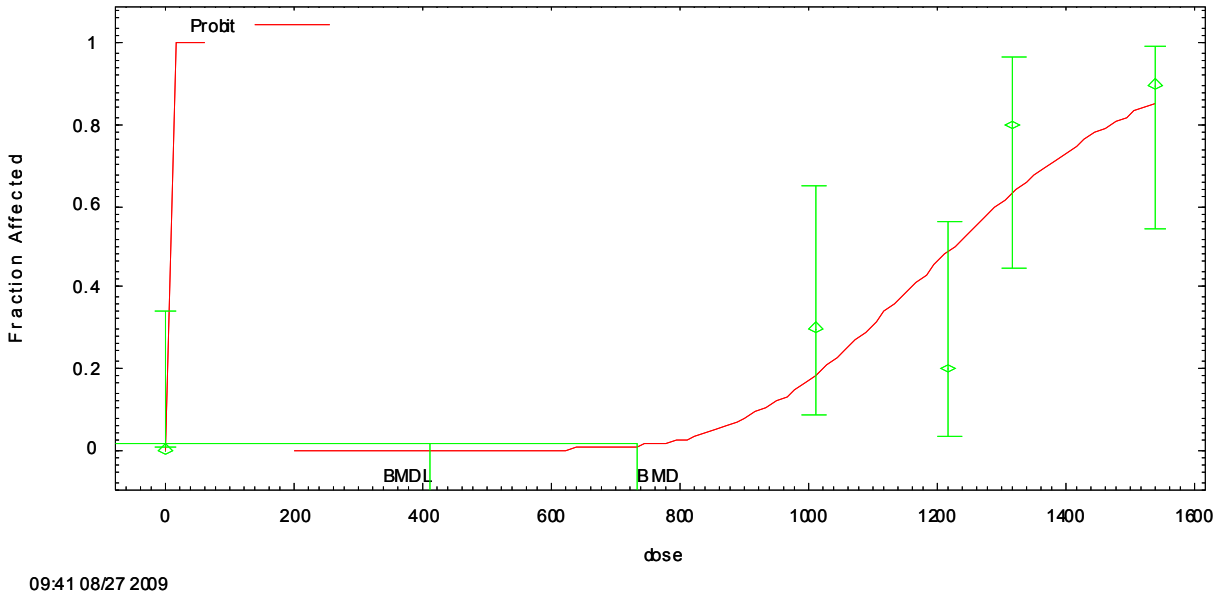

FIGURE B-1 Probit model with 0.95 confidence level. Note: A log transformed model was used to generate the graph; the fact the x-axis does not indicate log dose is an artifact of the program.

APPENDIX C

RAW DATA FOR BORON TRIFLUORIDE CATEGORY PLOT

TABLE C-1 Raw Data for Boron Trifluoride Category Plot

Source	Species	Sex	No. Exposures	mg/m3	Min	Category[a]
NAC/AEGL-1				2.5	10	AEGL
NAC/AEGL-1				2.5	30	AEGL
NAC/AEGL-1				2.5	60	AEGL
NAC/AEGL-1				2.5	240	AEGL
NAC/AEGL-1				2.5	480	AEGL
NAC/AEGL-2				37	10	AEGL
NAC/AEGL-2				37	30	AEGL
NAC/AEGL-2				29	60	AEGL
NAC/AEGL-2				18	240	AEGL
NAC/AEGL-2				9.3	480	AEGL
NAC/AEGL-3				110	10	AEGL
NAC/AEGL-3				110	30	AEGL
NAC/AEGL-3				88	60	AEGL
NAC/AEGL-3				55	240	AEGL
NAC/AEGL-3				28	480	AEGL
Vernot et al. 1977	Rat	Male		1,100	60	PL
Vernot et al. 1977	Rat	Female		1,000	60	PL
DuPont Company 1948	Rat			3,900	240	PL

Stokinger and Spiegl 1953	Rat	2,100	330	PL
Stokinger and Spiegl 1953	Rat	370	654	0
Kasparov and Kiriĭ 1972	Rat	1,180	240	PL
Rusch et al. 1986	Rat	1,010	240	PL
	Rat	1,220	240	PL
	Rat	1,320	240	PL
	Rat	1,540	240	PL
Stokinger and Spiegl 1953	Mice	2,100	330	PL
	Mice	370	654	0
Kasparov and Kiriĭ 1972	Mice	3,460	120	PL
DuPont Company 1948	Guinea pig	2,760	5	3
DuPont Company 1948	Guinea pig	720	180	PL
Stokinger and Spiegl 1953	Guinea pig	2,100	330	3
Stokinger and Spiegl 1953	Guinea pig	970	84	PL
Stokinger and Spiegl 1953	Guinea pig	370	654	PL
Kasparov and Kiriĭ 1972	Guinea pig	109	240	PL
DuPont Company 1948	Dog	1,380	30	1
DuPont Company 1948	Dog	1,380	180	2
DuPont Company 1948	Rat	2,760	60	2
DuPont Company 1948	Rat	720	180	0
Bowden 2005	Rat	9	240	0
Bowden 2005	Rat	25	240	0
Bowden 2005	Rat	74	240	1

[a]0 = no effect; 1 = discomfort; 2 = disabling; PL = partially lethal; 3 = lethal.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR BORON TRIFLUORIDE

Derivation Summary

AEGL-1

10 min	30 min	1 h	4 h	8 h
2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3

Key reference: Bowden, A.M. 2005. Boron Trifluoride Dihydrate Acute (Four-H) Inhalation Irritation Threshold Study in Rats. Conducted by Huntingdon Life Sciences Ltd., Cambridgeshire, England; Sponsored by Honeywell International, Inc., Morristown, NJ.

Test species/Strain/Number: Rat, Sprague-Dawley, 10 male and 10 female per group

Exposure route/Concentrations/Durations: Inhalation; 0, 9, 25, or 74 mg/m^3 for 4 h

Effects:
9 mg/m^3: No effects
25 mg/m^3: No effects
74 mg/m^3: Histopathologic changes in the larynx and tracheal bifurcation indicative of irritation.

End point/Concentration/Rationale: 25 mg/m^3 is a no-effect level for irritation

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the irritation is a direct contact effect, so mechanism of action is not expected to vary greatly among species (NRC 2001; Section 2.5.3.2.3.).
Intraspecies: 3, because the mechanism of action is not expected to vary greatly in subpopulations (NRC 2001; Section 2.5.3.4.4.).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The 4-h AEGL value was applied to all AEGL durations because the point of departure is a no-effect level for mild irritation.

Data adequacy: The Bowden (2005) study is the only acute study addressing nonlethal end points after exposure to a quantified concentration of boron trifluoride. Data inadequacies include data addressing acute, nonlethal exposures.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
37 mg/m^3	37 mg/m^3	29 mg/m^3	18 mg/m^3	9.3 mg/m^3

Data adequacy: No acute toxicity data relevant to deriving AEGL-2 values were available. Therefore, the AEGL-3 values wre divided by 3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
110 mg/m^3	110 mg/m^3	88 mg/m^3	55 mg/m^3	28 mg/m^3

Key reference: Rusch, G.M., G.M. Hoffman, R.F. McConnell, and W.E. Rinehart. 1986. Inhalation toxicity studies with boron trifluoride. Toxicol. Appl. Pharmacol. 83(1):69-78.

Test species/Strain/Number: Rat, F344, 5 male and 5 female per group

Exposure route/Concentrations/Durations: Inhalation; 0, 1,010, 1,220, 1,320, or 1,540 mg/m^3 for 4 h

Effects:

Concentration (mg/m^3)	Mortality
0	0/10
1,010	3/10
1,220	2/10
1,320	8/10
1,540	9/10

LC_{50}: 1,210 mg/m^3
LC_{01}: 736 mg/m^3
$BMCL_{05}$ = 554 mg/m^3

End point/Concentration/Rationale: 4-h $BMCL_{05}$ was chosen as point of departure for AEGL-3 to represent the threshold for lethality.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3, because boron trifluoride is a corrosive irritant and the mechanism of action is not expected to vary greatly among species.
Intraspecies: 3, because the mechanism of irritation is not expected to vary greatly among subpopulations; an uncertainty factor of 3 is also supported by the steep dose-response curve for lethality (3/10 rats died at 1,010 mg/m^3, while 9/10 rats died at 1,540 mg/m^3), which indicates there is not much variability in the response within a population.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to durations of 30-min and 1 h, and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because of the uncertainty with extrapolating from a 4-h exposure to 10 min.

Data adequacy: AEGL-3 values based on a calculated $BMCL_{05}$ from a study with measured concentrations of boron trifluoride. A limitation of the study was that mortality was observed at all exposure concentrations. Another limiting factor is that other studies addressing mortality after acute exposure did not provide analytic exposure concentrations; therefore, there are no other studies using the same or other species to support the values. Nonetheless, a study by Kasparov and Kiriĭ (1972) provide some supporting evidence with a 4-h LC_{50} of 1,180 mg/m^3 in rats.

APPENDIX E

SUMMARY OF ACUTE TOXICITY STUDIES WITH BORON TRIFLUORIDE COMPLEXES

TABLE E-1 Acute Toxicity Studies of Boron Trifluoride Complexes

Test Substance	Study Design	Results	References
Boron trifluoride dihydrate	Dermal irritation	6 rabbits, 0.5 mL, 24 h, total corrosion	Dunn 1980
	Eye irritation	6 rabbits, 0.1 mL, corrosive	
	Oral LD_{50}	Male rats, LD_{50} = 464 mg/kg; Female rats, LD_{50} = 282-363 mg/kg	Derelanko and Gad 1982
Boron trifluoride dinbutyl ether	Primary dermal irritation (PDI)	6 rabbits, PDI = 5.5, corrosive	Braun and Killeen 1975a
	Acute dermal toxicity	Rabbits (2 males, 2 females/group); only 2 groups tested; LD_{50} = 1-2 g/kg	Braun and Killeen 1975b
	Eye irritation	6 rabbits, 0.1 mL, corrosive	Braun and Killeen 1975c,d
	Oral LD_{50}	Rabbits (1 male and 1 female/dose), LD_{50} = 0.25 g/kg	
	Oral LD_{50}	Rats (5 males, 5 females/group), LD_{50} = 0.71 g/kg	Braun and Killeen 1975e
Boron trifluoride diethyl ether	Primary dermal irritation	6 rabbits, 0.5 mL, corrosive	Eibert 1969
	Dermal LD_{50}	Rabbits (6 males, 6 females/group, 2 groups), LD_{50} = 1-2 g/kg	
	Eye irritation	6 rabbits, 1.1 mL, corrosive	
	Oral, minimal lethal dose	Rabbits (1 male, 1 female/group), 0.32-1.0 g/kg, lethality at 0.32 g/kg	
	Oral LD_{50}	Rats, 6/group, LD_{50} = 375 mg/kg	
	Inhalation screen, 1 h exposure	Rats (5 males, 5 females/group), 2.54 mg/L, 3 males and 1 female died, 1-h LC_{50} ≥2.54 mg/L	
Boron trifluoride diethyl etherate	Oral	Rats (5 males, 5 females/group); male: LD_{50} >0.28 but <0.56 g/kg; females: 0.30 g/kg	Bonnette 2001

2

Bromoacetone[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 B. Bast (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Roberta Grant (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

Bromoacetone is a colorless liquid with a pungent odor. It is described as a dermal, ocular, and respiratory irritant. Bromoacetone was first used as a chemical weapon during World War I, and may currently be used in organic synthesis, although production data were not found. Bromoacetone is prepared by treating acetone with bromine and sodium chlorate. It occurs naturally in the essential oil of a seaweed species that grows in the ocean around the Hawaiian Islands (HSDB 2011).

AEGL-1 values for bromoacetone were based on a concentration of 0.1 ppm that caused ocular irritation in humans (Dow Chemical 1968). An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. Time scaling was not performed, because the critical effect (ocular irritation) is a function of direct contact with the bromoacetone vapor and is unlikely to increase with duration of exposure (NRC 2001). However, because of the lack of human data on exposure to bromoacetone longer than a few seconds and because the point of departure was a nominal concentration, a modifying factor of 3 was applied.

When rat irritation data were used to derive AEGL-2 values for bromoacetone, it yielded values essentially identical to the AEGL-3 values calculated from lethality data. Thus, although the concentration-response relationship for bromoacetone is not particularly steep, the AEGL-3 values were divided by 3 to calculate AEGL-2 values.

AEGL-3 values were based on lethality studies in rats exposed to bromoacetone at concentrations of 1-131 ppm and for durations of 6-120 min (Dow Chemical 1968). The threshold for lethality at each AEGL-3 exposure duration was calculated using probit analysis, based on the dose-response program of ten Berge (2006) (see Appendix B). The threshold for lethality was set at LC_{01} (lethal concentration, 1% lethality). The LC_{01} was chosen over the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) because values derived using the $BMCL_{05}$ were less consistent with human data (2.5 ppm for 10 min, 0.94 ppm for 30 min, 0.44 ppm for 1 h, 0.089 ppm for 4 h, and 0.039 ppm for 8 h; and only ocular irritation was found in humans exposed at 0.1 and 1.0 ppm). A time-scaling value of 1.3 ($C^{1.3} \times t = k$) was derived from the data. Interspecies and intraspecies uncertainty factors of 3 each were applied (total of 10), because bromoacetone is an irritant (causes lacrimation, nasal discharge, gasping, wheezing, and labored breathing in rats and ocular irritation in humans), and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

The AEGL values for bromoacetone are summarized in Table 2-1.

1. INTRODUCTION

Bromoacetone is a colorless liquid that rapidly turns violet, even in the absence of air. It has a pungent odor. It was first used as a chemical weapon during World War I, and was referred to as BA by the British and B-stoff (white cross) by the Germans. It might currently be used in organic synthesis, although production data were not found. It is prepared by treating acetone with bromine and sodium chlorate. Bromoacetone occurs naturally in the essential oil of a seaweed species that grows in the ocean around the Hawaiian Islands (HSDB 2011). Chemical and physical data for bromoacetone is provided in Table 2-2.

TABLE 2-1 AEGL Values for Bromoacetone

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	Ocular irritation in humans (Dow Chemical 1968)
AEGL-2 (disabling)	1.4 ppm (7.8 mg/m^3)	0.57 ppm (3.2 mg/m^3)	0.33 ppm (1.8 mg/m^3)	0.11 ppm (0.62 mg/m^3)	0.063 ppm (0.35 mg/m^3)	One-third AEGL-3 values
AEGL-3 (lethality)	4.1 ppm (23 mg/m^3)	1.7 ppm (9.5 mg/m^3)	0.98 ppm (5.5 mg/m^3)	0.32 ppm (1.8 mg/m^3)	0.19 ppm (1.1 mg/m^3)	Threshold for lethality (LC_{01}) in rats (Dow Chemical 1968)

TABLE 2-2 Chemical and Physical Data for Bromoacetone

Parameter	Value	Reference
Synonyms	Acetonyl bromide; acetylmethyl bromide; bromomethyl methyl ketone; 1-bromo-2-propanone; bromo-2-propanone; monobromoacetone	HSDB 2011
CAS registry no.	598-31-2	HSDB 2011
Chemical formula	C_3H_5BrO	HSDB 2011
Molecular weight	136.98	HSDB 2011
Physical state	Colorless liquid	HSDB 2011
Melting point	-36.5°C	HSDB 2011
Boiling point	138°C	HSDB 2011
Specific gravity	1.634 (air = 1) at 23°C	HSDB 2011
Relative vapor density	4.75 (air = 1)	HSDB 2011
Solubility in water	"Slightly" soluble; soluble in alcohol, acetone, and ether	HSDB 2011
Vapor pressure	9 mm Hg at 20°C	HSDB 2011
Flash point	51.1°C	IPCS 2005
Conversion factors in air	1 ppm = 5.6 mg/m^3 1 mg/m^3 = 0.18 ppm	HSDB 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data on bromoacetone were not located.

2.2. Nonlethal Toxicity

Six human volunteers (age and sex not specified) were self-exposed to bromoacetone at 0.1 ppm (nominal concentration) or 1.0 ppm (analytic concentration) to investigate acute irritative effects and odor (Dow Chemical 1968). Exposure duration was not report, but it appears to have been no more than a few seconds. The ocular irritation test was conducted by passing the prepared vapor sample from a Saran™ bag into modified chemical-worker goggles worn by the subject. The odor test was conducted by having the subjects sniff the gas from the exposure chamber or gas sampling bag. All six subjects reported considerable ocular irritation at 1.0 ppm, and two at 0.1 ppm. None of the subjects reported an objectionable odor at 1.0 ppm. No information on respiratory irritation or other respiratory effects was provided in the study report.

2.3. Case Reports

No case reports were found.

2.4. Developmental and Reproductive Effects

No information on the developmental or reproductive toxicity of bromoacetone in humans was available.

2.5. Genotoxicity

No information on the genotoxicity of bromoacetone in humans was available.

2.6. Carcinogenicity

No information on the carcinogenicity of bromoacetone in humans was available.

2.7. Summary

There is little human inhalation data on bromoacetone. Bromoacetone caused ocular irritation in two of six subjects at 0.1 ppm and in all six subjects at 1.0 ppm; however, no information on respiratory irritation or other respiratory effects was provided in the study report. No objectionable odor was reported at 1.0 ppm. No data on the developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of bromoacetone were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of five male rats (strain not specified) were exposed to bromoacetone at 17-131 ppm (analytic concentrations) for durations of 6-120 min, followed by a 14-day observation period (Dow Chemical 1968). Concentration-duration information is presented in Table 2-3. The tests were performed in a 160-L glass exposure chamber. Constant chamber airflow was maintained by means of a rotary air pump located at the exhaust side of the chamber; airflow was monitored with a rotameter. Bromoacetone was vaporized by aerosolizing a metered quantity of liquid with a positive pressure spray nozzle enclosed within a temperature-controlled round bottomed flask. Vapor laden air was then diluted with filtered room air, and passed through an aerosol trap before being drawn into the exposure chamber. Chamber concentrations were measured by gas chromatography.

During exposure, all animals showed severe ocular and nasal irritation, as evidenced by profuse lacrimation and salivation. Dyspnea followed these effects. After exposure ended, all animals exhibited mucoid nasal and oral secretions, respiratory wheezing, and severe dyspnea. Death occurred within hours and at up to 2 weeks, depending on exposure concentration and duration. Gross necropsies of animals dying during the observation period showed congested nasal passages and slight congestion and patchy hemorrhages in the lungs. The most notable observation was enormous distension of the stomach and intestines by gas, to the extent that pressure on the diaphragm may have interfered with respiratory function. No abnormalities were noted in the liver, kidneys, or other major organs. Necropsies of animals surviving the 14-day observation period showed only moderate focal pneumonia. Experimental parameters, clinical signs, and mortality incidence data are summarized in Table 2-3.

TABLE 2-3 Acute Inhalation Toxicity of Bromoacetone in Male Rats

Concentration (ppm)	Duration (min)	Mortality	Day of Death	Effects During Exposure	Effects After Exposure
17	12	0/5	–	Lacrimation, nasal discharge, and labored breathing.	None.
28	30	2/5	1		Bloody nasal discharge and weight loss.
28	60	4/5	14		Gasping, wheezing, bloody nasal discharge, and weight loss.
28	120	5/5	1		Gasping, wheezing, and bloody nasal discharge.
48	60	5/5	12	Same as above, except more rapid onset and more severe.	Wheezing and bloody nasal discharge.
48	120	5/5	1		Gasping, wheezing, and bloody nasal discharge.
51	6	0/5	–		Weight loss
51	12	0/5	–		None
51	30	3/5	2		Wheezing, bloody nasal discharge, and weight loss.
131	10	5/5	11	Same as above, except much faster onset and more severe.	Wheezing, bloody nasal discharge, and weight loss.
131	30	5/5	3		Gasping, wheezing, and bloody nasal discharge.

Source: Dow Chemical 1968.

3.1.2. Summary of Animal Lethality Data

Only one study on lethality from bromoacetone was available. That study demonstrated that bromoacetone is an irritant in rats, causing lacrimation, nasal discharge, gasping, wheezing, and labored breathing).

3.2. Nonlethal Toxicity

3.2.1. Rats

In a companion study to the acute lethality study described earlier, groups of four male rats (strain not specified) were exposed to bromoacetone at 0-18 ppm (analytic concentrations) for 15-87 min, followed by a 14-day observation period (Dow Chemical 1968). The experimental methodology was as described in Section 3.1.1, and concentration-duration information is presented in Table 2-4. The purpose of the study was to determine an irritation threshold in rats. Rats exposed to bromoacetone at 2 ppm showed definite signs of ocular irritation, and those exposed at 10 ppm had signs of respiratory tract irritation. Postexposure nasal discharge persisted only in rats exposed at 18 ppm. During the observation period, weight loss was reported in the 10 and 18 ppm groups; however, the magnitude of the weight loss was not reported. No treatment-related abnormalities were observed in any of the rats at necropsy. Experimental parameters, clinical signs, and mortality incidence data are summarized in Table 2-4.

TABLE 2-4 Acute Irritation of Bromoacetone in Male Rats

Concentration (ppm)	Duration (min)	Mortality	Effects During Exposure	Time to Response (sec)	Effects After Exposure
0	15	0/4	None	–	None
1.0	15	0/4	Mild blinking (reported as +/-)	101	None
2.0	20	0/4	Blinking	98	None
6.3	74	0/4	Blinking	56	None
10.0	43	0/4	Blinking, lacrimation, and sneezing	68	Body weight loss
18.0	87	Not reported	Blinking, lacrimation, sneezing, and dyspnea.	25	Nasal discharge and body weight loss

Source: Dow Chemical 1968.

3.2.2. Summary of Nonlethal Toxicity in Animals

Only one study on nonlethal effects from acute inhalation of bromoacetone was available (Dow Chemical 1968). Bromoacetone was an irritant in rats, causing blinking, lacrimation, sneezing, and shortness of breath.

3.3. Developmental and Reproductive Effects

No developmental or reproductive data on bromoacetone were found.

3.4. Genotoxicity

No genotoxicity data on bromoacetone were found.

3.5. Carcinogenicity

No carcinogenicity data on bromoacetone were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No metabolism data on bromoacetone were available.

4.2. Mechanism of Toxicity

The few inhalation studies available on bromoacetone suggest that bromoacetone is an irritant. Two of six human subjects reported ocular irritation at 0.1 ppm, and all six had irritation at 1 ppm. Rats exhibited lacrimation, nasal discharge, gasping, wheezing, and labored breathing after being exposed to bromoacetone (Dow Chemical 1968). HSDB (2011 also describes bromoacetone as a dermal, ocular, and respiratory irritant.

4.3. Structure-Activity Relationships

Bromoacetone is structurally similar to chloroacetone, which is also an irritant. However, bromoacetone appears to be a more potent irritant than chloroacetone. Humans exposed to chloroacetone first experience lacrimation at approximately 5 ppm (Sargent et al. 1986), whereas ocular irritation from bromoacetone has been reported at lower concentrations of 0.1 and 1.0 ppm (Dow Chemical 1968).

A 1-h LC_{50} of 316 ppm was reported for chloroacetone in male rats, and no mortality occurred in rats exposed at 132 ppm for 1 h (Arts and Zwart 1987).

However, in studies with bromoacetone, death occurred in four of five male rats exposed at 28 ppm and in all five rats exposed at 48 ppm for 1 h (Dow Chemical 1968).

4.4. Species Variability

Data are insufficient to determine species variability for bromoacetone. Bromoacetone is an irritant and clinical signs are likely caused by a direct chemical effect on tissues. This type of portal-of-entry effect is not likely to vary greatly between species.

4.5. Temporal Extrapolation

The concentration-time relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was determined by analyzing the available lethality data on bromoacetone in rats using the DoseResp software of ten Berge (2006). On the basis of the concentration-specific data presented in Tables 2-3 and 2-4, the analysis produced an exponent value of 1.3, with confidence limits of 0.80 and 1.7. Details of the analysis are provided in Appendix B.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Immediate ocular irritation was observed in six of six humans exposed to bromoacetone at 1.0 ppm, and in two of six humans exposed at 0.1 ppm (Dow Chemical 1968).

5.2. Animal Data Relevant to AEGL-1

Slight blinking was observed in rats exposed to bromoacetone at 1.0 ppm for 15 min (Dow Chemical 1968).

5.3. Derivation of AEGL-1 Values

A concentration of 0.1 ppm was selected as the point of departure for deriving AEGL-1 values for bromoacetone. That concentration caused ocular irritation in two of six humans (Dow Chemical 1968). An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. Time scal-

ing was performed, because ocular irritation is a function of direct contact with the bromoacetone vapor and is unlikely to increase with duration of exposure (NRC 2001). However, because of the lack of human data on exposures longer than a few seconds and because the point of departure is a nominal concentration, a modifying factor of 3 was applied. AEGL-1 values for bromoacetone are presented in Table 2-5, and their derivation presented in Appendix A.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values were found.

6.2. Animal Data Relevant to AEGL-2

Blinking, lacrimation, sneezing, and body weight loss were observed in rats exposed to bromoacetone at 10 ppm for 43 min (Dow Chemical 1968).

6.3. Derivation of AEGL-2 Values

Although the concentration-response relationship for bromoacetone is not particularly steep, the AEGL-3 values were divided by 3 to calculate AEGL-2 values for bromoacetone. This approach was used instead of basing the values on rat data, because when rat irritation data were used to calculate AEGL-2 values, they were essentially identical to the AEGL-3 values based on lethality data. (AEGL-2 values derived with a point of departure of 10 ppm for 43 min, with interspecies and intraspecies uncertainty factors of 3 each, and with a time-scaling exponent of 1.3 [see Section 4.5] resulted in the following values: 3.2 ppm for 10 min, 1.3 ppm for 30 min, 0.77 ppm for 1 h, 0.26 ppm for 4 h, and 0.15 ppm for 8 h.)

AEGL-2 values for bromoacetone are presented in Table 2-6, and calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values were found.

TABLE 2-5 AEGL-1 Values for Bromoacetone

10 min	30 min	1 h	4 h	8 h
0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)

TABLE 2-6 AEGL-2 Values for Bromoacetone

10 min	30 min	1 h	4 h	8 h
1.4 ppm (7.8 mg/m^3)	0.57 ppm (3.2 mg/m^3)	0.33 ppm (1.8 mg/m^3)	0.11 ppm (0.62 mg/m^3)	0.063 ppm (0.35 mg/m^3)

7.2. Animal Data Relevant to AEGL-3

Animal lethality data were available for rats exposed to varying concentrations of bromoacetone for different time periods (Dow Chemical 1968). Exposure durations ranged from 6 to 120 min and concentrations ranged from 1.0 to 131 ppm. Mortality incidences ranged from 0 to 100%, depending on concentration-duration pairings. The experimental parameters were summarized earlier in Tables 2-3 and 2-4.

7.3. Derivation of AEGL-3 Values

Using the data from the studies by Dow Chemical (1968) presented in Tables 2-3 and 2-4, the lethality threshold at each AEGL-3 exposure duration was calculated using the probit analysis based on the dose-response program of ten Berge (2006) (see Appendix B). The lethality threshold was set at the LC_{01} (lethal concentration, 1% lethality). The LC_{01} was chosen over the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) because values derived with the $BMCL_{05}$ were less consistent with human data (2.5 ppm for 10 min, 0.94 ppm for 30 min, 0.44 ppm for 1 h, 0.089 ppm for 4 h, and 0.039 ppm for 8 h; and only ocular irritation was noted in humans at 0.1 and 1.0 ppm). A time-scaling value of 1.3 ($C^{1.3} \times t = k$) was determined from the data. These calculated values were used as the basis for the AEGL-3 values.

Interspecies and intraspecies uncertainty factors of 3 each were applied (total of 10) and were considered sufficient because bromoacetone is an irritant, and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

The resulting AEGL-3 values are shown in Table 2-7, and their derivation summarized in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL values for bromoacetone are summarized in Table 2-8. AEGL-1 values are based on ocular irritation in humans, and AEGL-3 values are based on a lethality threshold (LC_{01}) in rats. AEGL-2 values were derived by dividing the AEGL-3 values by 3.

TABLE 2-7 AEGL-3 Values for Bromoacetone

10 min	30 min	1 h	4 h	8 h
4.1 ppm (23 mg/m^3)	1.7 ppm (9.5 mg/m^3)	0.98 ppm (5.5 mg/m^3)	0.32 ppm (1.8 mg/m^3)	0.19 ppm (1.1 mg/m^3)

TABLE 2-8 AEGL Values for Bromoacetone

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)
AEGL-2 (disabling)	1.4 ppm (7.8 mg/m^3)	0.57 ppm (3.2 mg/m^3)	0.33 ppm (1.8 mg/m^3)	0.11 ppm (0.62 mg/m^3)	0.063 ppm (0.35 mg/m^3)
AEGL-3 (lethality)	4.1 ppm (23 mg/m^3)	1.7 ppm (9.5 mg/m^3)	0.98 ppm (5.5 mg/m^3)	0.32 ppm (1.8 mg/m^3)	0.19 ppm (1.1 mg/m^3)

8.2. Comparisons with Other Standards and Guidelines

There are no other standards or guidelines for bromoacetone.

8.3. Data Adequacy and Research Needs

Additional acute animal studies in species other than rats would be helpful.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR BROMOACETONE

Derivation of AEGL-1 Values

Key study:	Dow Chemical. 1968. Inhalation Exposure Toxicity of Bromoacetone and a Fumigant Mixture Containing Bromoacetone with Cover Letter Dated 041086. EPA Document No. 86860000027. Microfiche No. OTS0510179.
Critical effect:	Ocular irritation in two of six humans at 0.1 ppm
Time scaling:	None applied. The critical effect (ocular irritation) is a function of direct contact with the bromoacetone vapors and unlikely to increase with duration of exposure (NRC 2001).
Uncertainty factors:	1 for interspecies differences 3 for intraspecies variability; contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. Total uncertainty factor of 3
Modifying factor:	3 because of the lack of human data on exposure durations longer than a few seconds and because the point of departure is a nominal concentration.
Calculations:	
10- and 30-min, 1-, 4-, and 8-h AEGL-1:	0.1 ppm ÷ 3 ÷ 3 = 0.011 ppm

Derivation of AEGL-2 Values for Bromoacetone

AEGL-2 values were derived by taking one-third of the respective AEGL-3 values, even though there were data relevant to AEGL-2 values and the

concentration-response relationship for bromoacetone is not particularly steep. However, when rat irritation data was used the point of departure, AEGL-2 values were essentially identical to AEGL-3 values calculated from lethality data (see below).

Calculations based on one-third of the AEGL-3 values:

10-min AEGL-2:	4.1 ppm (10-min AEGL-3) ÷ 3 = 1.4 ppm
30-min AEGL-2:	1.7 ppm (30-min AEGL-3) ÷ 3 = 0.57 ppm
1-h AEGL-2:	0.98 ppm (1-h AEGL-3) ÷ 3 = 0.33 ppm
4-h AEGL-2:	0.32 ppm (4-h AEGL-3) ÷ 3 = 0.11 ppm
8-h AEGL-2:	0.19 ppm (8-h AEGL-3) ÷ 3 = 0.063 ppm

Calculations based on relevant animal data:

Key study:	Dow Chemical. 1968. Inhalation Exposure Toxicity of Bromoacetone and a Fumigant Mixture Containing Bromoacetone with Cover Letter Dated 041086. EPA Document No. 86860000027. Microfiche No. OTS0510179.
Toxicity end point:	Irritation in rats at 10 ppm for 43 min (0.717 h)
Time scaling:	$C^n \times t = k$ where n = 1.3 $C^{1.3} \times t = k$ $(10\ ppm)^{1.3} \times 0.717\ h = k$ k = 14.3 ppm-h
Uncertainty factors	3 for interspecies differences 3 for intraspecies variability: 3 Total uncertainty factor of 10
10-min AEGL-2:	$C^{1.3} \times 0.167\ h = 14.3$ ppm-h $C^{1.3} = 85.6$ ppm C = 30.6 ppm 30.6 ÷ 10 = 3.1 ppm

30-min AEGL-2:	$C^{1.3} \times 0.5$ h = 14.3 ppm-h $C^{1.3}$ = 28.6 ppm C = 13.2 ppm 13.2 ÷ 10 = 1.3 ppm
1-h AEGL-2:	$C^{1.3} \times 1$ h = 14.3 ppm-h $C^{1.3}$ = 14.3 ppm C = 7.7 ppm 7.7 ÷ 10 = 0.77 ppm
4-h AEGL-2:	$C^{1.3} \times 4$ h = 14.3 ppm-h $C^{1.3}$ = 3.57 ppm C = 2.66 ppm 2.66 ÷ 10 = 0.27 ppm
8-h AEGL-2:	$C^{1.3} \times 8$ h = 14.3 ppm-h $C^{1.3}$ = 1.79 ppm C = 1.56 ppm 1.56 ÷ 10 = 0.16 ppm

Derivation of AEGL-3 Values for Bromoacetone

Key study:	Dow Chemical. 1968. Inhalation Exposure Toxicity of Bromoacetone and a Fumigant Mixture Containing Bromoacetone with Cover Letter Dated 041086. EPA Document No. 86860000027. Microfiche No. OTS0510179.
Toxicity end point:	Threshold for lethality in rats (L_{01}) calculated using probit-analysis dose-response program of ten Berge (2006). LC_{01} point estimates obtained for 10 and 30 min, and 1, 4, and 8 h.
Time scaling:	$C^n \times t = k$ where n = 1.3 based on rat lethality data (see Appendix B for time-scaling calculations)
Uncertainty factors:	3 for interspecies differences; considered sufficient because bromoacetone is an irritant (lacrimation, nasal discharge, gasping, wheezing, and labored breathing in rats and ocular irritation in humans) and

clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species.

3 for intraspecies variability; considered sufficient because bromoacetone is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals.

Total uncertainty factor of 10

Data for Calculations

Concentration (ppm)	Exposure duration (min)	Mortality incidence
28	120	5/5
28	60	4/5
28	30	2/5
17	12	0/5
48	120	5/5
48	60	5/5
51	30	3/5
51	12	0/5
51	6	0/5
131	30	5/5
131	10	5/5
1.0	15	0/4
2.0	20	0/4
6.3	74	0/4
10.0	43	0/4

ten Berge (2006) Program Output

Exposure Duration	LC_{01} point estimate (ppm)
10 min	40.69
30 min	16.97
1 h	9.773
4 h	3.241
8 h	1.867

n = 1.3

Calculations:

10-min AEGL-3:	40.69 ppm ÷ 10 4.1 ppm
30-min AEGL-3:	16.97 ppm ÷ 10 1.7 ppm
1-h AEGL-3:	9.773 ppm ÷ 10 0.98 ppm
4-h AEGL-3:	3.241 ppm ÷ 10 0.32 ppm
8-h AEGL-3:	1.867 ppm ÷ 10 0.19 ppm

APPENDIX B

Time-Scaling Calculations for Bromoacetone

An n of 1.3 was obtained after analysis of lethality data in rats (Dow Chemical 1968) using the software of ten Berge (2006). This exposure-time relationship for lethality was considered appropriate for AEGL-3 development but because bromoacetone-induced ocular irritation is the result of direct-contact irritation. No time scaling was used in the development of AEGL-1 values. AEGL-2 values were derived by taking one-third of the AEGL-3 values, so no time scaling was necessary.

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = Concentration (ppm), ln-transformed
X2 = Min, ln-transformed

Chi-square	= 4.50
Degrees of freedom	= 12
Probability Model	= 9.73E-01

Ln(Likelihood)	= -5.61

B 0 = -1.3833E+01	Student *t* = -2.8141
B 1 = 2.9799E+00	Student *t* = 3.6728
B 2 = 2.3722E+00	Student *t* = 3.6582

Variance B 0	0 = 2.4161E+01
Covariance B 0	1 = -3.8264E+00
Covariance B 0	2 = -2.9135E+00
Variance B 1	1 = 6.5827E-01
Covariance B 1	2 = 4.0467E-01
Variance B 2	2 = 4.2051E-01

Estimation ratio between regression coefficients of ln(concentration) and ln(min)
Point estimate = 1.256
Lower limit (95% CL) = 0.800
Upper limit (95% CL) = 1.713

Estimation of concentration (ppm) at response of 1%
Min = 10
Point estimate concentration (ppm) = 4.069E+01 for response of 1%
Lower limit (95% CL) concentration (ppm) = 1.623E+01 for response of 1%
Upper limit (95% CL) concentration (ppm) = 5.881E+01 for response of 1%

Filename: Bromoacetone Dow Chemical Rat for Log Probit Model

Date: 08 September 2008 Time: 11:14:28

Sequence Number	Concentration (ppm)	Min	Sex	Exposed	Responded
1	28	120	1	5	5
2	28	60	1	5	4
3	28	30	1	5	2
4	17	12	1	5	0
5	48	120	1	5	5
6	48	60	1	5	5
7	51	30	1	5	3
8	51	12	1	5	0
9	51	6	1	5	0
10	131	30	1	5	5
11	131	10	1	5	5
12	10	43	1	4	0
13	6	74	1	4	0
14	2	20	1	4	0
15	1	15	1	4	0
Observations 1 through 15 considered					
1	28	120		5	5
2	28	60		5	4
3	28	30		5	2
4	17	12		5	0
5	48	120		5	5
6	48	60		5	5
7	51	30		5	3
8	51	12		5	0
9	51	6		5	0
10	131	30		5	5
11	131	10		5	5
12	10	43		4	0
13	6	74		4	0
14	2	20		4	0
15	1	15		4	0

Estimation of concentration (ppm) at response of 1%
Min = 30
Point estimate concentration (ppm) = 1.697E+01 for response of 1%
Lower limit (95% CL) concentration (ppm) = 5.890E+00 for response of 1%
Upper limit (95% CL) concentration (ppm) = 2.405E+01 for response of 1%
Estimation of concentration (ppm) at response of 1%
Min = 60
Point estimate concentration (ppm) = 9.773E+00 for response of 1%
Lower limit (95% CL) concentration (ppm) = 2.829E+00 for response of 1%
Upper limit (95% CL) concentration (ppm) = 1.503E+01 for response of 1%

Estimation of concentration (ppm) at response of 1%
Min = 120
Point estimate concentration (ppm) = 5.628E+00 for response of 1%
Lower limit (95% CL) concentration (ppm) = 1.303E+00 for response of 1%
Upper limit (95% CL) concentration (ppm) = 9.794E+00 for response of 1%

Estimation of concentration (ppm) at response of 1%
Min = 240
Point estimate concentration (ppm) = 3.241E+00 for response of 1%
Lower limit (95% CL) concentration (ppm) = 5.857E-01 for response of 1%
Upper limit (95% CL) concentration (ppm) = 6.537E+00 for response of 1%

Estimation of concentration (ppm) at response of 1%
Min = 480
Point estimate concentration (ppm) = 1.867E+00 for response of 1%
Lower limit (95% CL) concentration (ppm) = 2.597E-01 for response of 1%
Upper limit (95% CL) concentration (ppm) = 4.424E+00 for response of 1%

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVESL FOR BROMOACETONE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)	0.011 ppm (0.062 mg/m^3)

Reference: Dow Chemical. 1968. Inhalation Exposure Toxicity of Bromoacetone and a Fumigant Mixture Containing Bromoacetone with Cover Letter Dated 041086. EPA Document No. 86860000027. Microfiche No. OTS0510179.

Test Species/Strain/Number: Human subjects (age and sex not specified); six subjects

Exposure route/Concentrations/Durations: Vapor exposure at 0.1 or 1 ppm; duration not reported, but appears to be seconds.

Effects: Ocular irritation in two of six subjects at 0.1 ppm; considerable ocular irritation in all six subjects at 1 ppm. No objectionable odor reported.

End point/Concentration/Rationale: Ocular irritation at 0.1 ppm in two of six subjects.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because human data were used.
Intraspecies: 3, because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals.

Modifying factor: 3, because of the lack of human data on exposures longer than a few seconds and because the point of departure is a nominal concentration.

Animal-to-human dosimetric adjustment: None

Time scaling: none

Data adequacy: Sparse data set; modifying factor necessary.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.4 ppm (7.8 mg/m^3)	0.57 ppm (3.2 mg/m^3)	0.33 ppm (1.8 mg/m^3)	0.11 ppm (0.62 mg/m^3)	0.063 ppm (0.35 mg/m^3)

End point/Concentration/Rationale: Values were calculated as one-third the AEGL-3 values, because AEGL-2 values derived from relevant rat data were essentially identical to the AEGL-3 values calculated from lethality data.

Data adequacy: Sparse data set for AEGL-2 effects. AEGL-2 values derived using clinical signs in rats exposed at 10 ppm for 43 min, with interspecies and intraspecies uncertainty factors of 3 each, and with a time-scaling exponent of 1.3 [see Section 4.5] would have resulted in the following values: 3.2 ppm for 10 min, 1.3 ppm for 30 min, 0.77 ppm for 1 h, 0.26 ppm for 4 h, and 0.15 ppm for 8 h. AEGL-2 values based on one-third of the AEGL-3 values are considered protective.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
4.1 ppm (23 mg/m^3)	1.7 ppm (9.5 mg/m^3)	0.98 ppm (5.5 mg/m^3)	0.32 ppm (1.8 mg/m^3)	0.19 ppm (1.1 mg/m^3)

Reference: Dow Chemical, 1968. Inhalation Exposure Toxicity of Bromoacetone and a Fumigant Mixture Containing Bromoacetone with Cover Letter dated 041086. EPA Document No. 86860000027. Microfiche No. OTS0510179.

Test species/Strain/Sex/Number: Rat, strain not specified, male, 4-5 per group

Exposure route/Concentrations/Durations: Inhalation, 1.0-131 ppm for 6-120 min

Effects: Lethality

Concentration (ppm)	Duration (min)	Mortality
28	120	5/5
28	60	4/5
28	30	2/5
17	12	0/5
48	120	5/5
48	60	5/5
51	30	3/5
51	12	0/5
51	6	0/5
131	30	5/5
131	10	5/5
1	15	0/4
2	20	0/4
6.3	74	0/4
10	43	0/4

End point/Concentration/Rationale: Threshold for lethality in rats (L_{01}) calculated using probit-analysis dose-response program of ten Berge (2006). The LC_{01} was chosen over the $BMCL_{05}$ because values derived with the $BMCL_{05}$ were less consistent with human data (2.5 ppm for 10 min, 0.94 ppm for 30 min, 0.44 ppm for 1 h, 0.089 ppm for 4 h, and 0.039 ppm for 8 h; and only ocular irritation was noted in humans at 0.1 and 1.0 ppm).

(Continued)

AEGL-3 Continued

Uncertainty factors/Rationale Total uncertainty factor: 10 Interspecies: 3, considered sufficient because bromoacetone is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species. Intraspecies: 3, considered sufficient because bromoacetone is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals.
Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: $C^n \times t = k$, where n = 1.3 as determined by analysis of rat lethality data using ten Berge (2006) software.
Data adequacy: Sparse data set. One well-conducted study in rats with effects relevant to AEGL-3 values.

APPENDIX C

CATEGORY PLOT OF TOXICITY DATA AND AEGL VALUES FOR BROMOACETONE

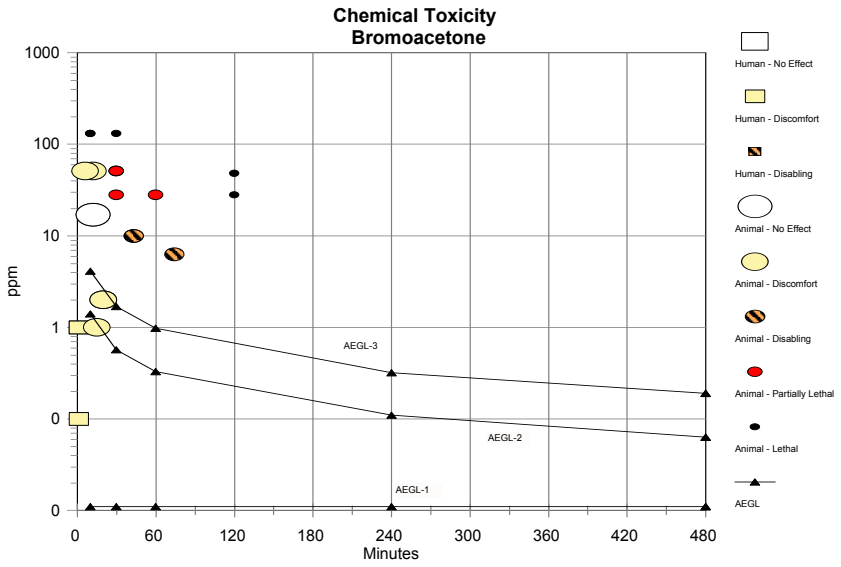

FIGURE C-1 Category graph of toxicity data on bromoacetone compared with AEGL values.

TABLE C-1 Data Used in the Category Graph

Source	Species	Sex	No. of Exposures	ppm	Min	Category	Comments
AEGL-1				0.011	10	AEGL	
AEGL-1				0.011	30	AEGL	
AEGL-1				0.011	60	AEGL	
AEGL-1				0.011	240	AEGL	
AEGL-1				0.011	480	AEGL	
AEGL-2				1.4	10	AEGL	
AEGL-2				0.57	30	AEGL	
AEGL-2				0.33	60	AEGL	
AEGL-2				0.11	240	AEGL	
AEGL-2				0.063	480	AEGL	
AEGL-3				4.1	10	AEGL	
AEGL-3				1.7	30	AEGL	
AEGL-3				0.98	60	AEGL	
AEGL-3				0.32	240	AEGL	
AEGL-3				0.19	480	AEGL	
	Rat	Male	1	28	120	3	5/5 mortality; lacrimation, gasping, wheezing, and nasal discharge.

Rat	Male	1	28	60	PL	4/5 mortality; lacrimation, gasping, wheezing, nasal discharge, and body weight loss.
Rat	Male	1	28	30	PL	2/5 mortality; lacrimation, gasping, wheezing, nasal discharge, and body weight loss.
Rat	Male	1	17	12	0	No effects.
Rat	Male	1	48	120	3	5/5 mortality; lacrimation, gasping, wheezing, and nasal discharge.
Rat	Male	1	48	60	5	5/5 mortality; lacrimation, wheezing, and nasal discharge.
Rat	Male	1	51	30	PL	3/5 mortality; lacrimation, wheezing, nasal discharge, and body weight loss.
Rat	Male	1	51	12	1	Lacrimation and nasal discharge.
Rat	Male	1	51	6	1	Lacrimation and nasal discharge.
Rat	Male	1	131	30	3	5/5 mortality; lacrimation, gasping, wheezing, and nasal discharge.
Rat	Male	1	131	10	3	5/5 mortality; lacrimation, gasping, wheezing, nasal discharge, and body weight loss.
Rat	Male	1	1	15	1	Mild blinking.

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Min	Category	Comments
	Rat	Male	1	2	20	1	Blinking.
	Rat	Male	1	6.3	74	2	Blinking, lacrimation, sneezing, and body weight loss.
	Rat	Male	1	10	43	2	Blinking, lacrimation, sneezing, dyspnea, and body weight loss.
	Human		1	0.1	1	1	2/6 ocular irritation; estimated duration.
	Human		1	1	1	1	6/6 considerable ocular irritation; estimated duration.

Categories: 0 = no effect; 1 = discomfort; 2 = disabling; PL = partially lethal; 3 = lethal.

3

Chloroacetone[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), 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).

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

Chloroacetone is produced by the direct chlorination of acetone. It also has been manufactured by reacting chlorine with diketene followed by boiling with water. It is used in the manufacture of couplers for color photography, as a photosensitizer for polyester-vinyl polymerization, as a fungicide and bactericide, and as an intermediate in the production of perfumes, antioxidants, and pharmaceuticals (Sargent et al. 1986). Chloroacetone has a pungent, suffocating odor similar to hydrogen chloride. It is toxic by inhalation, ingestion, and dermal contact, and causes immediate lacrimation at low concentrations. Other effects from exposure to chloroacetone include contact burns of the skin and eyes, nausea, bronchospasm, delayed pulmonary edema, and death.

Data were insufficient for deriving AEGL-1 and AEGL-2 values for chloroacetone. The available data on acute toxicity suggest that chloroacetone has a steep dose-response relationship. Therefore, the AEGL-2 values were calculated by taking a three-fold reduction in the corresponding AEGL-3 values; those values are considered estimates of a threshold for irreversible effects.

A 1-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 131 ppm in the male rat was used as the basis of the AEGL-3 values (Arts and Zwart 1987). Interspecies and intraspecies uncertainty factors of 3 each were applied, because the preponderance of the data suggests that the effects of inhaled chloroacetone are likely caused by a direct chemical

effect on the tissues; this type of port-of-entry effect does not exhibit toxicokinetic variability and, thus, is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 also is supported by data suggesting little species variability in lethality from oral and dermal exposure to chloroacetone (rat oral LD_{50} values: 100-141 mg/kg; mouse oral LD_{50} values: 127-141 mg/kg; rabbit dermal LD_{50} = 141 mg/kg), and the 1-h LC_{50} of 500 ppm for male and female rats (Arts and Zwart 1987) is approximately a dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 mL minute volume, and a rat body weight of 250 g). The intraspecies uncertainty factor of 3 also is considered sufficient because data from male rats, which are more sensitive than female rats, were used as the point-of-departure. Thus, the total uncertainty factor is 10. It has been shown that 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 were unavailable for an empirical derivation of n for chloroacetone, so default values were applied (NRC 2001). An n of 3 was applied to extrapolate to the 10- and 30-min AEGL durations, and an n of 1 was applied to extrapolate to the 4- and 8-h durations (NRC 2001). The calculated values are presented Table 3-1.

1. INTRODUCTION

Chloroacetone is a colorless to amber liquid at ambient temperature and pressure. It has a pungent, suffocating odor similar to hydrogen chloride (Sargent et al. 1986). It is toxic by inhalation, ingestion, and dermal contact, and causes immediate lacrimation at low concentrations. Other effects from exposure to chloroacetone include contact burns of the skin and eyes, nausea, bronchospasm, delayed pulmonary edema, and death (HSDB 2011).

TABLE 3-1 Summary of AEGL Values for Cloroacetone

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)	8.0 ppm (30 mg/m^3)	5.5 ppm (21 mg/m^3)	4.4 ppm (17 mg/m^3)	1.1 ppm (4.2 mg/m^3)	0.53 ppm (2.0 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	24 ppm (91 mg/m^3)	17 ppm (65 mg/m^3)	13 ppm (49 mg/m^3)	3.3 ppm (13 mg/m^3)	1.6 ppm (6.1 mg/m^3)	Estimated lethality threshold for male rats (BMD_{05}) (Arts and Zwart 1987)

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

Chloroacetone is produced by the direct chlorination of acetone. It has also been manufactured by reacting chlorine with diketene followed by boiling with water (Sargent et al. 1986). In 1914, the French introduced chloroacetone as a war gas in hand and rifle grenades. It is now used in the manufacture of couplers for color photography, as a photosensitizer for polyester-vinyl polymerization, as a fungicide and bactericide, and as an intermediate in the production of perfumes, antioxidants, and pharmaceuticals (Sargent et al. 1986). Production is listed for only one manufacturer in the United States and four manufacturers worldwide (HSDB 2011). In 1977, U.S. production was reported to be at least 4.54 × 107 g, and U.S. imports were at least 4.54×10^5 g. In 1982, U.S. production was reported to be greater than 4.54×10^6 g (HSDB 2011).

The chemical structure of chloroacetone is depicted below, and the physicochemical properties of chloroacetone are presented in Table 3-2.

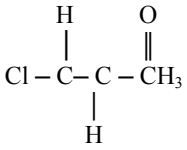

TABLE 3-2 Physical and Chemical Properties for Chloroacetone

Parameter	Data	Reference
Common name	Chloroacetone	IPCS 2006
Synonyms	1-Chloro-2-propanone; chloropropanone; acetonyl chloride; monochloroacetone	IPCS 2006
CAS registry no.	78-95-5	IPCS 2006
Chemical formula	$ClCH_2COCH_3$	IPCS 2006
Molecular weight	92.5	IPCS 2006
Physical state	Colorless liquid (turns dark on exposure to light)	IPCS 2006
Melting point	-45°C	IPCS 2006
Boiling point	120°C	IPCS 2006
Specific gravity	1.123 (25°C)	HSDB 2011
Relative Vapor density	3.2 (air = 1)	IPCS 2006
Solubility	Soluble in water; miscible with alcohol, ether, and chloroform	HSDB 2011
Vapor pressure	12.0 mm Hg (25°C)	HSDB 2011
Flash point	40°C (open cup)	OSHA 2012
Octanol/water partition coefficient (log P_{ow})	0.28	IPCS 2006
Conversion factors in air	1 ppm = 3.8 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Chloroacetone at a concentration of 605 ppm was reported to be lethal to humans after 10 min (Prentiss 1937). No further details were available.

2.2. Nonlethal Toxicity

Prentiss (1937) reported that chloroacetone was extremely effective as a war gas unless a full-face gas mask was deployed quickly; a concentration of 26 ppm was reportedly intolerable after 1 min of exposure. No further details were provided.

Sargent et al. (1986) provided the only information on human exposure to chloroacetone. The authors reported that employee occupational health monitoring in 1981-1986 indicated that 25 employees reported to "Health Services" as a result of exposure to chloroacetone. Of these, eight had ocular irritation, seven had localized dermal irritation, one had contact dermatitis, and the remaining nine showed no clinical signs.

Sargent et al. (1986) also reported a case of direct exposure of one employee to hot chloroacetone as a result of a line break. The line break resulted in the release of chloroacetone vapors and hot liquid under pressure with combined inhalation and dermal exposure. The employee was hospitalized. Effects included immediate lacrimation and ocular irritation, upper-respiratory-tract irritation, and dermal irritation, producing slight erythema. Erythema subsided, but the exposed skin began to blister and the eyelids reddened and swelled and became painful to touch 8-h after exposure. After 24 h, the skin areas had completely blistered, were swollen, and were painful to touch, suggesting that some major dermal effects are delayed. All effects resolved within 7 days, and there was no evidence of pulmonary edema at the low concentration, despite the initial upper-respiratory-tract irritation. No additional information to quantify exposure for this worker was available from the investigators.

The Sargent et al. (1986) report included a summary table in which a chloroacetone concentration of 4.7 ppm was associated with lacrimation and burning sensation of the skin. However, the study authors did not provide information regarding the basis for that value (e.g., method of sampling or analysis, exposure duration, number of exposed individuals, number of affected individuals). An odor threshold for chloroacetone was not found.

2.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding acute human exposure to chloroacetone were not available.

2.4. Genotoxicity

Genotoxicity studies on acute human exposure to chloroacetone were not available.

2.5. Carcinogenicity

Carcinogenicity studies on human exposure to chloroacetone were not available.

2.6. Summary

There are few human studies of the toxicity of chloroacetone. The chemical is highly irritating and causes ocular, upper-respiratory tract, and dermal irritation. Immediate lacrimation has been reported at a concentration of approximately 5 ppm. Chloroacetone was reportedly intolerable at 26 ppm after 1 min, and lethal after 10 min of exposure at 605 ppm. No reports on developmental and reproductive toxicity, genotoxicity, or carcinogenicity of chloroacetone in humans were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of five male and five female SPF (Bor:WISW) rats were exposed to chloroacetone at 132, 263, 553, 816, 1,105, or 2,079 ppm (analytic concentrations) for 1 h, followed by a 14-day observation period (Arts and Zwart 1987). Animals were exposed in a horizontally placed glass tube that allowed observation of all animals during exposure. The volume of the exposure chamber was 0.015 m^3, and air flow was 1.2 m^3/h; relative humidity and temperature were measured at least once per hour. The test atmosphere was generated by delivering appropriate quantities of chloroacetone to an evaporator at the inlet port of the chamber, and the concentration of chloroacetone was determined by vapor phase infrared spectrometry and calibrated in a closed-loop system. Exposure concentration was calculated as the mean of recorded concentrations during the entire exposure period. Rats were observed during exposure and daily during the observation period for clinical signs. Body weight was recorded before exposure and on days 1, 2, 4, 7, and 14. Surviving rats were killed at the end of the observation period and subjected to gross necropsy. "Shortly" after the start of exposure, restlessness, rubbing of snouts, closed eyes, and humped posture were observed. Salivation, wet nares, and nasal discharge was observed within 3-5 min; these effects were noted "especially in those animals exposed to higher concentrations." The skin of the extremities became

red during the second half of the exposure period in rats exposed at the higher concentrations. In the "highest concentration groups," all rats showed labored respiration, accompanied by dyspnea and mouth breathing. Treatment-related mortality occurred shortly after exposure, usually within hours, or within 1-2 days after exposure. Mortality was greater in males than in females. The rats that died within the first two days of the observation period had pulmonary edema, accompanied by hydrothorax. The stomachs of these rats were filled with air, and some also had air in the cecum and intestine. Grey, discolored lungs was the only effect noted in animals necropsied at the end of the observation period. Animals surviving the study showed no treatment-related effect on body weight gain. One-hour LC_{50} values of 500 ppm (95% confidence interval [CI]: 421-579 ppm; males and females combined), 316 ppm (95% CI: 289-342 ppm; male rats), and 710 ppm (95% CI: 658-753 ppm; female rats) were calculated. One-hour BMC_{01} (benchmark concentration, 1% response) values of 170 ppm (males and females combined), 223 ppm (males), and 394 ppm (females) were calculated. One-hour $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) values of 144 ppm (males and females combined), 131 (males), and 258 ppm (females) were calculated. Mortality data are summarized in Table 3-3.

TABLE 3-3 Mortality in Rats Exposed to Chloroacetone for One Hour

Concentration (ppm)	Males	Females	Males and Females
Observed			
132	0/5	0/5	0/10
263	1/5	0/5	1/10
553	5/5	1/5	6/10
816	5/5	3/5	8/10
1,105	5/5	5/5	10/10
2,079	5/5	5/5	10/10
Calculated			
316 (289-342)	LC_{50}	—	—
500 (421-579)	—	—	LC_{50}
710 (658-753)	—	LC_{50}	—
170			BMC_{01}
223	BMC_{01}	—	—
394	—	BMC_{01}	—
131	$BMCL_{05}$	—	—
144	—	—	$BMCL_{05}$
258	—	$BMCL_{05}$	—

Abbreviations: BMC_{01}, benchmark concentration, 5% response; $BMCL_{01}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Arts and Zwart 1987.

Eastman Kodak (1992) conducted a series of experiments each using groups of three male rats (strain not specified). Rats exposed to chloroacetone at 462 ppm exhibited nasal irritation, gasping, and pink extremities within 1 h, rough coat after 2 h, and all were dead after 4.5 h. Another group exposed at 3,120 ppm exhibited nasal irritation, gasping, and pink extremities in 0.5 h, and all were dead after 1.5 h. Finally, groups of rats was sequentially exposed to chloroacetone at 52 and 105 ppm for 6 h at each concentration. At 52 ppm, pink extremities were noted in 2.25 h, but no rats died. Nasal irritation, gasping, and pink extremities were noted after 2.5 h at 105 ppm, and all rats died within 24 h of the initiation of exposure. The authors estimated a 6-h LC_{50} of 50-100 ppm. No other experimental details were provided.

Sargent et al. (1986) exposed a group of five male and five female Sprague-Dawley rats to chloroacetone at 7,522 ppm for up to 1 h. A vapor-laden stream of chloroacetone was produced by bubbling air through the test material at a flow rate of 4 L/min. Lacrimation and excessive salivation were observed immediately, and all rats died within 55 min. No other experimental details were provided.

In another experiment, Sargent et al. (1986) exposed groups of five male and five female Sprague-Dawley rats to chloroacetone at 95, 204, 254, 302, or 874 ppm (nominal concentrations) for 1 h, followed by a 14-day observation period. An LC_{50} of 262 ppm was calculated. No other experimental details were provided.

Groups of five male and five female Wistar rats were administered chloroacetone at 0, 50, 71, 100, 140, or 200 mg/kg by gavage in corn oil, followed by a 2-day and 14-day observation period (Sargent et al. 1986). Clinical signs observed in all treatment groups included ataxia, red nasal discharge, urinary and fecal staining of the abdomen, decreased activity, and piloerection. An oral LD_{50} of 100 mg/kg was determined with the 14-day observation period, and an oral LD_{50} of 113 mg/kg was determined with the 2-day observation period.

Eastman Kodak (1992) reported an oral LD_{50} of 141 mg/kg for male rats. Clinical signs included rough coat, diarrhea, ataxia, and prostration. No other experimental details were provided.

3.1.2. Mice

Groups of five female CF_1S mice were administered chloroacetone at 0, 50, 71, 100, 140, or 200 mg/kg by gavage in corn oil, followed by a 14-day observation period (Sargent et al. 1986). Clinical signs included ataxia, lethargy, prostration, piloerection, and a generally unhealthy appearance. An oral LD_{50} of 127 mg/kg was determined.

Eastman Kodak (1992) reported an oral LD_{50} of 141 mg/kg for male mice. Clinical signs included rough coat, diarrhea, ataxia, and prostration. No other experimental details were provided.

3.1.3. Rabbits

In an acute dermal toxicity study, four New Zealand white rabbits were administered chloroacetone at 50, 100, 200, or 400 mg/kg and were observed for 14 days (Sargent et al. 1986). The test substance was applied to the clipped skin, covered with impervious plastic sheeting, and allowed to remain in contact with the skin for 24 h. The rabbits were fitted with collars to prevent ingestion of the chloroacetone. In the high-dose groups, signs of toxicity presented within 24 h and included ataxia, clear oral discharge, general unhealthy appearance, soft stools, and decreased activity. Moderate to severe erythema and edema were observed in all treatment groups, and eschar formation and necrosis were observed in all surviving animals during the second week of the study. An acute dermal LD_{50} of 141 mg/kg was calculated.

3.1.4. Guinea Pigs

Eastman Kodak (1992) reported that the dermal LD_{50} of chloroacetone in guinea pigs is "probably between 0.1 and 1.0 mL/kg." No other information was provided.

3.2. Nonlethal Toxicity

No acute toxicity studies of nonlethal effect of chloroacetone in animals were found.

3.3. Repeated-Exposure Studies

Eastman Kodak (1992) conducted a series of experiments each using one rat (strain and sex not specified). The rats were repeatedly exposed to chloroacetone by inhalation for up to 11 exposures. No additional experimental details were reported. Data are summarized in Table 3-4.

Groups of five male rats (strain not specified) were administered chloroacetone at 0, 10, 50, or 100 mg/kg by gavage, 5 days/week for up to 13 days (Eastman Kodak 1992). One rat in the 100-mg/kg group died after three doses, and the other four were sacrificed on day four because of poor condition. Food intake and body weight gain were "severely depressed" at 100 mg/kg, and food intake was "moderately depressed" and weight gain "severely depressed" 50 mg/kg. At 10 mg/kg, food consumption and body weight gain were "moderately depressed." Clinical signs in the 50-mg/kg group included salivation, slight hyperactivity, pale eyes, and dark urine. No clinical signs were noted in the 10-mg/kg group. Gross necropsy of high-dose animals revealed necrotizing gastritis, fluid in the thoracic and abdominal cavities, adhesions

TABLE 3-4 Effects of Chloroacetone on Rats Repeatedly Exposed to Chloroacetone

Average Concentration (ppm)	No. of exposures	No. of rats	Observations
20	11	1	Pink extremities, gasping, nasal irritation, rough hair, body weight loss, survived
22	9	1	Pink extremities, gasping, nasal irritation, rough hair, body weight loss
25	11	1	Pink extremities, gasping, nasal irritation, rough hair, body weight loss, survived
39	4	1	Pink extremities, gasping, nasal irritation, rough hair, body weight loss, death
58	2	1	Pink extremities, gasping, nasal irritation, death in 2 days

Source: Eastman Kodak 1992.

between abdominal viscera, pale livers, and small seminal vesicles. In the 50-mg/kg group, one rat had adhesions between the stomach and diaphragm and thickening of the nonglandular mucosa of the stomach; another rat in this group had a raised firm red area on the visceral surface of the stomach. No gross abnormalities were noted in the 10-mg/kg group. Histopathologic observations in the 100-mg/kg rats included gastric necrosis, ulceration, and perforation. Necrosis of the liver, spleen, adrenal glands, and testes were considered secondary to severe gastric irritation and subsequent peritonitis. Moderate to severe cortical atrophy of the thymus was noted in all rats of the 100-mg/kg group. In the 50-mg/kg group, one rat had necrosis of the nonglandular stomach mucosa, one had necrosis of the glandular stomach mucosa, one had ulceration of the nonglandular stomach, and all had hyperkeratosis of the esophageal mucosa. Three rats in the 10-mg/kg group had minor hyperkeratosis of the gastric nonglandular stomach.

3.4. Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies of animal exposure to chloroacetone were not available.

3.5. Genotoxicity

Chloroacetone at concentrations of 100-2,000 nmole/plate did not induce mutation in *Salmonella typhimurium* strains TA1535 or TA100, with or without exogenous metabolic activation (Merrick et al. 1987). Negative results were also obtained in *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and hisG46 at concentrations of 1,500-3,000 µg/plate, with and without metabolic activation (Sargent et al. 1986). Chloroacetone was negative in the SOS chromotest at

concentrations of 0.01-3,000 µg/mL without S9 activation and at 0.1-100 µg/mL with activation, and was also negative for clastogenicity in a newt micronucleus test at 0.1-0.4 µg/mL (Le Curieux et al. 1994). Chloroacetone was positive in an Ames-fluctuation test with *S. typhimurium* strain TA100 at concentrations of 1-30 µg/mL with metabolic activation, but was negative without activation (Le Curieux et al. 1994). Chloroacetone increased the frequency of sex-linked recessive lethals in *Drosophila melanogaster* exposed via inhalation (Lee et al. 1983).

3.6. Carcinogenicity

Robinson et al. (1989) gave 40 female SENCAR mice dermal treatments of chloroacetone at 0 or 50 mg/kg in 0.2 mL ethanol six times over a 2-week period or oral doses of chloroacetone at 0 or 50 mg/kg three times over a 2-week period (total dermal dose was 300 mg/kg; total oral dose was 150 mg/kg). Two-weeks after the final doses, 1.0 µg TPA (12-O-tetradecanoly-phorbol-13-acetate) in 0.2 mL acetone was applied to the skin three times per week for 20 weeks. No evidence of increased tumor incidence was found in animals treated with chloroacetone by either route compared with controls.

In another study, groups of 10 male and 10 female outbred stock albino mice were given dermal treatments of chloroacetone (0.2 mL of a 0.3% chloroacetone solution in acetone) twice a week for 12 weeks (Searle 1966). Mice were then given dermal treatments of croton oil (0.2 mL, 0.5% in acetone) twice a week for 20 weeks; surviving mice were killed after another 20 weeks without treatment. Controls were treated with acetone followed by croton oil. There was no treatment-related effect on mortality; however, a greater number of papillomas wasfound in treated mice than in controls during subsequent croton oil treatment. The overall tumor incidences appeared to be similar between treated and control groups (cumulative incidence was not reported, and statistical analysis was not performed), but the total number of tumors was higher in treated mice compared with controls, and males developed more tumors than females. Total numbers of tumors observed at 40 weeks were as follows: three for male controls, seven for female controls, 29 for chloroacetone-treated males, and 16 for chloroacetone-treated females. Both the incidences and the total number of tumors were lower at 40 weeks than at 30 weeks, suggesting that some of the tumors regressed; the authors reported that there were no malignant tumors in chloroacetone-treated mice.

3.7. Summary

Animal toxicity data are limited to acute lethality studies in rats, mice, and rabbits, and repeated-exposure studies in rats. The data suggest that male rats are approximately 2.3 times more sensitive than female rats to the effects of chloroacetone administered by inhalation. Oral lethality data suggest that mice

and rats have similar sensitivities. Oral and dermal LD_{50} values show little variability with regard to species and route of exposure. Clinical signs included restlessness, labored breathing, nasal irritation, salivation, lacrimation, dyspnea, and pulmonary edema at necropsy. No developmental or reproductive data were available. Genotoxicity results were equivocal; findings were negative for reverse mutation in five *S. typhimurium* strains, negative in SOS chromotest, and negative for clastogenicity, but were positive in an Ames fluctuation test and a sex-linked recessive lethal assay. Searle (1966) showed that chloroacetone increased the numbers of skin tumors, but not the skin tumor incidence, in male and female mice given dermal applications of chloroacetone twice per week for 12 weeks and subsequently administered croton oil. However, there was no increase in tumor incidence in female mice administered chloroacetone orally or dermally over two weeks, followed by TPA administration (Robinson et al. 1989). The inconsistent results might be due to differences in mouse strain, vehicle, dose, or length of exposure. In summary, the carcinogenic potential of chloroacetone cannot be evaluated with the available data.

Selected acute toxicity data are summarized in Table 3-5.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism

No in vivo metabolism information was found; however, in vitro data suggest that chloroacetone reacts directly with and depletes glutathione (GSH) (Merrick et al. 1987). The purpose of the in vitro study was to determine whether chloroacetone was directly cytotoxic as a result of chemical reactivity with sulfhydryl nucleophiles and to compare the toxicity of single and multiple chlorinated propanones. When equimolar (10 mM) concentrations of GSH and 1,3-dichloropropanone (1,3-DCP), 1,1-dichloropropopanone (1,1-DCP), or chloroacetone (monochloropropanone) were allowed to react in phosphate buffer, concentrations of GSH decreased within 1 min, reaching less than 15% of initial values within 20 min. The greatest decrease occurred with 1,3-DCP, followed by chloroacetone, and then 1,1-DCP. There was a concentration-related increase in aspartate transaminase (AST) enzyme leakage after 1 h, when primary hepatocyte cultures from male Sprague-Dawley rats were incubated with 1,3-DCP, 1,1-DCP, or chloroacetone. The greatest leakage occurred with 1,3-DCP, followed by chloroacetone, and then 1,1-DCP. AST release from the hepatocytes was associated with reduction of GSH, with relative order being the same.

4.2. Mechanism of Toxicity

No information regarding the mechanism of toxicity of chloroacetone was found. Symptoms of acute inhalation poisoning with chloroacetone suggest that

TABLE 3-5 Summary of Selected Acute Toxicity Data on Chloroacetone in Animals

Species	Concentration or Dose	Exposure Duration	Effect	Reference
Inhalation				
Rat	52 ppm	6 h	Pink extremities after 2.25 h; no mortality (0/3)	Eastman Kodak 1992
Rat	50-100 ppm	6 h	Estimated LC_{50}	Eastman Kodak 1992
Rat	105 ppm (same rats exposed to 52 ppm above)	6 h	Nasal irritation, gasping, and pink extremities within 2.5 h; 100% mortality within 24 h	Eastman Kodak 1992
Rat	132 ppm	1 h	No mortality (0/10); restlessness, rubbing of snouts, lacrimation, salivation, and humped posture	Arts and Zwart 1987
Rat	262 ppm	1 h	LC_{50} (male and female combined)	Sargent et al. 1986
Rat	316 ppm	1 h	LC_{50} (male)	Arts and Zwart 1987
Rat	462 ppm	4.5 h	Nasal irritation, gasping, and pink extremities after 1 h; rough coat after 2 h; 100% mortality (3/3 males) at 4.5 h	Eastman Kodak 1992
Rat	500 ppm	1 h	LC_{50} (male and female combined)	Arts and Zwart 1987
Rat	710 ppm	1 h	LC_{50} (female)	Arts and Zwart 1987
Rat	1,105 ppm	1 h	100% mortality	Arts and Zwart 1987
Rat	3,120 ppm	1.5 h	Nasal irritation, gasping, and pink extremities after 0.5 h; 100% mortality (3/3 males) at 1.5 h	Eastman Kodak 1992
Rat	7,522 ppm	1 h	Immediate lacrimation and salivation; 100% mortality (10/10)	Sargent et al. 1986
Oral				
Rat	100 mg/kg	Single gavage	LD_{50} (male and female)	Sargent et al. 1986
Rat	141 mg/kg	Single gavage	LD_{50} (male)	Eastman Kodak, 1992
Mouse	127 mg/kg	Single gavage	LD_{50} (female)	Sargent et al. 1986
Mouse	141 mg/kg	Single gavage	LD_{50} (male)	Eastman Kodak, 1992
Dermal				
Rabbit	141 mg/kg	24 h	LD_{50}	Sargent et al. 1986

it acts as an irritant, causing immediate lacrimation at low concentrations and contact burns to the skin and eyes, nausea, bronchospasm, delayed pulmonary edema, and death at higher concentrations (HSDB 2011). In a study of repeated oral exposure to chloroacetone (Eastman Kodak 1992), the primary effects were from irritation, and included gastric necrosis, ulceration, and perforation. However, sex differences in the response to inhaled chloroacetone have been observed (e.g., rat LC_{50} values in males are lower than in females). Such differences are not consistent with a mode of action of direct-acting irritation, which would be unlikely to vary significantly within or across species.

Some information from oral and dermal lethality studies suggests the possibility that chloroacetone might exert systemic effects. Ataxia and lethargy were noted in rats and mice exposed via gavage to chloroacetone (Sargent et al. 1986). Rabbits exposed topically to lethal concentrations of chloroacetone (under conditions designed to limit or prevent oral and inhalation exposure) exhibited clinical signs of toxicity, including ataxia, hypoactivity, clear oral discharge, and soft stools (Sargent et al. 1986). Whether these clinical signs are indicative of systemic absorption and toxicity of chloroacetone or occur as a consequence of profound irritation and injury at the site of exposure is uncertain. In summary, while there is suggestive evidence for systemic effects after oral and dermal exposure, the preponderance of the available information suggests that the primary effects of chloroacetone inhalation are due to direct-acting irritation.

4.3. Concurrent Exposure Issues

No information was found.

4.4. Structure-Activity Relationships

Structure-activity data were only available from the in vitro metabolism study described in Section 4.1 and genotoxicity data. Merrick et al. (1987) found that 1,3-dichloropropanone was highly mutagenic in *S. typhimurium*, 1,1-dichloropropanone was a weaker mutagen, and chloroacetone was not mutagenic with or without metabolic activation. Le Curieux et al. (1994) found that chloropropanones with chlorine substituents on both carbon positions (1,3-dichloropropanone and 1,1,3-trichloropropanone) were more genotoxic than chloropropanones with substituents on only one carbon position (1,1-dichloropropanone and 1,1,1-trichloropropanone), which were, in turn, more genotoxic than chloroacetone.

4.5. Species Differences

The few available studies suggest that mice and rats have similar sensitivities to orally administered chloroacetone with regard to lethality. Oral

and dermal LD_{50} values show little variability with regard to species and route of exposure (see Table 3-5). For example, oral LD_{50} values range from 100 to 141 mg/kg for rats and from 127 to 141 mg/kg in mice, and a dermal LD_{50} of 141 mg/kg was reported for rabbits. Furthermore, the 1-h LC_{50} of 500 ppm for male and female rats (Arts and Zwart 1987) gives an approximate dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 mL minute volume, and a rat body weight of 250 g).

4.6. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate for deriving an empirically-derived chemical-specific scaling exponent for chloroacetone. Available toxicity data for chloroacetone are limited to 1-h exposures (calculated LC_{50} values) and 6-h exposures (0/3 deaths at 52 ppm and 3/3 deaths at the 105 ppm). Thus, data from different exposure durations were not adequate for use in plotting and calculating a value for n. However, the available data suggest that exposure duration may alter the lethal concentration of chloroacetone; specifically, the 1-h LC_{50} in male and female rats (combined) was estimated to be in the range of 262-500 ppm (Sargent et al. 1986; Arts and Zwart 1987) whereas an estimate of the 6-h rat LC_{50} is 50-100 ppm (Eastman Kodak 1992). To obtain conservative and protective AEGL values in the absence of an empirically-derived chemical-specific scaling exponent, temporal scaling was be performed using the default values of n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The study by Sargent et al. (1986) provides the only information on human experience with chloroacetone. A concentration of 4.7 ppm was associated with lacrimation and a burning sensation of the skin, but no further information (e.g., ambient or personal monitoring, method of analysis, exposure duration, number of individuals affected, number of exposed individuals) was provided to support this association. This information is not considered adequate for the purpose of deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

No animal data consistent with the definition of AEGL-1 were available.

5.3. Derivation of AEGL-1

The available data on chloroacetone are insufficient, so AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No adequate human data consistent with the definition of AEGL-2 were available. Immediate lacrimation and ocular and upper respiratory irritation were noted in a worker accidentally exposed to chloroacetone vapors and hot liquid for an undetermined duration at an unspecified concentration; the exposure included inhalation and dermal components (Sargent et al. 1986).

6.2. Animal Data Relevant to AEGL-2

Restlessness, rubbing of snouts, lacrimation, salivation, and humped posture were noted in male and female rats exposed to chloroacetone at 132 ppm for 1 h (Arts and Zwart 1987).

6.3. Derivation of AEGL-2

The only data consistent with the definition of AEGL-2 are the clinical signs observed in rats exposed to chloroacetone at 132-2,079 ppm for 1 h (Arts and Zwart 1987). Chloroacetone exhibited a steep dose-response relationship. In that study, 132 ppm was the only concentration causing no mortality and is greater than the concentration used as the point-of-departure for AEGL-3 values ($BMCL_{05}$ of 131 ppm; see below). Due to the steep dose-response relationship and limitations in the available data, the AEGL-2 values for chloroacetone were determined by a taking 3-fold reduction in the AEGL-3 values (see below); this was considered an estimate of a threshold for irreversible effects (NRC 2001). AEGL-2 values for chloroacetone are presented in Table 3-6, and the calculations for these AEGL-2 values are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data consistent with the definition of AEGL-3 were available.

7.2. Animal Data Relevant to AEGL-3

There are few animal studies with data consistent with the definition of AEGL-3. One-hour LC_{50} values of 500 ppm (95% CI: 421-579 ppm for male

and female rats combined), 316 ppm (95% CI: 289-342 ppm for male rats), and 710 ppm (95% CI: 658-753 ppm for female rats) were calculated. One-hour BMC_{01} values of 170 ppm (males and females combined), 223 ppm (males only), and 394 ppm (females only) were calculated. One-hour $BMCL_{05}$ values of 144 ppm (males and females combined), 131 ppm (males only), and 258 ppm (females only) also were calculated (Arts and Zwart 1987).

7.3. Derivation of AEGL-3

The $BMCL_{05}$ of 131 ppm (Arts and Zwart 1987) was be used as the basis for calculating AEGL-3 values for chloroacetone. Interspecies and intraspecies uncertainty factors of 3 each were applied. The mechanism of chloroacetone toxicity is uncertain; although direct irritation effects are observed after exposure through all routes, some information suggests the potential for systemic effects after dermal and oral exposure (see Section 4.2). However, the preponderance of the available information suggests that the primary effects of chloroacetone inhalation are due to direct-acting irritation; this type of port-of-entry effect does not exhibit toxicokinetic variability and thus is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 is also supported by data suggesting little species variability with regard to lethality from oral and dermal exposure to chloroacetone (rat oral LD_{50} values: 100-141 mg/kg; mouse oral LD_{50} values: 127-141 mg/kg; rabbit dermal LD_{50} = 141 mg/kg). Furthermore, the 1-h LC_{50} of 500 ppm for male and female rats (Arts and Zwart 1987) is approximately a dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 mL minute volume, and a rat body weight of 250 g). The intraspecies uncertainty factor of 3 is also considered sufficient because data from the more sensitive males were used as the point-of-departure. Thus, the total adjustment was 10.

It has been shown 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 (ten Berge et al. 1986). Data on chloroacetone were inadequate to derive an empirical value for n. The available information suggests that the lethal concentration is lower after longer exposure durations; the 1-h LC_{50} in male and female rats was 262-500 ppm (Sargent et al. 1986; Arts and Zwart 1987), while the 6-h LC_{50} is approximately 50-100 ppm (Eastman Kodak 1992). Therefore, default estimates of n were used to extrapolate from the 1-h point-of-departure to other time points. An n of 3 was applied to extrapolate to the 10- and 30-min time periods,

TABLE 3-6 AEGL-2 Values for Chloroacetone

10 min	30 min	1 h	4 h	8 h
8.0 ppm (30 mg/m^3)	5.5 ppm (21 mg/m^3)	4.4 ppm (17 mg/m^3)	1.1 ppm (4.2 mg/m^3)	0.53 ppm (2.0 mg/m^3)

and an n of 1 was applied to extrapolate to the 4- and 8-h time periods to provide AEGL values that would be protective of human health (NRC 2001). AEGL-3 values for chloroacetone are presented in Table 3-7, and the calculations for these AEGL-3 values are presented in Appendix A.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for chloroacetone are summarized in Table 3-8. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were set at one-third the AEGL-3 values, and AEGL-3 values were based on a 1-h estimated threshold for lethality in male rats.

8.2. Comparison with Other Standards and Guidelines

Table 3-9 shows exposure criteria for chloroacetone that have been established. ACGIH (2012) recommended a threshold limit value (TLV) ceiling of 1.0 ppm for chloroacetone. The TLV-ceiling is a concentration that should not be exceeded during any part of the working exposure; as such, there is no parallel value among the AEGL exposure durations. The Dutch maximal accepted concentration (MAC) of 1 ppm is equivalent to an 8-h TLV. However, there is no published method for measuring occupational exposure to chloroacetone (OSHA 2012), and efforts to locate occupational monitoring data on chloroacetone were not successful. Thus, there is no information with which to determine whether workers have been exposed at concentrations at or approaching the 1 ppm limit without adverse effects.

TABLE 3-7 AEGL-3 Values for Chloroactone

10 min	30 min	1 h	4 h	8 h
24 ppm (91 mg/m^3)	17 ppm (65 mg/m^3)	13 ppm (49 mg/m^3)	3.3 ppm (13 mg/m^3)	1.6 ppm (6.1 mg/m^3)

TABLE 3-8 Summary of AEGL Values for Chloroacetone

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)	8.0 ppm (30 mg/m^3)	5.5 ppm (21 mg/m^3)	4.4 ppm (17 mg/m^3)	1.1 ppm (4.2 mg/m^3)	0.53 ppm (2.0 mg/m^3)
AEGL-3 (lethality)	24 ppm (91 mg/m^3)	17 ppm (65 mg/m^3)	13 ppm (49 mg/m^3)	3.3 ppm (13 mg/m^3)	1.6 ppm (6.1 mg/m^3)

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

TABLE 3-9 Extant Standards and Guidelines for Chloroacetone

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	8.0 ppm	5.5 ppm	4.4 ppm	1.1 ppm	0.53 ppm
AEGL-3	24 ppm	17 ppm	13 ppm	3.3 ppm	1.6 ppm
TLV-Ceiling (ACGIH)[a]	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
MAC (The Netherlands)[b]					1 ppm

[a]TLV-Ceiling (threshold limit value - ceiling) (American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is based on human exposure data (lacrimation and other irritation) reported by Sargent et al. (1986). The TLV-ceiling is a concentration that should not be exceeded during any part of the working exposure. Includes a skin notation. [b]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands, (MSZW 2004) is defined analogous to the ACGIH TLV-TWA (a 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).

8.3 Data Adequacy and Research Needs

The available human data have limitations because they are anecdotal and do not provide robust concentration or duration exposure parameters. Animal data also had limitations; however, oral exposure data corresponded well with inhalation data, showing similar effects at similar dose equivalents. Data were insufficient for derivation of AEGL-1 values.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CHLOROACETONE

Derivation of AEGL-1 Values

Data are insufficient for derivation of AEGL-1 values for chloroacetone.

Derivation of AEGL-2 Values

Key study:	Arts, J.H.E., and A. Zwart. 1987. Acute (one-hour) inhalation toxicity study of chloroacetone in rats. Civo Institutes, TNO. Report No. V87.093/261236. The Netherlands. EPA Document No. 88870000029. Microfiche No. OTS0513466.
Toxicity end point:	One-third of the AEGL-3 values
10-min AEGL-2:	24 ppm ÷ 3 = 8.0 ppm
30-min AEGL-2:	17 ÷ 3 = 5.5 ppm
1-h AEGL-2:	13 ÷ 3 = 4.4 ppm
4-h AEGL-2:	3.3 ÷ 3 = 1.1 ppm
8-h AEGL-2:	1.6 ÷ 3 = 0.53 ppm

Derivation of AEGL-3 Values

Key study:	Arts, J.H.E., and A. Zwart. 1987. Acute (one-hour) inhalation toxicity study of chloroacetone in rats. Civo Institutes, TNO. Report No. V87.093/261236. The Netherlands. EPA Document No. 88870000029. Microfiche No. OTS0513466.
Toxicity end point:	Male rat 1-hr $BMCL_{05}$ = 131 ppm.
Scaling:	$C^3 \times t = k$ (10-min, 30-min) $(131\ ppm)^3 \times 1\ h = 2,248,091\ ppm\text{-}h$ $C^1 \times t = k$ (4-h, 8-h) $(131\ ppm)^1 \times 1\ h = 131\ ppm\text{-}h$

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10-min AEGL-3:	$C^3 \times 0.167$ h = 2,248,091 ppm-h C^3 = 13,461,623 ppm C = 238 ppm 238 ÷ 10 = 24 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 2,248,091 ppm-h C^3 = 4,496,182 ppm C = 165 ppm 165 ÷ 10 = 17 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 2,248,091 ppm-h C^3 = 2,248,091 ppm C = 131 ppm 131 ÷ 10 = 13 ppm
4-h AEGL-3:	$C^1 \times 4$ h = 131 ppm-h C^1 = 32.7 ppm C = 32.7 ppm 32.7 ÷ 10 = 3.3 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 131 ppm-h C^1 = 16.4 ppm C = 16.4 ppm 16.4 ÷ 10 = 1.6 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLOROACETONE

Derivation Summary

AEGL-1 VALUES

Data on chloroacetone were insufficient for derivation of AEGL-1 values. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
8.0 ppm	5.5 ppm	4.4 ppm	1.1 ppm	0.53 ppm

Data adequacy: No acute toxicity data relevant to deriving AEGL-2 values were available. Therefore, the AEGL-3 values were divided by 3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
24 ppm	17 ppm	13 ppm	3.3 ppm	1.6 ppm

Key reference: Arts, J.H.E., and A. Zwart. 1987. Acute (one-hour) inhalation toxicity study of chloroacetone in rats. Civo Institutes, TNO Report No. V87.093/261236. The Netherlands. EPA Document No. 88870000029. Microfiche No. OTS0513466.

Test species/Strain/Number: Rat; SPF (Bor:WISW); 5/sex/group

Exposure route/Concentrations/Durations: Inhalation; 132, 263, 553, 816, 1,105, and 2,079 ppm for 1 h

Effects:

132 ppm:	No mortality; clinical signs: restlessness, rubbing of snouts, lacrimation, salivation, and humped posture
263 ppm:	Clinical signs; mortality: 1/5 males; 0/5 females
553 ppm:	Clinical signs; mortality: 5/5 males; 1/5 females
816 ppm:	Clinical signs; mortality: 5/5 males; 3/5 females
1,105 ppm:	Clinical signs; mortality: 5/5 males; 5/5 females
2,079 ppm:	Clinical signs; mortality: 5/5 males; 5/5 females
LC_{50}:	500 ppm for males and females; 316 ppm for males; 710 ppm for females

(Continued)

AEGL-3 VALUES Continued

BMC_{01}:	170 ppm for males and females; 223 ppm for males; 394 ppm for females
$BMLC_{05}$:	144 ppm for males and females; 131 ppm for males; 258 ppm for females

End point/Concentration/Rationale: Threshold for death; $BMCL_{05}$ for male rats of 131 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, available information suggests that the primary effects of chloroacetone via inhalation are due to direct-acting irritation; this type of port-of-entry effect does not exhibit toxicokinetic variability and, thus, is not expected to vary greatly between species. Factor is also supported by data suggesting little species variability in lethality from oral and dermal exposure to chloroacetone (rat oral LD_{50} values: 100-141 mg/kg; mouse oral LD_{50} values: 127-141 mg/kg; rabbit dermal LD_{50} = 141 mg/kg), and the 1-h LC_{50} of 500 ppm for male and female rats is approximately a dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 mL minute volume, and a rat body weight of 250 g).
Intraspecies: 3, available information suggests that the primary effects of chloroacetone via inhalation are due to direct-acting irritation; this type of port-of-entry effect does not exhibit toxicokinetic variability and, thus, is not expected to vary greatly among individuals. A factor of 3 is also considered sufficient because the point-of-departure was from more sensitive male rats.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where an n of 3 was applied to extrapolate to the 10- and 30-min durations and an n of 1 was applied to extrapolate to the 4- and 8-h durations (NRC 2001).

APPENDIX C

CATEGORY PLOT FOR CHLOROACETONE

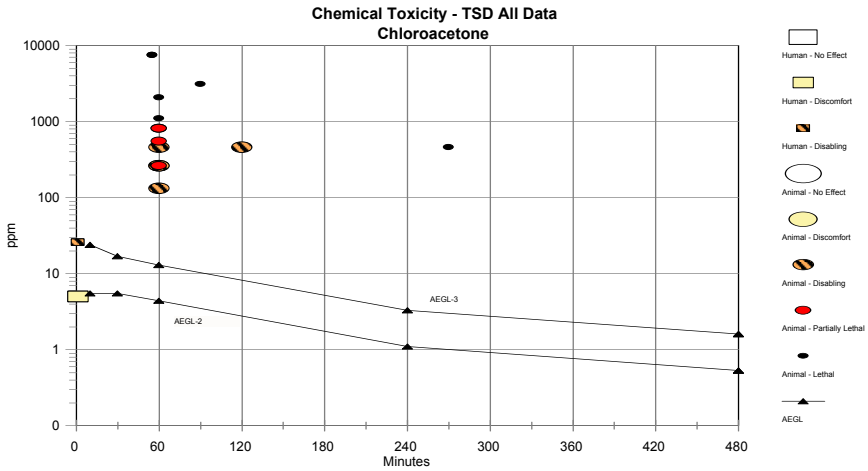

FIGURE C-1 Category plot of animal and human data and AEGL values for chloroacetone.

4

Hexafluoroacetone[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 Robert Young (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Manager Paul Tobin (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

Hexafluoroacetone (HFA) is a colorless gas with a musty odor used in the synthesis of various polymers, medicines, agriculture chemicals, and as an intermediate in various organic syntheses. HFA is highly reactive, reacting vigorously with water and resulting in a series of hydrates (sesquihydrate, monohydrate, and dihydrate) and ultimately producing a stable trihydrate.

There are no inhalation exposure-response data on humans exposed to HFA and no information regarding an odor threshold.

Information on lethality was available from studies in rats and dogs, and evidence of testicular degeneration was found in rats after acute inhalation exposure to HFA. A 30-min LC_{50} (lethal concentration, 50% lethality) of 900 ppm and a 3-h LC_{50} of 275 ppm were reported for rats. Other studies reported no lethality after a single 30-min exposure to HFA at 3,600 ppm or after a single 4-h exposure at 200 ppm (300 ppm for HFA nonahydrate). Effects, including lethality, appeared to be mediated systemically and often occurred during post-exposure periods. The most prevalent nonlethal responses were lacrimation and salivation during exposure and developmental effects in the offspring of dams exposed to HFA for several days during gestation. Exposure of male rats to HFA resulted in testicular degeneration after repeated exposures at 12 ppm or a single 4-h exposure at 200 ppm.

The mode of action for HFA-induced toxicity is uncertain. The effects of HFA appeared to be systemically mediated with pulmonary damage in rats occurring only at concentrations exceeding minimal lethality levels. Results of

available toxicity studies are indicative of contact irritation (lacrimation and signs of nasal irritation), as well as systemic effects (testicular atrophy, central nervous system depression and neuromuscular dysfunction, weight loss, and renal dysfunction).

Neither qualitative nor quantitative data were available for development of AEGL-1 values for HFA, so no values were established.

Few studies on HFA relevant to AEGL-2 effects were available. Several studies reported reproductive toxicity in male rats after acute inhalation exposure to HFA, and developmental toxicity after female rats were exposed during gestation. Testicular atrophy observed in male rats appeared to be reversible after exposure was stopped. Developmental toxicity was selected as the critical effect for developing AEGL-2 values because those effects occurred at concentrations lower than those linked with testicular effects. Specifically, exposure of pregnant rats to HFA at 1 ppm for 6 h/day on gestation days 7-16 resulted in a slight decrease in mean fetal weight. In the absence of notable maternal toxicity, these findings suggest that the fetus is more sensitive to HFA exposure. A concentration of 1 ppm was selected as the point of departure for calculating AEGL-2 values, under the assumption that a single 6-h exposure during gestation could be responsible for the observed effects. A total uncertainty factor of 30 was applied. A factor of 10 was use to account for uncertainties associated with extrapolating animal data to human exposure conditions. An uncertainty factor of 3 was used for intraspecies variability because HFA does not appear to undergo significant metabolism and because the fetus is considered a sensitive target. Further adjustment was considered unnecessary because of the assumption that the observed effects were the result of a single 6-h exposure during the 10-day gestational exposure period. Time scaling from the 6-h experimental duration to AEGL-specific durations was performed using the equation $C^n \times t = k$; n = 1 was empirically determined from available data (ten Berge et al. 1986). Because of the uncertainty associated with extrapolating a 6-h point of departure to a 10-min exposure duration, the 10-min AEGL-2 value was set equivalent to the 30-min value (NRC 2001).

Studies in rats by E. I. du Pont de Nemours & Co. provided the most comprehensive data from which to develop AEGL-3 values. Two reports (E. I. du Pont de Nemours & Co. 1962a,b) showed that 4-h exposure of rats to HFA at 200 ppm (300 ppm for the nonahydrate) was without lethality and that mortality increased to 50% at 300 ppm (50-75% at 400 ppm for the HFA nonahydrate). The concentration of 200 ppm was selected as the point of departure for AEGL-3 development. An uncertainty factor of 3 was applied to account for uncertainties associated with extrapolating animal data to human exposure conditions. A factor of 3 was used for intraspecies variability because HFA does not appear to undergo significant metabolism. Further adjustment in calculating the AEGL-3 values did not appear justified because the values would similar to or below concentrations shown to be nonlethal in 13-week rat and dog studies (E. I. du Pont de Nemours & Co. 1971). Time scaling from the 4-h experimental duration to AEGL-specific durations was performed using the equation $C^n \times t = k$; n = 1

was empirically determined from available data (ten Berge et al. 1986). Because of uncertainties associated with extrapolating a 4-h point of departure to a 10-min exposure duration, the 10-min AEGL-3 was set equivalent to the 30-min value (NRC 2001).

AEGL values for HFA are presented in Table 4-1.

1. INTRODUCTION

Hexafluoroacetone (HFA) is a colorless gas with a musty odor, and is used in the synthesis of various polymers, medicines, agriculture chemicals, and as an intermediate in various organic syntheses (HSDB 2009; NIOSH 2011). HFA is highly reactive, reacting vigorously with water resulting in a series of hydrates (sesquihydrate, monohydrate, and dihydrate) and ultimately producing a stable trihydrate (Kennedy 1970). Chemical and physical data for HFA are presented in Table 4-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available on lethality in humans after inhalation exposure to HFA.

TABLE 4-1 Summary of AEGL Values for Hexafluoroacetone

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]	
AEGL-2 (disabling)	0.40 ppm (2.7 mg/m^3)	0.40 ppm (2.7 mg/m^3)	0.20 ppm (1.4 mg/m^3)	0.050 ppm (0.34 mg/m^3)	0.025 ppm (0.17 mg/m^3)	NOAEL for developmental effects in rats (E. I. du Pont de Nemours & Co. 1989)
AEGL-3 (lethality)	160 ppm (1,100 mg/m^3)	160 ppm (1,100 mg/m^3)	80 ppm (540 mg/m^3)	20 ppm (140 mg/m^3)	10 ppm (68 mg/m^3)	Lethality threshold estimated from rat LC_{50} data (E. I. du Pont de Nemours & Co. 1962a,b)

Abbreviations: LC_{50}, lethal concentration, 50% lethality; NOAEL, no observed adverse effect level; NR, not recommended.

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

TABLE 4-2 Chemical and Physical Data for Hexafluoroacetone

Parameter	Value	Reference
Synonyms	Hexafluor-2-propane; 1,1,1,3,3,3-hexafluoro-2-propanone; HFA; perfluoroacetone	AIHA 1996; NIOSH 2011
CAS registry no.	684-16-2 (anhydrous gas)	NIOSH 2011
Chemical formula	C_3F_6O	NIOSH 2011
Structure	C(C(C(F)(F)F)=O)(F)(F)F	HSDB 2009
Molecular weight	166.0	NIOSH 2011
Physical state	Colorless gas	NIOSH 2011
Melting point	-125.45°C	HSDB 2009
Boiling point	-27°C	HSDB 2009
Density/specific gravity	1.33 g/mL at 25°C	HSDB 2009
Relative vapor density	5.76	NIOSH 2011
Solubility in water	Highly reactive	NIOSH 2011
Vapor pressure	5 mm Hg at 25°C	HSDB 2009
Conversion factors in air	1 mg/m^3 = 0.15 ppm 1 ppm = 6.8 mg/m^3	NIOSH 2011

2.2. Nonlethal Toxicity

No definitive data were available regarding nonlethal effects in humans following inhalation exposure to HFA. It is likely that inhaling HFA would be irritating but quantitative data are only available from an abstract reporting that exposure at 4 ppm was irritating to the upper respiratory tract (Kuznetsova 1972). No odor threshold values were available.

2.3. Developmental and Reproductive Effects

No human developmental or reproductive toxicity data on HFA were available.

2.4. Genotoxicity

No human genotoxicity data on HFA were available.

2.5. Carcinogenicity

No data on the carcinogenic potential of HFA in humans were found.

2.6. Summary

There is very little information on the effects of HFA in humans.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

In a preliminary study conducted by Haskell Laboratory (E. I. du Pont de Nemours & Co. 1962a), groups of four male rats (250-300 g; age and strain not specified) were exposed to HFA dihydrate at nominal concentrations of 200, 400, or 800 ppm for 4 h. Test atmospheres were generated by vaporization (50-60°C) in dried air of a known amount of the test article. Mortality ratios were 0/4, 3/4, and 4/4 for the 200-, 400-, and 800-ppm groups, respectively. At 800 ppm, two rats died within 2.5 h, one died on day 3, and one on day 5. At 400 ppm, three rats died on day 4. Clinical signs in rats exposed at 400 and 800 ppm included unconsciousness, prostration, hind-leg paralysis, diarrhea, and labored respiration. In some cases, apparent recovery occurred followed by death. Post-mortem examination revealed exposure-dependent involvement of the brain, spinal cord, liver, kidney, and pancreas, as well as severe effects on stem cells and developing sperm. Specific responses in rats exposed at 200 ppm is uncertain, because no clinical signs were reported in study's tabulated data but elsewhere in the report it was stated that rats in this group exhibited similar but less severe signs as those in the 400-ppm group (hind-leg dysfunction, diarrhea, and chromodacorryhea). Histopathologic examination, however, noted involvement (non-specified) of the gastrointestinal tract, spleen, and pituitary (hypoplasia) in all exposure groups with lesser severity and incidence in the 200-ppm group.

The acute lethal toxicity of HFA and HFA nonahydrate was evaluated using groups of four ChR-CD rats exposed for 4 h (E. I. du Pont de Nemours & Co. 1962b). Nominal HFA concentrations were 100, 200, 300, and 400 ppm and HFA nonahydrate concentrations were 300, 400, 500, and 1,000 ppm. There was a 14-day post-exposure observation period. Lethal concentrations were estimated to be 300 ppm for HFA and 400 ppm for HFA nonahydrate (see Table 4-3). Pathologic examination revealed marked concentration-dependent testicular damage (aspermatogenesis, interstitial damage).

Additional studies at Haskell Laboratory examined the lethal response of male ChR-CD rats after exposure to HFA for 15-30 min, and the course of testicular effects after exposure at 200 ppm for 4 h (E. I. du Pont de Nemours & Co. 1965). A control group was placed in the same exposure system but without HFA. In the lethality assessment, groups of four rats (235-327 g) were exposed to HFA at nominal concentrations of 1,200, 3,600, 4,800, or 6,000 ppm for 30 min or at 9,600 ppm for 15 min. Test atmospheres were generated as described in previous Haskell Laboratory studies. At all concentrations, rats exhibited lac-

rimation, salivation, nasal discharge, intermittent gasping, and inactivity during exposure; those that died were cyanotic and exhibited weakness of the extremities. Mortality results are summarized in Table 4-4. All rats lost weight during the post-exposure period. The most prevalent histopathologic finding in both surviving rats and rats that died was marked degeneration and necrosis of the germinal cells of the testes. Lung and thymus changes (no specifics provided) also were observed in all groups, including rats killed at 14 days post-exposure.

Borzelleca and Lester (1965) reported a 30-min LC_{50} (lethal concentration, 50% lethality) of 900 ppm and a 3-h LC_{50} of 275 ppm for male and females Wistar rats (150 g; 5/sex/group) exposed at a series of non-specified concentrations of HFA (99.99%) for 0.5, 3, or 6 h. Exposure atmospheres were prepared by mixing a stream of HFA with dry air. Concentrations in the 10-L exposure chamber were adjusted by a calibrated flow meter before mixing or by means of a motor-driven syringe (for low concentrations). Rats that survived the exposure were observed for 15 days. There were no sex-related differences observed, little or no lung damage, and no histopathologic findings in the heart, kidneys, or liver.

TABLE 4-3 Lethal Toxicity in Male Rats Exposed to Hexafluoroacetone and Hexafluoroacetone Nonahydrate for Four Hours

Chemical	Concentration (ppm)	Mortality ratio	Details
HFA	100	0/4	
	200	0/4	
	300	2/4	Deaths on post-exposure days 3 and 6
	400	2/4	Deaths on post-exposure days 5 and 7
HFA nonahydrate	300	0/4	
	400	1/4	Death on post-exposure day 5
	500	3/4	Deaths on post-exposure days 4, 7, and 10
	1,000	4/4	Deaths within 17 h to post-exposure day 5

Source: E. I. du Pont de Nemours & Co. 1962b.

TABLE 4-4 Lethal Toxicity of Hexafluoroacetone in Male Rats After Acute Inhalation Exposure

Concentration (ppm)	Duration (min)	Mortality Ratio	Details
2,400	30	0/4	
3,600	30	0/4	
4,800	30	3/4	Deaths at 4-days post-exposure
6,000	30	4/4	Deaths at 1-4 days post-exposure
9,600	15	3/4	Deaths at 1-2 days post exposure

Source: E. I. du Pont de Nemours & Co. 1965.

In a pilot study conducted by Haskell Laboratories (E. I. du Pont de Nemours & Co. 1988) to determine exposures for assessing the developmental toxicity of HFA, four of six female rats exposed at 60 ppm for 6 h per day for 2 days had to be killed in extremis. Four of six dams exposed at 30 ppm during gestation days 7-16 died, but the day of each death was not specified.

3.1.2. Dogs

The effect of HFA on anesthetized mongrel dogs was studied by Borzelleca and Lester (1965). Male and female dogs were anesthetized with sodium pentobarbitol (intravenous injection of 30 mg/kg) and exposed to HFA at concentrations of 5,000 or 10,000 ppm. HFA concentrations were generated similar to that described for rats (see Section 3.1.1), with HFA mixing with room air in a bag and the mixture being administered to the dogs via an endotracheal tube. Dogs inhaled through the mixing bag and exhaled into a hood. At 5,000 ppm, all three dogs survived a 30-min exposure and one of two survived a 45-min exposure. At 10,000 ppm, two of three dogs each survived a 30-min or 45-min exposure. Deaths occurred 1-3 days post-exposure. Postmortem exams revealed pulmonary hemorrhage and edema but no observable changes in the trachea, heart, spleen, liver, kidneys, gastrointestinal tract, or urinary bladder.

3.2. Nonlethal Toxicity

3.2.1. Rats

A single 4-h exposure of male rats to HFA at 100 or 200 ppm or to HFA nonahydrate at 300 ppm was not lethal (E. I. du Pont de Nemours & Co. 1962b). Lethality in this study was evaluated over a 14-day post-exposure period. This study also reported no lethality in rats repeatedly exposed (10 times) to HFA at 60 ppm for 4 h.

Exposure of groups of four ChR-CD male rats to HFA at 3,600 or 2,400 ppm for 30 min was not lethal (E. I. du Pont de Nemours & Co. 1965). Lethality was assessed up to a 14 days post-exposure. Another phase of this study examined the post-exposure course of testicular effects in rats following a 4-h exposure to HFA at 200 ppm (see Section 3.3). During exposure, rats exhibited deeper respiration than controls, lacrimation, salivation, and redness of the ears. Some rats exhibited chromodacryorrhea for 1-7 days post-exposure, and all treated rats experienced body weight loss for 1-3 days.

A 13-week inhalation exposure study, groups of 30 male and 30 female ChR-CD rats (245-327 g and 180-248 g, respectively) were exposed to HFA at 0, 0.1, 1.0, or 12 ppm for 6 h/day, 5 days/week (E. I. du Pont de Nemours & Co. 1971). Post-exposure assessments were conducted at 28 and 84 days. Test atmospheres were generated via metered distribution from supply cylinders and mixing with dry air and supply air (50% relative humidity). Air from each

chamber was sampled daily and analyzed for HFA by gas chromatography analysis of trifluoromethane generated by reacting the HFA-containing samples with sodium hydroxide. There were no observations at exposure durations consistent with AEGL durations. No gross, biochemical, hematologic, or histopathologic changes were found in rats exposed at 0.1 ppm, and the only treatment-related effects noted in the 1.0-ppm group was reversible kidney dysfunction. In the 12-ppm group, the most notable effects were testicular atrophy with interstitial edema and oligospermia at 30 days, and cessation of spermiogenesis, severe interstitial edema, and sloughing of germinal cells at 90 days. The investigators reported that these effects were reversible on the basis of 28- and 84-day post-exposure observations.

3.2.2. Dogs

Groups of six male beagles (8.6-10 kg) were exposed to HFA at 0, 0.1, 1.0, or 12 ppm for 6 h/day, 5 days/week for 13 weeks, followed by post-exposure assessment at 45 days (E. I. du Pont de Nemours & Co. 1971). Testes weight was decreased and pituitary and lung weights were increased, but the effects were reversible. Reversible testicular damage was observed in dogs at 12 ppm, but no testicular effects were observed at 0.1 or 1 ppm.

3.3. Developmental and Reproductive Effects

As previously noted in Section 3.1.1, no clinical signs were observed in a group of four rats exposed to HFA dehydrate at 200 ppm for 4 h (E. I. du Pont de Nemours & Co. 1962b). However, pathologic examination revealed effects on the gastrointestinal tract, spleen, pituitary gland, and spermatazoa.

Subsequent studies at Haskell Laboratory examined the course of testicular effects in rats exposed to HFA by inhalation (E. I. du Pont de Nemours & Co. 1965). Twelve rats were exposed to HFA at 200 ppm for 4 h. A control group was placed in the same exposure system but without HFA. Three rats were killed on post-exposure days 7, 14, 28, and 57 for histopathologic assessment. Rats in this phase of the study exhibited similar signs of exposure (lacrimation, salivation, and post-exposure weight loss) as did those exposed to nonlethal concentrations in the previous experiments assessing lethality. Both absolute and relative (to body weight) weights of the testes decreased in exposed animals compared with controls. Although some recovery from testicular degeneration was noted by day 57, some spermatogenic tubules still had no germinal cells.

An additional study conducted by E. I. du Pont de Nemours & Co. (1989) examined the developmental toxicity of HFA in groups of 24 Crl:CD7BR rats exposed by nose-only (0, 0.11, 1.0, or 6.9 ppm, mean chamber concentrations) for 6 h/day on gestation days 7-16. The exposure system was described in detail and affirmed uniform distribution of the test atmosphere. Exposure concentra-

tions in the test chamber were measured hourly and determined by HFA-hydrate formation and its analysis by gas chromatography. Nose-only exposure was used to minimize hydrate aerosol formation, dermal and oral absorption, and subsequent deposition onto the pelt of the animals. All female rats survived to scheduled sacrifice on gestation day 22, although a significant ($p \leq 0.05$) decrease in body weight change relative to controls was found in the high-dose group on gestation days 17-22. However, absolute body weights adjusted to eliminate the products of conception (live and dead fetuses) were not significantly different from controls. Both absolute and relative (to body weight) liver weights were significantly greater ($p \leq 0.05$) in rats of the 1- and 6.9-ppm groups. Reproductive effects included a significant ($p \leq 0.05$) treatment-related decrease in total live fetuses and number of female live fetuses in the 6.9-ppm group. Fetal effects included significantly lower ($p \leq 0.05$) fetal body weights in the 1- and 6.9-ppm groups, increased incidences of malformations, and external and skeletal developmental variations in the 6.9-ppm group. Major findings of this study are summarized in Table 4-5. The investigators concluded that HFA at 6.9 ppm resulted in significant increases in resorptions, malformations, developmental variations, and variations due to retarded development, and that exposure at 1 ppm resulted in increased incidences of skeletal developmental variations and decreases in fetal weights. Developmental effects at 1 and 6.9 ppm were considered by the investigators to be of greater severity than the severity of concurrent maternal responses.

TABLE 4-5 Effects of Hexafluoroacetone in Rats Exposed During Gestation

Effect	Control	0.1 ppm	1.0 ppm	6.9 ppm
Maternal effects				
Liver weight (absolute)	14.3 g	14.7 g	15.7 g[a]	16.2 g[a]
Liver weight (relative)	4.9 g	4.8 g	5.2 g[a]	5.4 g[a]
Reproductive effects				
No. live fetuses	300	270	339	277
Live fetuses/litter	14.3	13.5	14.1	11.5[a]
Total resoprtions/litter	1.0	1.8	1.0	3.5[a]
Fetal effects				
Mean fetal weight	5.30	5.21	4.94[a]	4.11[a]
Malformations[b]	0	0	3	68[a]
Variations[b]				
Developmental	60	36	86	204
Retarded development	27	26	64	194

[a]$p \leq 0.05$ relative to untreated controls.
[b]Total number of fetuses affected; includes external, visceral, head, and skeletal malformations.
Source: E. I. du Pont de Nemours & Co. 1989.

Testicular atrophy was also reported for Crl:CD7BR rats exposed to HFA at 12 ppm for 6 h/day, 5 days/week for 30 days (Lee and Kennedy 1991). After 90 days of exposure, more severe atrophy was observed. No significant testicular effects were observed in rats exposed at 0.1 or 1.0 ppm, and some evidence of regeneration of atrophic testes was observed in the 12-ppm group at post-exposure day 28, but normal spermatogenesis was only partially restored at post-exposure day 84.

3.4. Genotoxicity

HFA sesquihydrate was not mutagenic in *Salmonella typhimurium* strains TA 1535, 1537, and 1538 with or without activation (S-9) at concentrations up to 7,500 μg/plate (E. I. du Pont de Nemours & Co. 1975).

3.5. Carcinogenicity

There were no data with which to evaluate the carcinogenic potential of HFA.

3.6. Summary

A 30-min LC_{50} of 900 ppm and a 3-h LC_{50} of 275 ppm have been reported for HFA in rats. Other studies reported no lethality after a single 30-min exposure to HFA at 3,600 ppm or a single 4-h exposure at 200 ppm. Effects, including lethality, appeared to be mediated systemically and often occurred during post-exposure periods. Mortality results of repeated exposures to HFA are equivocal; four of six rats died after being exposed to HFA at 60 ppm for 6 h/day for two days, but in another study it was reported that no lethality was observed when rat were exposed 10 times to HFA at 60 ppm for 4 h/day. At 30 ppm, it was reported that four of six pregnant rats died after being exposed to HFA for 10 days. The most prevalent nonlethal responses to HFA after inhalation exposure were lacrimation and salivation during exposure and developmental effects in rats when dams were exposed to HFA for several days during gestation. Exposure of male rats to HFA consistently resulted in testicular degeneration after multiple exposures at 12 ppm or a single 4-h exposure at 200 ppm.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was available regarding the metabolism and disposition of HFA following inhalation exposure. Gillies and Rickard (1984) reported that [^{14}C]HFA exhibited biphasic elimination from the blood after it was adminis-

tered subcutaneously in rats at 3 mg/kg. The half-life for the initial and elimination phases were 22.6 and 75.1 h, respectively. HFA was eliminated unchanged in the urine (81% at 120 h) and feces (9% at 120 h). Although toxicity data clearly indicate the testes as a target organ, there was no unusual accumulation or sequestration of [C^{14}]HFA.

4.2. Mechanism of Toxicity

The mechanism(s) by which HFA exerts toxic effects is uncertain. No studies were available that specifically addressed the topic. Borzelleca and Lester (1965) noted that HFA effects appeared to be systemically mediated with pulmonary damage in rats occurring only at air concentrations exceeding minimal lethality levels. Studies described in Section 3 indicate contact irritation effects (lacrimation and signs of nasal irritation) and systemic effects (testicular atrophy, central nervous system depression, neuromuscular dysfunction, weight loss, and renal dysfunction).

Results of a study by Gillies and Lee (1983) suggested that HFA-induced alteration of lipid metabolism and the resulting inhibition of sterol synthesis was associated with testicular atrophy in rats.

4.3. Structure-Activity Relationships

No data were available with which to develop definitive structure-activity analyses.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No data were available regarding AEGL-1 type effects in humans.

5.2. Animal Data Relevant to AEGL-1

No exposure-response data in animals consistent with AEGL-1 effects were available.

5.3. Derivation of AEGL-1

Neither qualitative nor quantitative data were available regarding AEGL-1 type effects resulting from acute inhalation exposure to HFA. Therefore, no AEGL-1 values are recommended. Although some studies reported exposures that were without serious or lethal effects, no details were available about the severity of responses relevant to AEGL-1 effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No data were available on nonlethal adverse effects in humans resulting from inhalation exposure to HFA.

6.2. Animal Data Relevant to AEGL-2

Information regarding the adverse effects of HFA in animals after acute inhalation exposure was only available from studies conducted by E. I. du Pont de Nemours & Co. (see Sections 3.2 and 3.3). A single 4-h exposure of male rats to HFA at 200 ppm did not result in any effects consistent with AEGL-2 severity. However, follow-up evaluation for 57 days revealed decreased absolute and relative testicular weights compared with unexposed controls. Results of a developmental study in rats showed that nose-only exposure to HFA at 7 ppm for 6 h/day on gestation days 7-16 resulted in a significantly decreased mean fetal weight, decreased number of live fetuses per litter, and an increase in total resorptions per litter that, according to the investigators, was not a function of maternal effects (significantly decreased body weight [although not significant when adjusted for products of conception] and increased absolute and relative liver weight).

6.3. Derivation of AEGL-2

There is a paucity of information on HFA with which to develop AEGL-2 values. No human data were available. Several studies have reported developmental and reproductive toxicity of HFA after acute inhalation exposure of male rats (E. I. du Pont de Nemours & Co. 1965) and exposure of female rats during gestation (E. I. du Pont de Nemours & Co. 1989). Testicular atrophy observed in male rats tended to be reversible. Evidence of developmental toxicity in rats occurred at lower concentrations than did testicular effects and were selected as the critical effect for development of AEGL-2 values for HFA.

Exposure of dams to HFA at 6.9 ppm for 6 h/day on gestation days 7-16 resulted in a significant decrease in the number of live fetuses per litter, total resorptions per litter, and mean fetal weight, and exposure at 1 ppm resulted in a slight decrease in mean fetal weight (E. I. du Pont de Nemours & Co. 1989). In the absence of notable maternal toxicity, these findings suggest that the fetus is uniquely sensitive to HFA exposure. The concentration of 1.0 ppm was selected as the point of departure for AEGL-2 development under the assumption that a single 6-h exposure during gestation could be responsible for the observed effects. A total uncertainty factor of 30 was applied. A factor of 10 was applied to account for uncertainties associated with extrapolating animal data to human exposure conditions. An uncertainty factor of 3 was used to account for intra-

species variability because HFA does not appear to undergo significant metabolism and because the fetus is considered a sensitive target. Further adjustment was considered unnecessary because of the assumption that the observed effects were the result of a single 6-h exposure during the 10-day gestational exposure period. For time scaling from the 6-h experimental duration to AEGL-specific durations, the equation $C^n \times t = k$ was applied. The value of n was empirically determined from the available data to be 1 (ten Berge et al. 1986).

AEGL-2 values for HFA are presented in Table 4-6, and their derivation is summarized in Appendix A. Because of the uncertainty associated with extrapolating a 6-h point of departure to a 10-min exposure duration, the 30-min AEGL-2 value was set equal to the 30-min value.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data were available regarding lethality of inhaled HFA in humans.

7.2. Animal Data Relevant to AEGL-3

Lethality data on HFA were available from studies in rats and dogs, although the latter involved the use of anesthetized animals and was not definitive regarding a lethality threshold. Results of acute inhalation exposure studies in rats by E. I. du Pont de Nemours & Co. (1962a,b) indicated that 200 ppm was a 4-h nonlethal exposure, but that 300 ppm produced 50% mortality and 400 ppm produced 75% mortality. A study of HFA nonahydrate suggested slightly lower toxicity; 25% mortality occurred in rats after a 4-h exposure at 400 ppm. A subsequent study by E. I. du Pont de Nemours & Co. (1965) showed that higher concentrations were required for a lethal effect when exposure duration was decreased. Specifically, 30-min exposure at 2,400 or 3,600 ppm was not lethal to groups of four rats. However, exposure at 9,600 ppm for 15 min or at 4,800 ppm for 30 min resulted in 75% mortality. A 30-min and a 3-h LC_{50} of 900 and 275 ppm, respectively, were reported by Borzelleca and Lester (1965). Post-exposure observation periods in most of the studies revealed systemic involvement, and deaths often occurred after exposure ended. Two 6-h/day exposures at 60 ppm resulted in four of six female rats being killed in extremis (E. I. du Pont de Nemours & Co. 1988).

TABLE 4-6 AEGL-2 Values for Hexafluoroacetone

10 min	30 min	1 h	4 h	8 h
0.40 ppm (2.7 mg/m^3)	0.40 ppm (2.7 mg/m^3)	0.20 ppm (1.4 mg/m^3)	0.050 ppm (0.34 mg/m^3)	0.025 ppm (0.17 mg/m^3)

7.3. Derivation of AEGL-3

The E. I. du Pont de Nemours & Co. studies in rats provided the most comprehensive data from which to develop AEGL-3 values. Two reports (E. I. du Pont de Nemours & Co. 1962 a,b) showed that 4-h exposure of rats to HFA at 200 ppm (300 ppm for the nonahydrate) was without lethality and that mortality increased to 50% at 300 ppm and 50-75% at 400 ppm. A 4-h exposure at 200 ppm was selected as the point of departure for AEGL-3 development. A factor of 3 was applied to account for uncertainties associated with extrapolating animal data to human exposure conditions. A factor of 3 was applied to account for individual variability, because HFA does not appear to undergo significant metabolism. Additional uncertainty factors were not applied because AEGL-3 values would be similar to or below the concentrations shown to be nonlethal in 13-week rat and dog studies (E. I. du Pont de Nemours & Co. 1971). For time scaling from the 4-h experimental duration to AEGL-specific durations, the equation $C^n \times t = k$ was applied. The value of n was empirically determined from the available data to be 1 (ten Berge et al. 1986).

AEGL-3 values for HFA are presented in Table 4-7 and their derivation is summarized in Appendix A. Because of the uncertainty in extrapolating from a 4-h point of departure to a 10 min exposure duration, the 30-min AEGL-2 value was set equal to the 30-min value.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

There were inadequate data for developing AEGL-1 values. AEGL-2 values were based on results of studies in rats conducted by E. I. du Pont de Nemours & Co. (1989) indicating that HFA was toxic to the fetus in the absence of significant maternal toxicity. Although the developmental study selected as the basis for AEGL-2 development used a multiple exposure protocol (gestation days 7-16), the point of departure was based on the assumption that the observed effects could have been the result of a single-day exposure. AEGL-3 values were developed using a no-effect level for lethality (200 ppm for 4 h) in rats as the point of departure. AEGL values for HFA are presented in Table 4-8. The relationship of the AEGL-2 and AEGL-3 values to available toxicity data are shown in a category plot in Appendix D.

TABLE 4-7 AEGL-3 Values for Hexafluoroacetone

10 min	30 min	1 h	4 h	8 h
160 ppm (1,100 mg/m^3)	160 ppm (1,100 mg/m^3)	80 ppm (540 mg/m^3)	20 ppm (140 mg/m^3)	10 ppm (68 mg/m^3)

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures in the United States are presented in Table 4-9. Additionally, the Health Council of the Netherlands Committee on Updating of Occupational Exposure Limits developed an occupational exposure limit of 0.05 mg/m^3 (≈0.0075 ppm) for HFA and its hydrates on the basis of HFA-induced developmental toxicity (Health Council of the Netherlands 2001).

TABLE 4-8 AEGL Values for Hexafluoroacetone

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)	0.40 ppm (2.7 mg/m^3)	0.40 ppm (2.7 mg/m^3)	0.20 ppm (1.4 mg/m^3)	0.050 ppm (0.34 mg/m^3)	0.025 ppm (0.17 mg/m$^{3)}$
AEGL-3 (lethality)	160 ppm (1,100 mg/m^3)	160 ppm (1,100 mg/m^3)	80 ppm (540 mg/m^3)	20 ppm (140 mg/m^3)	10 ppm (68 mg/m^3)

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

TABLE 4-9 Extant Standards and Guidelines for Hexafluoroacetone

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	0.40 ppm	0.40 ppm	0.20 ppm	0.050 ppm	0.025 ppm
AEGL-3	160 ppm	160 ppm	80 ppm	20 ppm	10 ppm
ERPG-1 (AIHA)[b]			—		
ERPG-2 (AIHA)			1 ppm		
ERPG-3 (AIHA)			50 ppm		
TLV-TWA (ACGIH)[c]					0.1 ppm
REL-TWA (NIOSH)[d]					0.1 ppm (skin)
MAC (the Netherlands)[e]					0.0075 ppm

[a]NR, not recommended; absence of AEGL-1 values does not imply that exposure below the AEGL-2 values is without adverse effects.
[b]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA] 1996).
ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. Not applicable for HFA.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.
ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one h without experiencing or developing life-threatening health effects.
[c]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2003]) 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.
[d]REL-TWA (recommended exposure limits - time weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA. The skin notation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.
[e]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands, MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

Human data on HFA are lacking. The available animal data on HFA include cursory lethality studies which used relatively small numbers of animals. Studies were conducted primarily in rats, with a few in dogs, so little information was available on species variability. There was no definitive information on exposure-response relationships for clinical effects or on the mode action of HFA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR HEXAFLUOROACETONE

Derivation of AEGL-1 Values

No AEGL-1 values were recommended because of inadequate data. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values is without effect.

Derivation of AEGL-2 Values

Key study:	E. I. du Pont de Nemours & Co. 1989. Developmental Toxicity Study of Hexafluoroacetone (HFA) in the Rat with Cover Letter Dated 042889. E. I. du Pont de Nemours & Co., Inc. Medical Research No. 8166-001. Du Pont HLR 776-88. Unpublished report.
Critical effect:	A significant ($p \leq 0.05$) decrease in live fetuses per litter, total resorptions per litter, and mean fetal weight was observed in pregnant rats exposed to HFA at 6.9 ppm for 6 h/day on gestation days 7-16. At 1 ppm, only mean fetal body weight was decreased. Thus, 1 ppm was selected as the point of departure. It was assumed that the observed effects could be induced by a single 6-h exposure.
Time scaling:	$C^n \times t = k$; n = 1 was determined empirically from available data (ten Berge et al. 1986). $(1\ ppm)^1 \times 6\ h = 6\ ppm\text{-}h$
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability, because HFA does not appear to undergo significant metabolism and because the fetus is considered a sensitive target. A larger factor was considered unnecessary because of the assumption that the effects reported in the key study were the result of

	a single 6-h exposure during the 10-day gestational exposure period. Total uncertainty factor of 30
Calculations:	
10-min AEGL-2:	Set equivalent to the 30-min AEGL-2 value of 0.40 ppm, because of the uncertainty with extrapolating a 6-h point of departure to a 10-min exposure duration (NRC 2001).
30-min AEGL-2:	C × 0.5 h = 6 ppm-h 12 ppm ÷ 30 = 0.40 ppm
1-h AEGL-2:	C × 1 h = 6 ppm-h 6 ppm ÷ 30 = 0.20 ppm
4-h AEGL-2 :	C × 4 h = 6 ppm-h 1.5 ppm ÷ 30 = 0.050 ppm
8-h AEGL-2:	C × 8 h = 6 ppm-h 0.75 ppm ÷ 30 = 0.025 ppm

Derivation of AEGL-3 Values

Key studies:	E. I. du Pont de Nemours & Co. 1962b. Inhalation Toxicity of Hexafluoroacetone Compound in Rats. Haskell Laboratory report No. 46-62. Haskell Laboratory for Toxicology and Industrial Hygiene, E. I. du Pont de Nemours & Co. Unpublished report. E. I. du Pont de Nemours & Co. 1962a. Inhalation Toxicity of Hexafluoroacetone Dihydrate in Rats. Haskell Laboratory report No. 47-62. Haskell Laboratory for Toxicology and Industrial Hygiene, E. I. du Pont de Nemours & Co. June 27, 1962. Unpublished report.
Critical effect:	No lethality in male rats exposed at 200 ppm for 4 h.

Time scaling:	$C^n \times t = k$; n = 1 was determined empirically from available data (ten Berge et al. 1986). $(200 \text{ ppm})^1 \times 4 \text{ h} = 800 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; no irreversible effects were observed in studies of rats and dogs exposed to HFA at 12 ppm for up to 13 weeks (6 h/day, 5 days/week). 3 for intraspecies variability; HFA does not appear to undergo significant metabolism and a larger adjustment would result in exposure concentrations below those shown to be nonlethal in multiple-exposure rat and dog studies (E. I. du Pont de Nemours & Co. 1971). Total uncertainty factor of 10
Calculations:	
10-min AEGL-3:	Set equivalent to the 30-min AEGL-3 value of 160 ppm, because of the uncertainty with extrapolating a 4-h point of departure to a 10-min exposure duration (NRC 2001).
30-min AEGL-3:	$C \times 0.5 \text{ h} = 800 \text{ ppm-h}$ $1{,}600 \text{ ppm} \div 10 = 160 \text{ ppm}$
1-h AEGL-3:	$C \times 1 \text{ h} = 800 \text{ ppm-h}$ $800 \text{ ppm} \div 10 = 80 \text{ ppm}$
4-h AEGL-3:	$C \times 4 \text{ h} = 800 \text{ ppm-h}$ $200 \text{ ppm} \div 10 = 20 \text{ ppm}$
8-h AEGL-3:	$C \times 8 \text{ h} = 800 \text{ ppm-h}$ $100 \text{ ppm} \div 10 = 10 \text{ ppm}$

APPENDIX B

TIME SCALING CALCULATIONS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and its toxicologic and pharmacologic properties. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC 1993) or Haber's Rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). According to this concept, exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is dependent equally on the concentration and the exposure duration.

75% Mortality Response in Rats (E. I. Du Pont de Nemours & Co. 1962a, 1965)

Time	Concentration	Log Time	Log Concentration
15	9,600	1.1761	3.9823
30	4,800	1.4771	3.6812
240	500	2.3802	2.6990

Regression output	
Intercept	5.2508
Slope	-1.0708
R squared	0.9997
Correlation	-0.9999
Degrees of freedom	1
Observations	3

n =	0.93
k =	80081.6

Min	Concentration
30	4,667.23
60	2,221.83
240	503.52
480	239.70

Hours	Concentration
0.5	374,226.05
1.0	178,150.07
4.0	40,372.90
8.0	19,219.49

However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. The relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific, and even a toxic-end-point specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health-effect end point. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of C vs. t yields a progressive decrease in the slope of the curve.

AEGL values for HFA were derived on the basis of 6-h (AEGL-2) and 4-h (AEGL-3) experimental durations. The equation $C^n \times t = k$ was applied. The value of n was empirically determined from available data to be 1 (ten Berge et al. 1986).

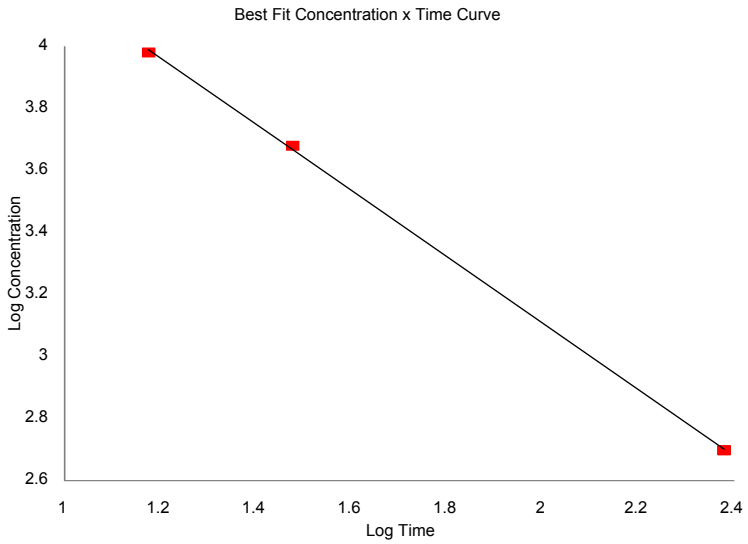

FIGURE B-1 Regression Plot of LC_{75} Values in Rats from Studies by E. I. Du Pont de Nemours & Co. (1962a, 1965).

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR HEXAFLUOROACETONE

Derivation Summary

Inadequate data exist for deriving AEGL-1 values for HFA. Absence of AEGL-1 values does not indicate that exposure below AEGL-2 values is without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.40 ppm	0.40 ppm	0.20 ppm	0.050 ppm	0.025 ppm

Reference: E. I. du Pont de Nemours & Co. 1989. Developmental Toxicity Study of Hexafluoroacetone (HFA) in the Rat with Cover Letter Dated 042889. E. I. du Pont de Nemours & Co., Inc. Medical Research No. 8166-001. Du Pont HLR 776-88. Unpublished report.

Test species/Strain/Sex/Number: Rat, Crl:CD7BR, female, 24

Exposure route/Concentrations/Durations: Nose-only inhalation, HFA at 0, 0.11, 1.0 or 6.9 ppm (mean chamber concentrations) for 6 h/day on gestation days 7-16.

Effects: Significant ($p \leq 0.05$) decreases in live fetuses per litter, total resorptions per litter, and mean fetal weight were observed at 6.9 ppm. At 1 ppm, only mean fetal body weight was decreased; so, 1 ppm was selected as the point of departure.

End point/Concentration/Rationale: It was assumed that the observed effects at 1 ppm could be induced by a single 6-h exposure.

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10 to account for extrapolating animal data to human exposure conditions.
Intraspecies: 3 for intraspecies variability, because HFA does not appear to undergo significant metabolism and because the fetus is considered a sensitive target. A larger factor was considered unnecessary because of the assumption that the observed effects were the result of a single 6-h exposure during the 10-day gestational exposure period.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: For time scaling from the 6-h experimental duration to AEGL-specific durations, the equation $C^n \times t = k$ was applied. The value of n was determined empirically from available data to be 1 (ten Berge et al. 1986). Because of the uncertainty in extrapolating a 6-h point of departure to a 10-min exposure duration, the 30-min AEGL-2 value was set equivalent to the 30-min value.

Data adequacy: Data were considered adequate for AEGL-2 development. However, no human exposure data were available to compare with the AEGL values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
160 ppm	160 ppm	80 ppm	20 ppm	10 ppm

Reference: E. I. du Pont de Nemours & Co. 1962b. Inhalation Toxicity of Hexafluoroacetone Compound in Rats. Haskell Laboratory report No. 46-62. Haskell Laboratory for Toxicology and Industrial Hygiene, E. I. du Pont de Nemours & Co. Unpublished report.

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Test Species/Strain/Sex/Number: Rat, ChR-CD, male, 4

Exposure Route/Concentrations/Durations: Inhalation; HFA at 100, 200, 300, and 400 ppm (nominal) for 4 h; HFA nonahydrate at 300, 400, 500, and 1,000 ppm (nominal) for 4 h

Effects: Lethality

End point/Concentration/Rationale: No lethality observed with HFA at 200 ppm or with HFA nonahydrate at 300 ppm HFA. HFA at 300 ppm resulted in 50% mortality and HFA nonahydrate at 400 ppm resulted in 25% mortality.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 was applied to account for uncertainties associated with extrapolating animal data to human exposure conditions; no irreversible effects were observed in studies of rats and dogs exposed to HFA at 12 ppm for up to 13 weeks (6 h/day, 5 days/week).
Intraspecies: 3 for intraspecies variability because HFA does not appear to undergo significant metabolism and because a larger factor would result in exposure concentrations below those shown to be nonlethal in multiple-exposure rat and dog studies (E. I. du Pont de Nemours & Co. 1971).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: For the time scaling from the 4-h experimental duration to AEGL-specific durations, the equation $C^n \times t = k$ was applied, where $n = 1$ was determined empirically from available data (ten Berge et al. 1986). Because of the uncertainty in extrapolating a 4-h point of departure to a 10-min exposure duration, the 30-min AEGL-3 value was set equivalent to the 30-min value.

Data adequacy: Lethality data were considered adequate for development of AEGL-3 values.

APPENDIX D

CATEGORY PLOT FOR HEXAFLUOROACETONE

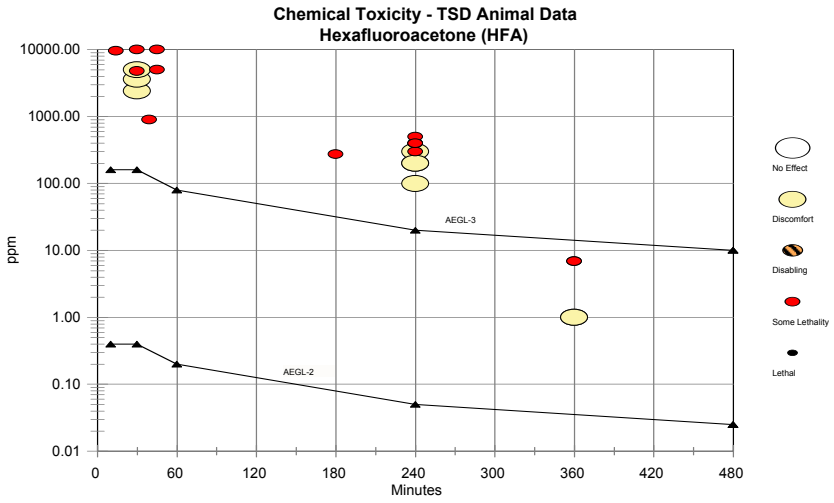

FIGURE D-1 Category plot of toxicity data and AEGL values for hexafluoroacetone. The 360-min data entries between the AEGL-2 and AEGL-3 values reflect multiple exposures during gestation (see Sections 3.3 and 6.3) and are not single 6-h exposures. Because of uncertainties in extrapolating from the experimental exposure durations to 10 min, the 30-min AEGL-2 and AEGL-3 values were set equivalent to the respective 30-min values. AEGL-1 values were not recommended because of insufficient data.

5

Perchloryl Fluoride[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 Dana Glass (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager George Cushmac (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

Perchloryl fluoride is a colorless, stable gas. It is used as a fluorinating agent, an oxidant in rocket fuels, and a gaseous dielectric for transformers. It is prepared by electrolysis of a saturated solution of sodium perchlorate in anhydrous hydrofluoric acid. Perchloryl fluoride is a strong oxidizer, and is strongly irritating to the eyes, mucous membranes, and lungs. Its systemic effects include induction of methemoglobinemia.

No human data were available for developing AEGL values, and only two relevant reports of studies in animals were found. Greene et al. (1960) performed several experiments in dogs, rats, mice, and guinea pigs. In acute studies with dogs, animals were treated with perchloryl fluoride at 224-622 ppm for 4 h, and hemoglobin and methemoglobin concentrations were evaluated. In studies with rats and mice, only 4-h LC_{50} (lethal concentration, 50% lethality) values were reported. Repeat-exposure studies in dogs, rats, mice, and guinea pigs also were performed. In the second report, mortality values were presented for rats at several time points, but details of the exposures to perchloryl fluoride were not included (Dost et al. 1974). No information relevant to time-scaling AEGL values for perchloryl fluoride was found.

The AEGL-1 values were derived from a study in which dogs and rats were exposed to perchloryl fluoride at 24 ppm for 6 h/day, 5 days/week for 26 weeks. All animals survived and no irritation or clinical signs of toxicity were

observed. The only long-term effect was increased fluoride deposition in the bone and urine. Therefore, 24 ppm was considered a no-effect level for an 8-h exposure, and was selected as the point of departure. That value was divided by a total uncertainty factor of 30 (3 for interspecies differences and 10 for intraspecies variability). An interspecies uncertainty factor of 3 was selected because lethality values for dogs, rats, and mice differed by less than a factor of 3. An intraspecies uncertainty factor of 10 was considered appropriate because infants are considerably more susceptible to methemoglobinemia than healthy adults. In the absence of time-scaling information, the 6-h value was scaled using the equation $C^n \times t = k$, using the default values of n = 3 and n = 1 to extrapolate to shorter or longer exposure durations, respectively. Because of the uncertainty associated with scaling a 6-h exposure to 10 min, the 10-min AEGL value was set equal to the 30-min AEGL value.

No acute studies were available that addressed relevant AEGL-2 effects. In the absence of appropriate chemical-specific data, AEGL 2 values were set at one-third of the AEGL-3 values (NRC 2001). This approach is supported by the apparent steep-concentration response curve for perchloryl fluoride. Two of two dogs exposed to perchloryl fluoride at 425 ppm survived a 4-h exposure, but one of two dogs was found moribund after a 4-h exposure at a slightly higher concentration of 451 ppm (Green et al. 1960).

AEGL-3 values were based on moderate cyanosis and hyperpnea observed in dogs exposed to perchloryl fluoride at 224 ppm for 4-h. No dogs died at the next highest concentration of 451 ppm, but that concentration is greater than the rat 4-h LC_{50} of 385 ppm in the same study. A total uncertainty factor of 30 was applied (3 for interspecies differences and 10 for intraspecies variability). An interspecies uncertainty factor of 3 was selected because lethality values among dogs, rats, and mice differed by less than a factor of 3, and lethal values for the rat were considered in selecting the point of departure. An intraspecies uncertainty factor of 10 was considered appropriate because infants are considerably more susceptible to methemoglobinemia than healthy adults. In the absence of time-scaling information, the 4-h value was scaled to the shorter- and longer-exposure durations using the same approach as that for the AEGL-1 values. Because of uncertainty in time scaling from a 4-h exposure to 10 min, the 10-min value was set equal to the 30-min AEGL value.

AEGL values for perchloryl fluoride are presented in the Table 5-1.

1. INTRODUCTION

Perchloryl fluoride is a colorless gas with a characteristic sweet odor. Chemically, it is the acyl fluoride of perchloric acid, and is prepared by electrolysis of a saturated solution of sodium perchlorate in anhydrous hydrofluoric acid. It is a very stable compound. Perchloryl fluoride is used as a fluorinating agent, an oxidant in rocket fuels, and a gaseous dielectric for transformers (Mendiratta et al. 2005). It is a strong oxidizer, and acts as a strong irritant of the

eyes, mucous membranes, and lungs. Absorption of the chemical results in methemoglobinemia. Dermal contact with the liquid form of perchloryl fluoride can produce burns.

Production data were not found for perchloryl fluoride. Perchloryl fluoride does not burn and is not flammable, but it can support combustion. Chemical and physical properties are provided in Table 5-2.

TABLE 5-1 Summary of AEGL Values for Perchloryl Fluoride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.8 ppm (7.6 mg/m^3)	1.8 ppm (7.6 mg/m^3)	1.5 ppm (6.3 mg/m^3)	0.92 ppm (3.9 mg/m^3)	0.60 ppm (2.5 mg/m^3)	No effects in dog or rats after 26-wk exposure (Greene et al. 1960)
AEGL-2 (disabling)	5.0 ppm (21 mg/m^3)	5.0 ppm (21 mg/m^3)	4.0 ppm (17 mg/m^3)	2.5 ppm (11 mg/m^3)	1.2 ppm (5.0 mg/m^3)	One-third of the AEGL-3 values
AEGL-3 (lethal)	15 ppm (63 mg/m^3)	15 ppm (63 mg/m^3)	12 ppm (50 mg/m^3)	7.5 ppm (32 mg/m^3)	3.7 ppm (16 mg/m^3)	Highest concentration causing no deaths in mice, rats, and dogs after 4 h (Greene et al. 1960)

TABLE 5-2 Chemical and Physical Properties of Perchloryl Fluoride

Parameter	Value	References
Synonyms	Trioxychlorofluoride, chlorine oxyfluoride, chlorine fluoride oxide	ACGIH 2008; HSDB 2008
CAS registry no.	7616-94-6	HSDB 2008
Chemical formula	$Cl\text{-}F\text{-}O_3$	HSDB 2008
Molecular weight	102.45	HSDB 2008
Physical state	Colorless gas	HSDB 2008
Melting point	-146°C	HSDB 2008
Boiling point	-46.8°C	HSDB 2008
Density Vapor Liquid	 0.64 (air = 1) 1.4 at 20°C (water = 1)	HSDB 2008
Solubility in water	Miscible with water	HSDB 2008
Vapor pressure	8,943.9 mm Hg at 25°C	HSDB 2008
Flammability limits	Not applicable, substance will not burn but can support combustion; strong oxidizer	HSDB 2008
Conversion factors	1 ppm = 4.2 mg/m^3 1 mg/m^3 = 0.24 ppm	ACGIH 1991

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human data were available on the acute lethality of perchloryl fluoride.

2.2. Nonlethal Toxicity

No human data were available on the nonlethal toxicity of perchloryl fluoride. Anecdotal information indicates symptoms of upper respiratory irritation, headaches, and dizziness after exposure to perchloryl fluoride vapors (HSDB 2008).

Perchloryl fluoride has a characteristic sweet odor. Greene et al. (1960) used human volunteers (number and gender of participants not specified) to estimate the median detectable concentration of perchloryl fluoride gas. The gas, mixed with air from the room, was metered into an inhalation chamber using a Fair-Wells osmoscope (no further study details provided). At 41 ppm, 50% of the volunteers detected the odor and described it as sweet, musty, or similar to nitric acid.

2.3. Neurotoxicity

No human data were available on the neurotoxicity of perchloryl fluoride.

2.4. Developmental and Reproductive Toxicity

No data human were available on the developmental or reproductive toxicity of perchloryl fluoride.

2.5. Genotoxicity

No human data were available on the genotoxicity of perchloryl fluoride.

2.6. Carcinogenicity

No human data were available on the carcinogenicity of perchloryl fluoride.

2.7. Summary

Data on perchloryl fluoride exposure in humans either by occupational exposure or under experimental conditions were not available. Greene et al. (1960) conducted an odor-threshold clinical study with human volunteers and reported that 50% of participants could detect perchloryl fluoride at 41 ppm. However, details of this study were minimal.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Dogs

Groups of two adult male beagle dogs were exposed to perchloryl fluoride at concentrations of 224, 425, or 451 ppm for 4 h (Greene et al. 1960). Two additional dogs were exposed at 622 ppm for 2.5 h (see Table 5-3). Perchloryl fluoride was metered through a calibrated flow meter and was diluted with air from the room before to entering the exposure chamber. Atmospheric concentrations of the chemical in the chamber were estimated from the weight of the compound. Blood was collected before and after exposure to determine hemoglobin and methemoglobin concentrations, and gross and histopathologic examinations were performed. Two of the eight dogs died; one exposed at 451 ppm for 4 h was moribund when removed from the chamber and one exposed at 622 ppm for 2.5 h was dead, but the time of death was not specified. The remaining dogs exposed at 451 or 622 ppm were injected with methylene blue (2 mg/kg) to counteract methemoglobinemia. All dogs experienced concentration-related cyanosis and hyperpnea. Dogs also exhibited convulsions and motor instability when exposed at 451 or 622 ppm. At 425 ppm, methemoglobin concentrations increased to 15.5% immediately after exposure, and decreased to 4.8% after an 18-h recovery period. Methemoglobin concentrations reached 28.7% and 70.9% in dogs exposed at 451 and 622 ppm, respectively, before methylene blue therapy. After methylene-blue therapy was initiated, methemoglobin concentrations were reduced to 3.8% and 0.0% in dogs exposed at 451 ppm and 622 ppm, respectively. No further study details were provided.

3.1.2. Rats

Greene et al. (1960) exposed rats to perchloryl fluoride in a manner similar to that described above for dogs. Groups of 10 adult male rats (derived Wistar CF-1 strain) were exposed to perchloryl fluoride at concentrations of 220-885 ppm for 4 h (individual concentrations not reported). The gas was metered through a calibrated flow meter and was diluted with air from the room before to entering the chamber. Atmospheric concentration of the chemical in the chamber was analyzed by using quantitative hydrolysis of perchloryl fluoride with 10% alcoholic potassium hydroxide in a series of bubblers. Rats that died had labored breathing, cyanosis, pronounced gasping, and convulsions. Most deaths occurred during exposure or within 2 days after exposure. Surviving rats were kept for 7 days postexposure. The 4-h LC_{50} for rats was 385 ppm (95% confidence limits of 367-404 ppm). Rats that died had moderate discoloration of the blood with accompanying discoloration of the viscera, especially the lungs. Microscopic examination showed marked congestion in the pulmonary vasculature

with some areas of hemorrhage in the alveoli. No raw data to confirm the results were included in the study report.

Dost et al. (1974) exposed male Sprague-Dawley rats to perchloryl fluoride at 5,000 ppm for 15 min, 2,000 ppm for 25 or 40 min, or 1,000 ppm for 60 min (number of rats not specified). Rats were placed in a 3.6-L chamber that accommodated two rats at a time. Exposure at 5,000 ppm for 15 min and 2,000 ppm for 40 min was lethal to all rats. All rats survived exposure at 2,000 ppm for 25 min and 1,000 ppm for 60 min. Methemoglobinemia was observed at all concentrations; at lethal concentrations, methemoglobin exceeded 60% of total hemoglobin. No further details were available.

3.1.3. Mice

In a mouse lethality study, Greene et al. (1960) exposed groups of 20 female Carworth Farms CF-1 strain mice to perchloryl fluoride at concentrations of 220 to 885 ppm for 4 h. The delivery system and concentration analysis were the same as those described for the rat above. Mice that died had labored breathing, cyanosis, pronounced gasping, and convulsions; most deaths occurred during or within 2 days postexposure. Surviving mice were kept for 14-days postexposure. The 4-h LC_{50} for mice was 630 ppm (95% confidence limits of 569 - 697 ppm). The mice that died had the same discoloration of the internal organs as observed in the rats, but to a lesser degree. No raw data to confirm the results were included in the study report.

3.1.4. Guinea Pigs

Kushneva (1999) reported an LC_{50} for perchloryl fluoride of 220 mg/m^3 (52 ppm) in guinea pigs, but the exposure duration was not specified.

3.2. Nonlethal Toxicity

Greene et al. (1960) conducted several repeat-exposure studies of perchloryl fluoride, in which dogs, rats, mice, and guinea pigs were exposed in various scenarios ranging from 5-26 weeks in duration. Chamber concentrations were determined analytically with samples collected by quantitative hydrolysis of perchloryl fluoride with 10% alcoholic potassium hydroxide in a series of three bubblers. Sample collections were 0.125-0.150 L/min. In all of the studies, data were reported in graphic format without providing specific values.

3.2.1. Dogs

Groups of three beagles were exposed to perchloryl fluoride at 0 or 24 ppm for 6 h/day, 5 days/week for 26 weeks (Greene et al. 1960). Dogs were

either killed at the end of the exposure period or allowed a 6-week recovery period (number of dogs not specified). Fluoride concentrations were measured in the blood and urine throughout the study and in the bone (femur) at the end of the exposure period or at the end of the recovery. All dogs survived, and no clinical signs of toxicity were observed. Urinary fluoride concentrations increased 4-fold over 6 months, but were comparable those of the controls at the end of the exposure and remained normal during the recovery period. Bone fluoride concentrations in treated dogs were 46% greater than that of control dogs. However, the investigators stated that the amount of fluoride in the bone did not reach 4,000 ppm, the concentration thought to cause histopathologic changes. Spleen congestion containing iron-bearing pigments was found in treated dogs killed after the final exposure, but not in treated dogs after a 6-week recovery period. No effects were observed in the lungs of any dogs.

3.2.2. Rats

Groups of 20 adult male rats (derived Wistar CF-1 strain) were exposed to perchloryl fluoride at 0, 104 ppm, or 185 ppm for 6 h/day, 5 days/week for 5 weeks (104 ppm) or 7 weeks (185 ppm) (Greene et al. 1960). Groups of three rats were killed immediately and 18 h after the first and fourth exposure period of each week. Blood was taken by cardiac puncture and the following hematology parameters were measured: red-blood-cell count, white-blood-cell count (with differential), reticulocyte count, methemoglobin, hemoglobin, fragility, sedimentation rate, and hematocrit. Select tissues were prepared for histologic examination. Fluoride deposition in the femur and urinary and blood fluoride were determined.

Mortality was 90% (18/20) in the 185-ppm group after 35 days and 5% (1/20) in the 104-ppm group after 25 days. Cyanosis was observed at both concentrations, and dyspnea at the highest concentration. After 1 week, rats exposed at 185 ppm had a 23% increase in methemoglobin concentrations and a 25% decrease in total hemoglobin compared with controls. Methemoglobin concentrations returned to normal after an overnight recovery period. Methemoglobin and hemoglobin measurements in the treated rats were comparable to those of controls after the second week. At gross examination, rats exposed at 185 ppm had darkened organs and splenic weight was increased 4-5 times that of the controls. Histopathologic lesions included splenic, hepatic, and renal hemosiderosis and pulmonary lesions, including alveolar edema that developed into bronchopneumonia. Rats also exhibited stained incisors from fluorosis. At 104 ppm, similar blood and tissue changes were observed, but were less severe. The only raw data provided for this study were graphs showing the findings for the rats exposed at 104 ppm.

Groups of 10 adult male rats (derived Wistar CF-1 strain) were also exposed to perchloryl fluoride at 0 or 24 ppm for 6 h/day, 5 days/week for 26 weeks (Greene et al. 1960). All rats survived the study. Bone (femur) fluoride

concentrations were three times greater than those of the controls at the end of the study. Urinary fluoride concentrations were not reported. As with dogs, rats had splenic congestion that disappeared after a recovery period, and no effects were observed in the lungs.

3.2.3. Mice

Groups of 20 adult female mice (Carworth Farms CF-1 strain) were exposed to perchloryl fluoride at 0 or 185 ppm for 6 h/day, 5 days/week for 7 weeks (Greene et al. 1960). Animals were observed for toxic effects and killed at the end of the study. Mortality was 51% (20/39) in the mice after 35 days of exposure, with dyspnea and cyanosis observed.

3.2.4. Guinea Pigs

Groups of 10 adult male guinea pigs (strain not specified) were exposed to perchloryl fluoride at 0, 104, or 185 ppm for 6 h/day, 5 days/week for 5 weeks (104 ppm) or 7 weeks (185 ppm) (Greene et al. 1960). Mortality was 100% in guinea pigs exposed at 185 ppm for 3 days or at 104 ppm for 25 days. Dyspnea and cyanosis were observed in the animals exposed at 185 ppm. Only cyanosis was observed at 104 ppm.

Groups of 30 adult male guinea pigs (strain not specified) were exposed to perchloryl fluoride at 0 or 24 ppm for 6 h/day, 5 days/week for 26 weeks (Greene et al. 1960). Animals were monitored for toxic effects and 10 animals per group were killed periodically for blood and tissue samples. Mortality was 3% (1/30) in the controls and 47% (14/30) in the treated animals, but the times of deaths were not provided. Clinical signs of toxicity were not observed. Although total hemoglobin was consistently lower in treated guinea pigs, the differences were not statistically significant. Blood fluoride concentrations were slightly greater (data not provided) in the treated guinea pigs, but blood volumes obtained were small making the data unreliable. Urinary fluoride concentrations increased 5-fold over a 6-month period but were comparable to those of controls at the end of the exposure and remained normal during the postexposure period. Bone (femur) fluoride concentrations in treated guinea pigs increased to four times that of controls at the end of the study. During the recovery period, the amount of fluoride in the femur did not diminish. Marked changes in the lungs were observed in both control and treated guinea pigs. Localized damage suggesting a chronic condition was observed in approximately 80-85% of the guinea pigs in the control and treated groups, indicating a cause other than perchloryl fluoride. *Bordetella bronchiseptica* was isolated in some guinea pigs, making the results of this study questionable and unreliable for determining AEGL values. Treated guinea pigs also had congestion of the spleen and a corresponding increase in splenic weight, but these effects were reversed after exposure stopped.

3.3. Developmental and Reproductive Toxicity

No animal data were available on the developmental or reproductive toxicity of perchloryl fluoride.

3.4. Genotoxicity

No animal data were available on the genotoxicity of perchloryl fluoride.

3.5. Chronic Toxicity and Carcinogenicity

No animal data were available on the chronic toxicity or carcinogenicity of perchloryl fluoride.

3.6. Summary

Greene et al. (1960) conducted both acute- and repeat-exposure studies. Dogs exposed for 4 h to perchloryl fluoride at 224 or 425 ppm survived, whereas 4-h exposures at 451 and 622 ppm were partially lethal. The 4-h LC_{50} values for rats and mice were 385 and 630 ppm, respectively. In repeat-exposure studies, dogs and rats survived a 26-week exposure to perchloryl fluoride at 24 ppm for 6 h/day, 5 days/week. Evidence of contact irritation (dyspnea, labored breathing) and of systemic absorption leading to methemoglobinemia (cyanosis) and fluoride deposition were observed in all species. Dost et al. (1974) reported that perchloryl fluoride at 2,000 ppm for 25 min or at 1,000 ppm for 60 min was not lethal to rats. A summary of the available animal data on perchloryl fluoride is presented in Table 5-3.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There were no studies available on the metabolism and disposition of perchloryl fluoride. In the longer-term repeat studies by Greene et al. (1960), rats, guinea pigs, and dogs had fluoride deposition in the bone (femur) and in the urine of dogs and guinea pigs, indicating that the molecule is broken down and fluoride is released. Enamel fluorosis was also observed in rats.

4.2. Mechanism of Toxicity

No studies were identified describing the mechanism of toxicity for perchloryl fluoride. Two mechanisms of action might be present. The oxidative properties of perchloryl fluoride might lead to direct-contact lung damage. Formation of methemoglobin in all species studied indicates that perchloryl fluoride

TABLE 5-3 Summary of Inhalation Data on Perchloryl Fluoride in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Acute Lethality Studies				
Dog[a]	224	4 h	Moderate cyanosis, hyperpnea.	Greene et al. 1960
Dog	425	4 h	Severe cyanosis, hyperpnea, emesis.	Greene et al. 1960
Dog	451	4 h	Severe cyanosis, hyperpnea, motor instability, convulsions; one dog moribund in chamber, other dog treated with methylene blue and survived.	Greene et al. 1960
Dog	622	2.5 h	Severe cyanosis, hyperpnea, salivation, motor instability; convulsions; one dog died, other dog treated with methylene blue and survived.	Greene et al. 1960
Rat	384	4 h	LC_{50}	Greene et al. 1960
Rat	5,000	15 min	100% mortality	Dost et al. 1974
Rat	2,000	25 min 40 min	No mortality 100% mortality	Dost et al. 1974
Rat	1,000	60 min	No mortality	Dost et al. 1974
Mouse	630	4 h	LC_{50}	Greene et al. 1960
Repeat-Exposure Studies[b]				
Dog	0, 24	6 h/d, 5 d/wk for 26 wk	All survived; no clinical signs; increased fluoride in femur after 6 mos	Greene et al. 1960
Rat	0, 104, 185	6 h/d, 5 d/wk for 5 wk (104 ppm) or 7 wk (185 ppm)	104 ppm: 1/20 died (>25 exposure days), cyanosis, increased methemoglobin, decreased hemoglobin, histopathologic changes (liver, spleen, kidney) 185 ppm: 18/20 died (>35 exposure days), dyspnea, same effects as 104 ppm but more severe	Greene et al. 1960

(Continued)

TABLE 5-3 Continued

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	0, 24	6 h/d, 5 d/wk for 26 wk	All survived; no clinical signs; increased fluoride in femur after 6 mos	Greene et al. 1960
Mouse	0, 185	6 h/d, 5 d/wk for 7 wk	20/39 died (after 35 exposure days); dyspnea and cyanosis	Greene et al. 1960
Guinea pig	0, 104, 185	6 h/d, 5 d/wk for 5 wk (104 ppm) or 7 wk (185 ppm)	104 ppm: 10/10 died (>25 exposure days); cyanosis 185 ppm: 10/10 died (>3 exposure days); dyspnea and cyanosis	Greene et al. 1960
Guinea pig	0, 24	6 h/d, 5 d/wk for 26 wk	1/30 control and 14/30 treated died[c], increased fluoride in bone, lung lesions[c]	Greene et al. 1960

[a]Two dogs per group.
[b]In all repeat-exposure studies, there were no effects observed in the controls unless otherwise stated.
[c]The high mortality and lung data are questionable because both the control and treated guinea pigs had *Bordetella bronchiseptica* infections.

or its metabolites oxidize the ferrous (Fe^{+2}) iron in hemoglobin to the oxidized ferric form (Fe^{+3}). Methemoglobin is unable to transport oxygen to the organs and tissues, resulting in cyanosis. Methemoglobin concentrations of more than 70% are considered the threshold for lethality (Kiese 1974; Seger 1992). Normal methemoglobin concentrations in humans are below 1%.

4.3. Structure-Activity Relationships

Greene et al. (1960) provided compared fluoride deposition in the femurs of rats exposed to perchloryl fluoride at 104 ppm and similar exposures to fluorine (F_2) and hydrogen fluoride. The amount of fluoride deposited from perchloryl fluoride was about one-fourth that of fluorine and one-half that of hydrogen fluoride. A possible explanation for the lower absorption of perchloryl fluoride is that it has a more stable structure compared with the other fluorides.

4.4. Other Relevant Information

4.4.1. Species Variability

The available data suggest little interspecies variability. Greene et al. (1960) exposed rats, mice, guinea pigs, and dogs to similar concentrations of perchloryl fluoride and observed similar effects in all species. Effects included labored breathing, cyanosis, convulsions, and changes in hemoglobin and methemoglobin concentrations in blood. The 4-h concentration at which one of two dogs was moribund was 451 ppm, and the LC_{50}s of 385 ppm for rats and 630 ppm for mice are within 3-fold of each other.

4.4.2. Susceptible Populations

As with other lung irritants, humans with compromised lung function would be more susceptible to the toxic effects of perchloryl fluoride. Young children and the elderly are naturally more susceptible to methemoglobinemia and could develop that condition more readily when exposed to perchloryl fluoride. Young children have increased hemoglobin concentrations, and the elderly may be on multiple oxidant medications that can lower their threshold for developing methemoglobinemia (Wilburn-Goo and Lloyd 1999). A rare genetic defect which causes a deficiency of nicotinamide adenine dinucleotide-cytochrome b5 reductase enzyme (NADH-cytochrome b5 reductase) has been documented. This enzyme cofactor reduces methemoglobin in normal erythrocytes. Fetal hemoglobin is more susceptible to oxidation than adult hemoglobin; this cofactor lacks full activity until infants are 4 months of age (Seger 1992). Humans can be carriers who show no clinical signs but have a lower threshold for developing acquired methemoglobinemia or, if autosomal recessive transmission occurs,

they exhibit cyanosis at birth and must be treated, as it can cause death within a few years (Da-Silva et al. 2003).

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n, so default values of n = 3 to extrapolate from longer-to-shorter durations and n = 1 for extrapolation from shorter-to-longer durations was used (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No applicable human data were available for deriving AEGL-1 values for perchloryl fluoride.

5.2. Summary of Animal Data Relevant to AEGL-1

There were two studies of perchloryl fluoride in laboratory animals that addressed lethality (Greene et al. 1960; Dost et al. 1974). A longer-term study in which dogs and rats were exposed to perchloryl fluoride at 24 ppm for 6 h/day, 5 days/week for 26 weeks, reported no acute effects (Greene et al. 1960).

5.3. Derivation of AEGL-1

The 26-week study by Greene et al. (1960) was used to derive the AEGL-1 values. The point of departure was 24 ppm, the concentration at which dogs and rats exposed for 6 h/day, 5 days/week, exhibited no clinical signs or evidence of irritation. The only long-term effect observed was increased fluoride deposition in the bone and urine. Therefore, 24 ppm was considered a no-effect level for an 8-h exposure. To calculate the AEGL-1 values, an interspecies uncertainty factor of 3 was considered appropriate because lethality values for dogs, rats, and mice differed by less than a factor of 3. An intraspecies uncertainty factor of 10 was applied because infants are considerably more susceptible to methemoglobinemia than healthy adults. Time scaling was performed using the equation $C^n \times t = k$, with n = 1 and n = 3 for longer- and shorter-exposure durations, respectively (NRC 2001). The 30-min AEGL-1 value was adopted as the 10-min value, because of the uncertainties associated with extrapolating a 6-h exposure to a 10-min AEGL value (NRC 2001). AEGL-1 values for perchloryl fluoride are presented in Table 5-4.

TABLE 5-4 AEGL-1 Values for Perchloryl Fluoride

10 min	30 min	1 h	4 h	8 h
1.8 ppm (7.6 mg/m^3)	1.8 ppm (7.6 mg/m^3)	1.5 ppm (6.3 mg/m^3)	0.92 ppm (3.9 mg/m^3)	0.60 ppm (2.5 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data were available for deriving AEGL-2 values for perchloryl fluoride.

6.2. Summary of Animal Data Relevant to AEGL-2

No animal data were available that defined effects consistent with the definition of AEGL-2.

6.3. Derivation of AEGL-2

In the absence of appropriate chemical-specific data, AEGL 2 values for perchloryl fluoride were derived by reducing the AEGL-3 values by a third (NRC 2001). This approach is supported by the steep concentration-response curve for perchloryl fluoride. Two of two dogs exposed to perchloryl fluoride at 425 ppm survived a 4-h exposure, but one of two dogs was found moribund after a 4-h exposure at a slightly higher concentration of 451 ppm (Green et al. 1960). AEGL-2 values for perchloryl fluoride are presented in Table 5-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data were available for deriving AEGL-3 values for perchloryl fluoride.

7.2. Summary of Animal Data Relevant to AEGL-3

Greene et al. (1960) exposed dogs, rats, and mice to varying concentrations of perchloryl fluoride for 4-h. Dogs exhibited clinical signs (cyanosis and hyperpnea) at a concentration of 224 ppm, but no mortality occurred. Cyanosis worsened at 425 ppm and one dog exposed at 451 ppm was found moribund. LC_{50} values for rats and mice were 385 and 630 ppm, respectively. No mortality occurred in rats exposed for perchloryl fluoride at 2,000 ppm for 25 min or at 1,000 ppm for 60 min (Dost et al. 1974). Details of this latter study were not provided.

TABLE 5-5 AEGL-2 Values for Perchloryl Fluoride

10 min	30 min	1 h	4 h	8 h
5.0 ppm (21 mg/m^3)	5.0 ppm (21 mg/m^3)	4.0 ppm (17 mg/m^3)	2.5 ppm (11 mg/m^3)	1.2 ppm (5.0 mg/m^3)

7.3. Derivation of AEGL-3

The study of Greene et al. (1960), in which groups of two dogs were exposed at several concentrations of perchloryl fluoride for 4 h, was chosen as the key study. Dogs survived at concentrations of 224 and 451 ppm. The concentration of 224 ppm was chosen as the point of departure because it is lower than the LC_{50} value of 384 ppm for rats in the same study. The point of departure was divided by interspecies and intraspecies uncertainty factors of 3 and 10. An interspecies uncertainty factor of 3 was considered appropriate because lethality values for dogs, rats, and mice differed by less than a factor of 3, and lethal values for the rat were considered in selecting the point of departure. An intraspecies uncertainty factor of 10 was applied because infants are considerably more susceptible to methemoglobinemia than healthy adults. Time scaling was performed using the equation $C^n \times t = k$, with n = 1 and n = 3 for longer- and shorter-exposure durations, respectively (NRC 2001). The 30-min AEGL-3 value was adopted as the 10-min value, because of the uncertainties associated with extrapolating a 4-h exposure to a 10-min AEGL value (NRC 2001). AEGL-3 values for perchloryl fluoride are provided in Table 5-6.

AEGL-3 values might appear low in light of the odor-threshold study in which human volunteers were exposed at several concentrations of perchloryl fluoride, including 41 ppm (Greene et al. 1960). However, the sparse database justifies the low concentrations.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Because of the lack of acute studies on perchloryl fluoride, a longer-term study at a concentration at which dogs and rats exhibited no acute effects was used for the derivation of AEGL-1 values. No studies that addressed effects consistent with the definition of an AEGL-2 were found. Because the concentration-response curve for lethality is steep, AEGL-2 values were derived by dividing the AEGL-3 values by 3. The point of departure for AEGL-3 values was a concentration of 224 ppm that caused no deaths in dogs exposed for 4 h, but was below the 4-h LC_{50} value of 384 ppm for rats. For AEGL-1 and AEGL-3, a total uncertainty factor of 30 (3 for interspecies differences and 10 for intraspecies variability) was applied. Time scaling was performed using the equation $C^n \times t = k$, with n = 1 and n = 3 for longer- and shorter-exposure durations, respectively (NRC 2001). AEGL values for perchloryl fluoride are provided in Table 5-7.

TABLE 5-6 AEGL-3 Values for Perchloryl Fluoride

10 min	30 min	1 h	4 h	8 h
15 ppm (63 mg/m^3)	15 ppm (63 mg/m^3)	12 ppm (50 mg/m^3)	7.5 ppm (32 mg/m^3)	3.7 ppm (16 mg/m^3)

TABLE 5-7 Summary of AEGL Values for Perchloryl Fluoride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	1.8 ppm (7.6 mg/m^3)	1.8 ppm (7.6 mg/m^3)	1.5 ppm (6.3 mg/m^3)	0.92 ppm (3.9 mg/m^3)	0.60 ppm (2.5 mg/m^3)
AEGL-2 (disabling)	5.0 ppm (21 mg/m^3)	5.0 ppm (21 mg/m^3)	4.0 ppm (17 mg/m^3)	2.5 ppm (11 mg/m^3)	1.2 ppm (5.0 mg/m^3)
AEGL-3 (lethal)	15 ppm (63 mg/m^3)	15 ppm (63 mg/m^3)	12 ppm (50 mg/m^3)	7.5 ppm (32 mg/m^3)	3.7 ppm (16 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

The threshold limit value - time weighted average (TLV-TWA) for perchloryl fluoride established by the American Conference of Governmental Industrial Hygienists and the permissible exposure limit - time weighted average (PEL-TWA) of the Occupational Safety and Health Administration (OSHA) were both determined on the basis of the studies by Greene et al. (1960). For both guidelines, the recommended value of 3 ppm is approximately one-tenth of the 24-ppm concentration that caused enamel fluorosis and hematologic alterations in experimental animals after repeated exposures (26 weeks). The 8-h AEGL-2 and AEGL-3 values appear low in comparison with the TLV-TWA and PEL-TWA, but those standards are for healthy adults, whereas the AEGL values are protective of sensitive infant and elderly populations. The National Institute of Occupational Safety and Health established a value that is Immediately Dangerous to Life and Health of 100 ppm, which was based on the study by Greene et al. (1960) that found a 4-h LC_{50} for rats of 385 ppm. Standards and guidelines for perchloryl fluoride are provided in Table 5-8.

8.3. Data Adequacy and Research

Human data on perchloryl fluoride are lacking. Animal data are also limited; although several species (dogs, rats, guinea pigs, and mice) were exposed by inhalation to perchloryl fluoride, most of the studies were conducted by the same laboratory and details were not reported.

TABLE 5-8 Extant Standards and Guidelines for Perchloryl Fluoride

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.8 ppm (7.6 mg/m^3)	1.8 ppm (7.6 mg/m^3)	1.5 ppm (6.3 mg/m^3)	0.92 ppm (3.9 mg/m^3)	0.60 ppm (2.5 mg/m^3)
AEGL-2	5.0 ppm (21 mg/m^3)	5.0 ppm (21 mg/m^3)	4.0 ppm (17 mg/m^3)	2.5 ppm (11 mg/m^3)	1.2 ppm (5.0 mg/m^3)
AEGL-3	15 ppm (63 mg/m^3)	15 ppm (63 mg/m^3)	12 ppm (50 mg/m^3)	7.5 ppm (32 mg/m^3)	3.7 ppm (16 mg/m^3)
IDLH (NIOSH)[a]		100 ppm (420 mg/m^3)			
TLV-TWA (ACGIH)[b]					3 ppm (14 mg/m^3)
PEL-TWA (OSHA)[c]					3 ppm (14 mg/m^3)
REL-TWA (NIOSH)[d]					3 ppm (14 mg/m^3)
TLV-STEL (ACGIH)[e]	6 ppm (25 mg/m^3) (15 min)				
REL-STEL (NIOSH)[f]	6 ppm (25 mg/m^3) (15 min)				
MAC (MSZW)[g]					3 ppm (14 mg/m^3)

[a]IDLH (immediately dangerous for 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 1991, 2008) 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 [2005]) 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 2010) 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 2008) 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, National Institute for Occupational Safety and Health) (NIOSH 2010) is defined analogous to the ACGIH TLV-STEL.
[g]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Ministry of Social Affairs and Employment, The Hague, The Netherlands [MSZW 2004]) is defined analogous to the ACGIH TLV-TWA.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PERCHLORYL FLUORIDE

Derivation of AEGL-1 Values

Key study:	Greene, E.A., J.L. Colbourn, E. Donati, and M.H. Weeks. 1960. The Inhalation Toxicity of Perchloryl Fluoride. U.S. Army Chemical Research and Development Laboratories Technical Report CRDLR 3010. Army Chemical Center, Edgewood, MD.
Toxicity end point:	No treatment-related adverse effects.
Time scaling:	$C^n \times t = k$ n = 3 for extrapolating to the 30-min and 1- and 4-h durations $(24 \text{ ppm})^3 \times 6 \text{ h} = 8.3 \times 10^4$ ppm-h n = 1 for extrapolating to the 8-h duration $(24 \text{ ppm})^1 \times 6 \text{ h} = 144$ ppm-h
Uncertainty factors:	3 for interspecies differences 10 for intraspecies variability
10-min AEGL-1:	1.8 ppm (set equal to the 30-min value because of the long exposure duration of the key study)
30-min AEGL-1:	$C^3 \times 0.5 \text{ h} = 8.3 \times 10^4$ ppm-h $C^3 = 1.7 \times 10^5$ ppm C = 55.4 ppm 55.4 ppm ÷ 30 = 1.8 ppm
1-h AEGL-1:	$C^3 \times 1 \text{ h} = 8.3 \times 10^4$ ppm-h $C^3 = 8.3 \times 10^4$ ppm C = 43.6 ppm 43.6 ppm ÷ 30 = 1.5 ppm
4-h AEGL-1:	$C^3 \times 4 \text{ h} = 8.3 \times 10^4$ ppm-h $C^3 = 20{,}750$ ppm C = 27.5 ppm 27.5 ppm ÷ 30 = 0.92 ppm

8-h AEGL-1:	$C^1 \times 8$ h = 144 ppm-h C^1 = 18 ppm 18 ppm ÷ 30 = 0.60 ppm

Derivation of AEGL-2 Values

Key study:	NRC (National Research Council). 2001. Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.
Toxicity end point:	For chemicals with a steep concentration-response curve, AEGL-2 values may be calculated by dividing AEGL-3 values by 3 (NRC 2001).
Time scaling:	See derivation of AEGL-3
Uncertainty factors:	See derivation of AEGL-3
10-min AEGL-2:	15 ppm ÷ 3 = 5.0 ppm
30-min AEGL-2:	15 ppm ÷ 3 = 5.0 ppm
1-h AEGL-2:	12 ppm ÷ 3 = 4.0 ppm
4-h AEGL-2:	7.5 ppm ÷ 3 = 2.5 ppm
8-h AEGL-2:	3.7 ppm ÷ 3 = 1.2 ppm

Derivation of AEGL-3 Values

Key study:	Greene, E.A., J.L. Colbourn, D. Donati, and M.H. Weeks. 1960. The Inhalation Toxicity of Perchloryl Fluoride. U.S. Army Chemical Research and Development Laboratories Technical Report CRDLR 3010. Army Chemical Center, Edgewood, MD.
Toxicity end point:	Highest 4-h concentration causing no mortality in dogs, but below the LC_{50} value for rats in the same study.

Scaling:	$C^n \times t = k$ n = 3 for extrapolating to the 30-min and 1-h durations $(224 \text{ ppm})^3 \times 4 \text{ h} = 4.5 \times 10^7 \text{ ppm-h}$ n = 1 for extrapolating to the 8-h duration $(224 \text{ ppm})^1 \times 4 \text{ h} = 896 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies variability 10 for intraspecies variability
10-min AEGL-3:	15 ppm (set equal to the 30-min value because of the long exposure duration of the key study)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 4.50 \times 10^7 \text{ ppm-h}$ $C^3 = 9.0 \times 10^7 \text{ ppm}$ C = 448 ppm 448 ppm ÷ 30 = 15 ppm
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 4.50 \times 10^7 \text{ ppm-h}$ $C^3 = 4.50 \times 10^7 \text{ ppm}$ C = 356 ppm 356 ppm ÷ 30 = 12 ppm
4-h AEGL-3	C = 224 ppm ÷ 30 C = 7.5 ppm
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 896 \text{ ppm-h}$ $C^1 = 112 \text{ ppm}$ 112 ppm ÷ 30 = 3.7 ppm

APPENDIX B

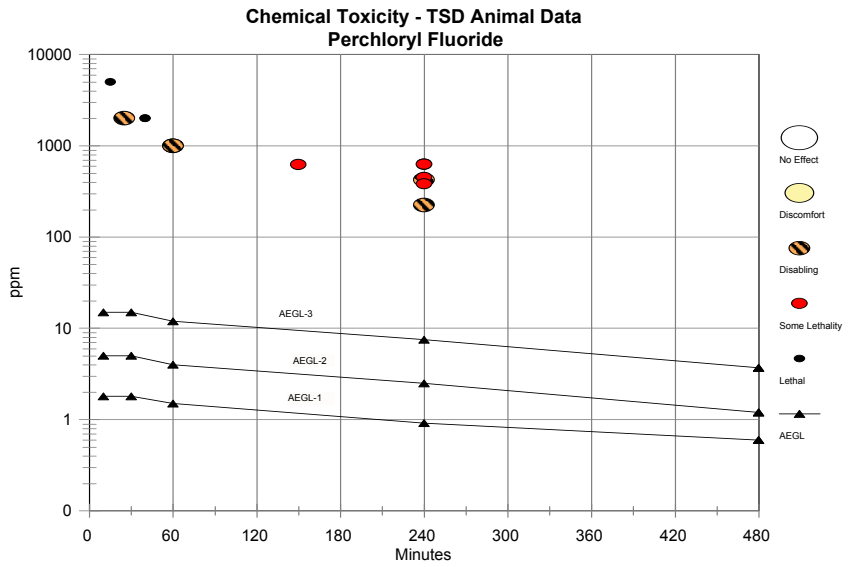

FIGURE B-1 Category plot of animal toxicity data on perchloryl fluoride compared with AEGL values.

TABLE B-1 Data Used in Category Plot of AEGL Values for Perchloryl Fluoride

Source	Species	Concentration (ppm)	Duration (min)	Category
NAC/AEGL-1		1.8	10	AEGL
NAC/AEGL-1		1.8	30	AEGL
NAC/AEGL-1		1.5	60	AEGL
NAC/AEGL-1		0.92	240	AEGL
NAC/AEGL-1		0.60	480	AEGL
NAC/AEGL-2		5	10	AEGL
NAC/AEGL-2		5	30	AEGL
NAC/AEGL-2		4	60	AEGL
NAC/AEGL-2		2.5	240	AEGL
NAC/AEGL-2		1.2	480	AEGL
NAC/AEGL-3		15	10	AEGL

NAC/AEGL-3		15	30	AEGL
NAC/AEGL-3		12	60	AEGL
NAC/AEGL-3		7.5	240	AEGL
NAC/AEGL-3		3.7	480	AEGL
Greene et al. 1960	Dog	224	240	2 (moderate cyanosis, hyperpnea)
	Dog	425	240	2 (severe cyanosis, hyperpnea, emesis)
	Dog	451	240	SL (severe cyanosis, hyperpnea, motor instability, convulsions, death of one of two dogs)
	Dog	622	150	SL (severe cyanosis, hyperpnea, salivation, motor instability, convulsions; death of one of two dogs)
	Rat	384	240	SL (LC_{50})
	Mouse	630	240	SL (LC_{50})
Dost et al. 1974	Rat	5,000	15	3 (100% mortality)
	Rat	2,000	25	2 (no mortality)
	Rat	2,000	40	3 (100% mortality)
	Rat	1,000	60	2 (no mortality)

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

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR PERCHLORYL FLUORIDE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.8 ppm	1.8 ppm	1.5 ppm	0.92 ppm	0.60 ppm

Key reference: Greene, E.A., J.L. Colbourn, D. Donati, and M.H. Weeks. 1960. The Inhalation Toxicity of Perchloryl Fluoride. U.S. Army Chemical Research and Development Laboratories Technical Report CRDLR 3010. Army Chemical Center, Edgewood, MD.

Test species/Strain/Number: Beagle dogs, 2 per group; Sprague-Dawley rats, 10 per group

Exposure route/Concentrations/Durations: Inhalation, 24 ppm for 6 h/day, 5 days/week for 26 weeks

Effects:
0 ppm: No effects observed
24 ppm: No clinical signs observed; some increases in fluoride deposition but only after long-term exposure.

End point/Concentration/Rationale: No effect except for increased fluoride deposition in bones after 26 weeks

Uncertainty factors/Rationale:
Total uncertainty factor: 30

Interspecies: 3, because the 4-h concentration at which 1 of 2 dogs were moribund (451 ppm) and the LC_{50} concentrations for rats (385 ppm) and mice (630 ppm) are within 3-fold of each other, and all species developed similar symptoms (dyspnea and cyanosis).

Intraspecies: 10, because perchloryl fluoride is systemically absorbed and the possible increased sensitivity of some humans, especially infants, for developing methemoglobinemia.

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to durations of 30-min, 1 h, and 4 h, and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001).

Data adequacy: Adequate

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
5.0 ppm	5.0 ppm	4.0 ppm	2.5 ppm	1.2 ppm

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

Test species/Strain/Number: See derivation of AEGL-3

Exposure route/Concentrations/Durations: See derivation of AEGL-3

Effects: See derivation of AEGL-3

End point/Concentration/Rationale: In the absence of chemical-specific data, NRC (2001) recommends taking one-third of AEGL-3 values when there is evidence of a steep concentration-response curve.

Uncertainty factors/Rationale: See derivation of AEGL-3

Modifying factor: See derivation of AEGL-3

Animal-to-human dosimetric adjustment: See derivation of AEGL-3

Time scaling: See derivation of AEGL-3

Data adequacy: Not adequate

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
15 ppm	15 ppm	12 ppm	7.5 ppm	3.7 ppm

Key reference: Greene, E.A., J.L. Colbourn, D. Donati, and M.H. Weeks. 1960. The Inhalation Toxicity of Perchloryl Fluoride. U.S. Army Chemical Research and Development Laboratories Technical Report CRDLR 3010. Army Chemical Center, Edgewood, MD.

Test species/Strain/Number: Male beagle dogs, 2 per group

Exposure route/Concentrations/Durations: Inhalation, 224, 425, or 451 ppm for 4-h.

Effects:
Rat: LC_{50} = 385 ppm
Mouse: LC_{50} = 630 ppm
Dogs: 224 ppm, both dogs had cyanosis and hyperpnea; 425 ppm, both dogs had severe cyanosis and hyperpnea; 451 ppm, 1 of 2 dogs moribund

End point/Concentration/Rationale: 224 ppm was highest nonlethal concentration in dogs with no projected mortality in rats and mice.

Uncertainty factors/Rationale:
Total uncertainty factor: 30

Interspecies: 3, because the 4-h concentration at which 1 of 2 dogs were moribund (451 ppm) and the LC_{50} concentrations for rats (385 ppm) and mice (630 ppm) are within 3-fold of each other, and all species developed similar symptoms (dyspnea and cyanosis).

(Continued)

AEGL-3 VALUES Continued
Intraspecies: 10, because perchloryl fluoride is systemically absorbed and the possible increased sensitivity of some humans, especially infants, for developing methemoglobinemia.
Modifying factor: Not applied
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to durations of 30-min, 1 h, and 4 h, and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001).
Data adequacy: Adequate

6

Piperidine[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Kowetha Davidson (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Managers Mark A. McClanahan and 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).

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

Piperidine is a cyclic aliphatic amine (Eller et al. 2000). It is a clear, colorless, and flammable liquid that produces vapors that reach explosive concentrations at room temperature. Piperidine has a dissociation constant (pK_b) of 2.88 and a pH of 12.6 (100 g/L, 20°C). Therefore, it is expected to be very corrosive. It has a strong pepper- or amine-like and pungent odor. Piperidine has many commercial uses, including use as a solvent, a curing agent for rubber and epoxy resins, an intermediate in organic synthesis, a food additive, and a constituent in the manufacturing of pharmaceuticals.

Daily exposure to piperidine is evidenced by its presence in the food supply and its excretion in human urine. It is a natural constituent in white and black pepper. Piperidine is formed naturally in the body from the degradation of lysine, cadaverine, and pipecolic acid. Exogenous piperidine is absorbed from the respiratory tract, gastrointestinal tract, and skin. It is found in most tissues of the body, including the brain, and is excreted as unchanged piperidine or its metabolites.

Studies in rats showed that nasal irritation and signs of ocular irritation occur at the lower concentrations of piperidine followed by corrosion around the nose and dyspnea at higher concentrations. Corneal damage, central nervous system (CNS) toxicity, and prostration occurred at the highest concentrations;

however, death occurred only at concentrations that caused dyspnea, CNS toxicity, and prostration. Therefore, the severity of effects from piperidine shows a clear continuum ranging from nasal irritation to death. Piperidine has no demonstrated carcinogenic activity, it is not genotoxic in *Salmonella typhimurium*, and it is not toxic to the developing rat fetus at the concentrations tested.

The database on piperidine in humans is very small. Inhalation exposure to piperidine may cause sore throat, coughing, labored breathing, and dizziness. The odor threshold is reported to be <2 ppm, and 2-5 ppm is reported to be tolerated by unacclimated individuals for only a brief time because of its pungent odor. The irritation threshold for humans was reported to be 26 ppm. At an odor threshold of 0.37 ppm, a level of distinct odor awareness would be 5.9 ppm (van Doorn et al. 2002).

AEGL-1 values were based on the no-effect level (20 ppm for 6 h) for nasal irritation in rats. Uncertainty factors of 3 for interspecies differences and 3 for intraspecies variability were applied. The rationale for selecting those factors included the following: (1) the effect observed at 50 ppm was mediated by direct contact of piperidine with the nasal epithelium without involvement of other regions of the respiratory tract; and (2) the cell composition of the nasal mucosa is similar between species and among individuals within the population, although the cell distribution and nasal morphology differ among species. In addition, the relationship between concentration vs. time for LC_{50} (lethal concentration, 50% lethality) values was similar in mice, guinea pigs, and rats; they did not vary by more than 30%. The linear correlation coefficient was -0.96. After applying a total uncertainty factor of 10, the resulting value of 5 ppm was time scaled based on the equation, $C^n \times t = k$, where n = 1.5. The value of n was derived from a regression analysis of the LC_{50} values for the mouse, guinea pig, and rat.

AEGL-2 values were based on exposure of rats to piperidine at 200 ppm for 6 h, which caused nasal irritation without salivation or evidence of ocular irritation. The rationale for selecting uncertainty factors and the time-scaling procedure were the same as those described for the AEGL-1 values.

AEGL-3 values were based on the LC_{01} (lethal concentration, 1% lethality) calculated from a 4-h acute inhalation study in rats. The LC_{01} of 448 ppm is less than the lowest concentration that caused one death among 20 rats (5% lethality) and greater than the highest concentration that caused no deaths or clinical moribund signs. Therefore, the LC_{01} appeared to be a good estimate of the threshold for lethality. Uncertainty factors of 3 for interspecies differences and 3 for intraspecies variability were applied to the LC_{01}. The rationale for selecting the uncertainty factors was the same as described for AEGL-1 values. In addition, larger factors for interspecies differences or intraspecies variability would have produced values for the 4-h and 8-h durations that were lower than the irritation threshold of 26 ppm. The time-scaling procedure was the same as described for AEGL-1 values.

AEGL values for piperidine are presented in Table 6-1.

TABLE 6-1 Summary of AEGL Values for Piperidine

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	10 ppm (35 mg/m^3)	10 ppm (35 mg/m^3)	6.6 ppm (23 mg/m^3)	2.6 ppm (9 mg/m^3)	1.7 ppm (6 mg/m^3)	No nasal irritation (BASF 1993)
AEGL-2 (disabling)	50 ppm (175 mg/m^3)	50 ppm (175 mg/m^3)	33 ppm (116 mg/m^3)	13 ppm (46 mg/m^3)	8.3 ppm (29 mg/m^3)	Nasal irritation (BASF 1990)
AEGL-3 (lethal)	370 ppm (1,295 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (385 mg/m^3)	45 ppm (158 mg/m^3)	28 ppm (98 mg/m^3)	Threshold for lethality (BASF 1980)

1. INTRODUCTION

Piperidine is a cyclic aliphatic amine (Eller et al. 2000). It is flammable (Trochimowicz et al. 1994) and produces explosive vapors at room temperature (HSDB 2008). Piperidine is a clear, colorless liquid and has a strong pepper- or amine-like pungent odor (Lewis 1993; Trochimowicz et al. 1994). Piperidine is a very strong base with a dissociation constant (pK_b) of 2.88 (Reed 1990); thus, it is a very corrosive agent. The vapor pressure indicates that exposure to piperidine could occur by the inhalation route under ambient conditions. Chemical and physical properties of piperidine are presented in Table 6-2.

Piperidine has many commercial uses. It is used as a solvent, a curing agent for rubber and epoxy resins, a catalyst in silicone esters, an intermediate in organic synthesis, and a wetting agent. It is used in the manufacture of pharmaceuticals (analgesics, anesthetics, and germicides) and as a food additive (Reed 1990; Trochimowicz et al. 1994; HSDB 2008). In 1983, the United States produced 2.75×10^8 g (~606,000 pounds) of piperidine (HSDB 2008).

Humans are exposed to piperidine on a daily basis, as evidenced by its wide presence in the food supply and, consequently, in human urine. As a food additive, piperidine is found at 2.5-3.33 ppm in nonalcoholic beverages, 4-5.67 ppm in candy, 9.69 ppm in baked goods, and 0.04-1.66 ppm in condiments, meats, and soups (HSDB 2008). Piperidine also occurs naturally in food products, including vegetables (Neurath et al. 1977). Pulverized white pepper contains as much as 1,322 ppm of piperidine, and black pepper up to 703 ppm (Lin et al. 1981). Baked ham contains 0.2 ppm of piperidine, milk 0.11 ppm, and dry coffee 1 ppm (Reed, 1990). Piperidine also is found in boiled beef (Golovnya et al. 1979). von Euler (1945) reported that humans excrete 7.6-8.5 mg of piperidine in a 24-h period; more recently, Tricker et al. (1992) reported excretion rates of 26.1-31.7 mg/day.

The toxicology database on piperidine consists of anecdotal human data and a small amount of animal data.

TABLE 6-2 Chemical and Physical Data on Piperidine

Parameter	Value	Reference
Chemical name	Piperidine	
Synonyms	Azacyclohexane, cyclopentimine, hexahydropyridine, UN2401	RTECS 2009
CAS registry no.	110-89-4	RTECS 2009
Chemical formula	$C_5H_{11}N$	Budavari et al. 1996
Molecular weight	85.15	Budavari et al. 1996
Physical state	Colorless liquid	Lewis 1993
Boiling point	106.3°C	Howard and Meylan 1997
Freezing point	-13 to -7°C	Budavari et al. 1996
Vapor density	3.0 (air = 1)	Trochimowicz et al. 1994
Specific gravity	0.8622 at 20°C	Reed 1990
Solubility	1.6×10^6 mg/L of water at 20°C	Howard and Meylan 1997
Vapor pressure	32.1 mm Hg at 25°C 40 mm Hg at 29.2°C	Howard and Meylan 1997 Trochimowicz et al. 1994
Flash point	16.11°C (61°F)	Trochimowicz et al. 1994
Refractive index (n_o)	1.4530	Weast et al. 1985
pH	12.6 at 100 g/L at 20°C	BG Chemie 2000
pK_b	2.88	Reed 1990
Log P	0.84	Howard and Meylan 1997
Conversion factors	1 ppm = 3.5 mg/m^3 at 25°C, 1 atm 1 mg/m^3 = 0.29 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were found on the acute lethality of piperidine in humans.

2.2. Nonlethal Toxicity

2.2.1. Experimental Studies, Case Reports, and Anecdotal Data

Bazarova and Migoukina (1975) reported an irritation threshold for piperidine of 90 mg/m^3 (26 ppm) in human volunteers. No additional details were provided.

Concentrations of 2-5 ppm (7.0-17.5 mg/m^3) were measured in a semi-closed environment as piperidine was transferred from drums. The report stated that unacclimated individuals could tolerate the pungent odor for only a brief time, although irritation was not perceived (A.C. Nawakowski, Upjohn Company, unpublished material, 1980, as cited in Trochimowicz et al. 1994). No additional details were provided.

EPA (1985) reported that piperidine is a strong local irritant that can cause permanent injury after a short exposure to small amounts. DASE (1980) reported that inhalation exposure causes sore throat, coughing, labored breathing, and dizziness. No exposure concentrations were provided in either report.

2.2.2. Other Studies

No human studies were found on the neurotoxicity, developmental toxicity, reproductive toxicity, carcinogenicity, or genetic toxicity of piperidine.

2.3. Summary

No human lethality data were found on piperidine. The irritation threshold for piperidine is 26 ppm (90 mg/m^3). Inhalation exposure to piperidine causes sore throat, coughing, labored breathing, and dizziness. Piperidine at 2-5 ppm (7.0-17.5 mg/m^3) is not irritating, but could be tolerated for only a brief time because of its pungent odor. These data indicate that the odor threshold for piperidine is less than 2 ppm (7.0 mg/m^3).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

BASF (1980) exposed groups of 10 male and 10 female Sprague-Dawley rats to piperidine (99%) at analytic concentrations of 2,190, 1,540, 1,190, 810, or 290 ppm (7,540, 5,300, 4,100, 2,800, or 1,000 mg/m^3, respectively) for 4 h, and the rats were observed for 14 days. Rats were exposed (whole body) in a glass-steel chamber under dynamic conditions. Vapor was generated with an evaporation unit at 69°C and mixed with fresh air to obtain the desired concentration. Clinical signs, mortality, food consumption, body weights, and gross and microscopic findings were evaluated during or after exposure. Multiple clinical signs were observed at all concentrations. Prostration was observed only at 1,540 and 2,190 ppm. Corrosion around the nose, smoky-milky clouded cornea, crouched position, tremors, and clonic convulsions were observed at concentrations >1,190 ppm. Rubbing of the snout, dyspnea, and corrosion around the nose were observed at concentrations >810 ppm; nasal corrosion was observed in

only one male rat. A strong watery-reddish or reddish secretion from the eyes and nose, lid closure, and ragged fur were observed at all concentrations, and spasmodic respiration was observed only at 290 ppm. No clinical signs were observed more than 2 days after exposure at 290 ppm. Mortality data are summarized in Table 6-3.

A clear dose-response relationship was shown for male rats but not female rats. LC_{50} (lethal concentration, 50% lethality) values for piperidine in rats were 1,330, 1,420, 1,390 ppm (4,600, 4,900, and 4,800 mg/m^3) for males, females, and both sexes combined, respectively. None of the rats exposed at 2,190 ppm survived until day 7. All male and female rats that did not survive until the end of the observation period died before day 7, except for one female rat exposed at 1,540 ppm and three female rats exposed at 1,190 ppm. Male and female rats exposed at 1,190 ppm and 1,540 ppm and females exposed at 810 ppm lost weight during the first week of observation, gained weight during the second week, and the males weighed 13-29% less than controls and the females weighed 14-19% less than controls at the end of the observation period. A postmortem evaluation was conducted, but no data were provided.

BASF (1981, as cited in BG Chemie 2000) reported that two of 12 and three of six Wistar rats died after exposure to an atmosphere of saturated piperidine vapor at 20°C (~45,000 ppm) for 3 or 10 min, respectively. No additional details were available.

Smyth et al. (1962) reported no deaths among six rats exposed to piperidine at 2,000 ppm (7,000 mg/m^3) for 4 h. However, six of six rats died after exposure to piperidine at 4,000 ppm (14,000 mg/m^3) for 4 h. The investigators also reported that inhalation of concentrated piperidine vapor for 15 min killed six of six rats; the exposure concentration was not reported.

Zayeva et al. (1968) reported a median lethal time (LT_{50}) of 80 min for an unknown mammalian species exposed to an unknown concentration of piperidine by inhalation. Bazarova and Migoukina (1975) reported an LC_{50} of 1,885 ppm (6,500 mg/m^3) for an unidentified mammalian species exposed for an unknown period of time. A 2-h LC_{50} in mice was reported to be 1,740 ppm (6,000 mg/m^3) (BG Chemie 2000; AIHA 2001), and a 1-h LC_{50} in guinea pigs was 3,480 ppm (12,000 mg/m^3) (AIHA 2001). Those lethality values were cited in a secondary source, and the primary sources could not be located to verify the values.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of five male and five female Wistar rats were exposed to piperidine vapor (99.4% purity) at nominal concentrations of 0, 50, 100, and 200 ppm (175, 350, and 700 mg/m^3, respectively) for 6 h/day for 5 days (BASF

TABLE 6-3 Lethality Data for Piperidine

Concentration, ppm (mg/m^3)	Mortality		
	Males	Females	Males and Females
290 (1,000)	0/10	0/10	0/20
810 (2,800)	0/10	1/10	1/20
1,190 (4,100)	3/10	7/10	10/20
1,540 (5,300)	6/10	1/10	7/20
2,190 (7,540)	10/10	10/10	20/20
LC_{50} [ppm (mg/m^3)][a]	1,330 (4,600)	1,420 (4,900)	1,390 (4,800)

[a]Calculated using Number Cruncher Statistical System Survival Analysis, Version 5.5, published by Jerry L. Hintze, July 1991.
Source: BASF 1980.

1990). Analytic concentrations were 0, 49, 102, and 203 ppm (0, 170, 360, and 710 mg/m^3), respectively. No animals died during the study. Clinical signs were observed during or immediately after exposure, and were concentration- and time-dependent. Nasal secretions and bloody encrustation on the edge of the nares were observed at all concentrations. "Stretched respiration posture," lid closure, and salivation were observed at 200 ppm. Males exposed at 100 and 200 ppm had decreased body weights after the first days of exposure, but body weight and weight gain were not affected in females. No treatment-related changes in clinical pathology or post-mortem pathology were observed at any concentration. Because clinical signs were observed and recorded after each exposure, this study can be used for derivation of AEGL values.

In a 28-day study, two groups of five male and five female Wistar rats each were exposed to piperidine vapor (99.4% purity) at concentrations of 0, 5, 20, or 100 ppm (0, 18, 70, and 350 mg/m^3, respectively) for 6 h/day, 5 days/week for 28 days (BASF 1993). The rats received 20 exposures. Additional groups of five male and five female rats exposed similarly at 0 or 100 ppm (0 and 350 mg/m^3) were maintained for an additional 2 weeks without exposure to piperidine to evaluate recovery. The animals were exposed whole body under dynamic conditions in a glass-steel inhalation chamber. The atmosphere in the breathing zones of the animals was monitored approximately every 20 min using a total hydrocarbon analyzer equipped with a flame ionization detector. Rats were observed daily for clinical signs before, during, and after exposure, and body weights were measured at the beginning of the study and at 1-week intervals thereafter. Subgroups of five animals/sex/group were subjected to an extensive battery of neurofunctional tests before exposure and on days 2, 8, 14, and 28. Subgroups of five rats/sex/group were used for clinical pathology evaluations of blood and urine. Post-mortem evaluations consisted of gross examination, organ weight measurements, and microscopic examination of selected tissues.

Treatment-related clinical signs at 100 ppm consisted of a reddish crust (positive for blood) observed on the nasal edges of three male rats on day 2 of the study, all males from day 3 to the end of the study, two females on day 3, one female on day 4, almost all females starting on day 8, and all females by the end of the study. The reddish crust was indicative of upper respiratory tract irritation. Each subgroup of five male rats exposed at 100 ppm weighed 3.4% (n.s.) and 5.7% (n.s.) less than controls. Females exposed at 100 ppm did not show a trend toward decreased body weights. The only notable effects on the neurofunctional battery were increased hindlimb grip strength on day 8 in males exposed at 100 ppm and decreased response to the hot plate test on day 14 in males exposed at 5 and 100 ppm. Because these effects were transient or showed no dose-related trend, they are unlikely to be treatment related. No treatment-related effects were observed on ocular, hematologic, or clinical chemistry parameters, or on post-mortem findings. Treatment-related effects were not observed at 5 or 20 ppm (BASF 1993). This study is of marginal use for deriving AEGL values, because adverse effects were observed after the second exposure but not after the first exposure. BASF (1993) reported no nervous system effects; however, Bazarova and Migoukina (1975) reported an acute-exposure threshold of 5.8 ppm (20 mg/m^3) for nervous system response in rats. No additional details were available in the translation.

Bazarova (1973) conducted a study in which groups of 20 rats (strain and sex not specified) were exposed to piperidine vapors at analytically measured concentrations of 0.002 ± = 0.0003 or 0.01 ± 0.001 mg/L (2 or 10 mg/m^3 [0.6 or 3 ppm]) for 4 h/day, 5 days/week for 4 months followed by a 1-month recovery period. A group of 20 rats served as the control. Animals were exposed in a 700-L dynamic chamber (not otherwise described), and chamber atmospheres were measured eight times during each 4-h exposure. The investigators assessed body weight changes, blood vessel penetrability, erythrocyte parameters, liver and kidney function, testicular morphology, and neural activity.

Rats exposed at 10 mg/m^3 weighed 14% less than the controls after 14 exposures and 16% less than controls at the end of the recovery period. Evidence of increased neural and muscular excitability was observed after exposure at 10 mg/m^3 for 1.5 months or at 2 mg/m^3 for 2.5 months. Respiration was decreased after exposure at 2 mg/m^3 for 1.5 months and increased after exposure at 10 mg/m^3 for 2.5 months. At both concentrations, blood vessels in the skin showed decreased penetrability (measured after application of xylol) during the early phase of the study, followed by increased penetrability during the late phase of the study that remained evident until the end of the recovery period. In addition, blood vessel stability was decreased throughout the study in the 10-mg/m^3 group, as measured by increased petechia (submucosal hemorrhage). Decreases in erythrocyte count (80% of control) and hemoglobin concentration (89% of control) were observed in this group at the beginning of exposure and remained lower after 1.5 months, but were increased compared with controls at the end of the recovery period. Leukocyte count was decreased after 2.5 months (53% of control) due to a decrease in the lymphocyte count (47.9% of control) in rats

exposed at 10 mg/m^3. Blood pressure was significantly decreased in rats exposed at 10 mg/m^3 after 2.5 and 4 months. At the end of exposure, an effect on liver function was evidenced by a 47% decrease in urinary hippuric acid, and effects on kidney function were evidenced by a 46% decrease in urinary volume, increase in specific gravity of the urine, and 65% increase in urinary protein. Histopathologic findings in the 10 mg/m^3 group included a decrease in the number of normal spermatogonia and degeneration of the seminiferous tubules in the testes, focal swelling of the interalveolar septa in the lungs, albuminous degeneration in the liver, hyalin droplet and albuminous degeneration in the kidney, stromal atrophy in the spleen, and necrosis and scaring in the cardiac muscle (Bazarova 1973). Descriptive details were lacking for an adequate evaluation of this study; some information about this study was also obtained from BG Chemie (2000).

3.2.2. Rabbits

Bazarova (1973) exposed groups of six rabbits under the same conditions as rats to piperidine at 0.01 or 0.002 mg/L (10 and 2 mg/m^3, respectively) for 4 h/day, 5 days/week for 4 months, followed by a 1-month recovery period. The only effect described for the rabbit was a 29% and 27% decrease in arterial blood pressure after exposure at 10 and 2 mg/m^3, respectively, for 14 days, and an 8% increase in pressure after exposure at 10 mg/m^3 for 4 months.

3.3. Developmental and Reproductive Toxicity

Hughes et al. (1990) reported on the developmental effects in rats exposed to piperidine vapor during organogenesis. Groups of 25 pregnant Crl:CD(SD) GR VAF/Plus strain rats were exposed whole body to piperidine at concentrations of 0, 5, 20, or 80 ppm (0, 18, 70, and 280 mg/m^3, respectively) for 6 h/day on gestation days 6-15. Dams were observed daily for clinical signs, weighed on gestation days 2, 3, and 6 and at 2-day intervals until gestation day 20, and had food consumption measured at intervals between weighing days. Dams were killed on gestation day 20 and their ovaries and uteri were examined. All dams survived to the end of the study. No treatment-related effects were observed on any litter parameter examined, including litter size, post-implantation loss, mean litter weight, or mean fetal weight. In addition, the incidences of visceral and skeletal malformations were similar between the exposed and control groups. Therefore, no effects were observed in developing fetuses of female rats exposed to piperidine concentrations up to 80 ppm during organogenesis.

However, a number of maternal effects were observed. During each exposure to piperidine at 80 ppm, clinical signs in dams included a lack of response to noise (a knock on chamber door) and closed or half-closed eyes. Other signs observed during exposure at that concentration included licking the inside of the

mouth (frequency not reported), piloerection (frequency not reported), hunched posture during almost all exposures, and increased respiration, salivation, and rubbing the chin and paws on the cage during one or two exposures. After daily exposures at 80 ppm, some rats had red/brown staining on the fur, two had "snuffles," and one showed sneezing and salivation. At 20 ppm, lack of response to a knock on the chamber door was noted on each exposure occasion, and closed or half-closed eyes and hunched posture were observed once during the study. No clinical signs were reported after daily exposure to piperidine at 20 ppm, and no clinical signs related to exposure were observed at 5 ppm. Body weights and weight gain at 80 ppm were reduced compared with controls during the exposure period, but showed signs of recovery after exposure ended and was similar to controls at the end of the study. Food consumption also was reduced at 80 ppm during the exposure period and remained reduced after exposure ended. No treatment-related effects were observed on body weights or food consumption in the 5- or 20-ppm groups and no treatment-related necropsy findings were observed at any exposure concentration. The lack of response to a knock on the chamber door was the only clinical sign observed daily in rats exposed at 20 ppm. It is doubtful that this nonspecific clinical signs is treatment related or toxicologically significant in the absence of any corroborating evidence of central nervous system toxicity. BASF (1993) observed no treatment-related effects in their battery of neurofunctional tests conducted in a 28-day study of rats exposed repeatedly to piperidine at concentrations up to 100 ppm. Nevertheless, this study can be used for AEGL derivation because of the maternal clinical signs observed at 80 ppm.

In a study by Timofievskaya and Silantyeva (1975), groups of 6-13 pregnant rats were exposed to piperidine vapor at concentrations of 0, 0.9, 4, or 30 ppm (0, 3, 15, or 100 mg/m^3, respectively) throughout pregnancy or on gestation day 9 or at 0.9 or 30 ppm on gestation day 4. Two control groups were included in this study. Dams were killed on gestation day 21 for assessment of maternal and fetal parameters. The duration of each exposure was not reported, so it was assumed that animals were exposed continuously. No behavioral effects were noted in the dams, but body weight gain was lower in dams exposed at 4 and 30 ppm compared with controls. In rats exposed at 30 ppm on gestation day 4, significant decreases in the number of fetuses per dam (5.5 vs. 8.5 and 11.08 for the two control groups) and in the number of implantation sites (6.1 vs. 9.4 for control) were observed. Piperidine at 30 ppm on gestation day 9 or throughout pregnancy had no effect on these parameters. Fetal body weights were decreased in dams exposed at all concentrations throughout pregnancy (66-78% of control fetal weight). Fetal body weights were 76% of control weights after exposure at 0.9 ppm on gestation day 4 or 9; no significant reductions in fetal weights were observed after exposure at 30 ppm on gestation day 4 or 9 or at 4 ppm on gestation day 9. Decreases in fetal body weights appeared to be unrelated to exposure to piperidine. A concentration-response relationship was not observed for the single exposures. In addition, no corresponding changes were observed in other

fetal parameters consistent with pronounced decreases in fetal weights. Fetal length and placental size did not show concentration-response relationships. However, the placenta coefficient (not described) was significantly decreased at all concentrations throughout gestation, at 0.9 ppm on gestation day 4, and at 0.9 and 4 ppm on gestation day 9. Description of this study lacks adequate detail to be used for AEGL derivation. Some of the information for this study was obtained from BG Chemie (2000).

3.4. Carcinogenicity

No inhalation carcinogenicity studies on piperidine were found, but one oral study was available. Lijinsky and Taylor (1977) conducted a study in which groups of 15 male and 15 female Sprague-Dawley rats were administered piperidine at 0.09% (9,000 ppm) in drinking water with and without 0.2% sodium nitrite for 50 weeks. No treatment-related neoplasms developed during the lifetime of either test group.

3.5. Genotoxicity

Piperidine was negative in *Salmonella typhimurium* assays using strains TA98, TA100, and TA1537 with and without metabolic activation with S9 from phenobarbital-induced mouse liver; piperidine was tested at concentrations of 1.25-25 mM (Riebe et al. 1982). Green and Savage (1978) tested piperidine in the Ames and mouse host-mediated mutagenicity assays. Piperidine was negative in the Ames assay using *S. typhimurium* strains TA1531, TA1532, TA1964, and TA1530 with and without metabolic activation with mouse liver S9 and in the host-mediated assay using *S. typhimurium* strains TA1534, TA1950, TA1951, and TA1952. Riebe et al. (1982) also obtained negative results when they tested piperidine in the *Escherichia coli pol* A+/*pol* AB recombination assay. Nevertheless, piperidine was mutagenic in the mouse lymphoma assay without metabolic activation with rat liver S9, but negative with S9 activation (Wangenheim and Bolcsfoldi 1988). Garberg et al. (1988) reported that piperidine induced DNA strand breaks in mouse lymphoma cells with rat liver S9, but not alkaline unwinding with or without S9.

3.6. Summary

Inhalation toxicity data on piperidine are summarized in Table 6-4. The LT_{50} for mice exposed to an unknown preset absolute concentration of piperidine was 80 min (Zayeva et al. 1968). The 4-h LC_{50} for piperidine in rats ranged from 1,330-1,420 ppm (4,600-4,900 mg/m^3) (BASF 1980). Smyth et al. (1962) reported, however, that no rats died after exposure at 2,000 ppm

TABLE 6-4 Summary of Acute Inhalation Toxicity Data of Piperidine in Laboratory Animals

Species	Exposure Conditions	Effects	Reference
Mouse	2-h LC_{100}	LT_{50} = 80 min	Zayeva et al. 1968
	2 h	LC_{50} = 1,740 ppm	AIHA 2001
Rat	290-2,190 ppm (1,000-7,540 mg/m^3) for 4 h	Respiratory irritation at all concentrations; deaths at >810 ppm (>2,800 mg/m^3); LC_{50} = 1,330 ppm (4,600 mg/m^3) (males); 1,420 ppm (4,900 mg/m^3) (females); 1,390 ppm (4,800 mg/m^3) (males and females)	BASF 1980
	2,000 ppm (7,000 mg/m^3) for 4 h	0/6 deaths	Smyth et al. 1962
	4,000 ppm (14,000 mg/m^3) for 4 h	6/6 deaths	Smyth et al. 1962
	Concentrated vapor:		
	15 min	6/6 deaths	Smyth et al. 1962
	10 min	3/6	BASF 1981
	3 min	2/12	BASF 1981
NR	NR	LC_{50} = 1,885 ppm (6,500 mg/m^3)	Bazarova and Migoukina 1975
Rats	50, 100, 200 ppm (175, 360, 710 mg/m^3), 6 h/d for 5 d	Upper respiratory tract irritation at all concentrations; closed eyes and salivation at 200 ppm.	BASF 1990
	5, 20, 100 ppm (20, 70, 350 mg/m^3), 6 h/d for 28 d	Upper respiratory tract irritation at 100 ppm (350 mg/m^3) on day 2.	BASF 1993
	3 ppm (10 mg/m^3), 4 h/d, 5 d/wk for 4 mos	No effects after a single exposure. After repeated exposure, body weight decreases; neural, muscular, cardiovascular, hematologic, and respiratory effects; and hepatic, renal, testicular, splenic, and cardiac muscle toxicity.	Bazarova 1973
	0.6 ppm (2 mg/m^3), 4 h/d, 5 d/wk for 4 mos	Cardiovascular, respiratory, neural, and muscular effects after multiple exposures.	Bazarova 1973

(Continued)

TABLE 6-4 Continued

Species	Exposure Conditions	Effects	Reference
Rabbit	0.6 or 3 ppm (2 or 10 mg/m^3), 4 h/d, 5 d/wk for 4 mos	Decreased arterial blood pressure at both concentrations.	Bazarova 1973
Rat	5.8 ppm (20 mg/m^3)	Threshold for nervous system response.	Bazarova and Migoukina 1975
Rat, pregnant	5, 20, 80 ppm (20, 70, 280 mg/m^3), gestation days 6-15	Dams: at 80 ppm, respiratory and ocular irritation, salivation during or after first exposure, hunched posture after most exposures; at 20 ppm, ocular irritation and hunched posture observed once Fetuses: no effects.	Hughes et al. 1990
Guinea pig	1 h	LC_{50} = 3,480 ppm	AIHA 2001

Abbreviations: LC_{100}, lethal concentration, 100% lethality; LC_{50}, lethal concentration, 50% lethality; LT_{50}, median lethal time; NR, not reported.

(7,000 mg/m^3) for 4 h, but that six of six died after exposure at 4,000 ppm (14,000 mg/m^3) for 4 h. The LC_{50} for an unidentified mammalian species exposed for an unknown period of time was reported as 1,885 ppm (6,500 mg/m^3) (Bazarova and Migoukina 1975). A 2-h LC_{50} for the mouse was reported as 1,740 ppm (6,000 mg/m^3) and a 1-h LC_{50} for the guinea pig was 3,480 ppm (12,000 mg/m^3) (AIHA 2001).

Male and female rats exposed to piperidine at concentrations ranging from 50 to 200 ppm (175-710 mg/m^3) for 6 h/day caused nasal irritation signs of ocular irritation and salivation also were observed after each daily exposure at 200 ppm (BASF 1990, 1993; Hughes et al. 1990). More severe nasal and ocular irritation were observed in rats exposed at 290 ppm (1,000 mg/m^3) for 4 h followed by the first evidence of corrosion around the nose and dyspnea at 810 ppm (2,800 mg/m^3). CNS toxicity, corneal damage, and more severe corrosion around the nose were observed at concentrations >1,190 ppm (>4,100 mg/m^3) followed by prostration at 1,540 and 2,190 ppm (5,300 and 7,540 mg/m^3) (BASF 1980). Clinical signs likely associated with death included prostration, CNS toxicity, and dyspnea, and the lowest concentration causing death in one rat was the lowest concentration that caused dyspnea. These data showed an exposure-related continuum that increased in severity from nasal irritation to death. Other studies were not reliable. Bazarova (1973) reported that repeated exposure of rats to piperidine at much lower concentrations of 0.6 and 3 ppm (2 or 10 mg/m^3) for 4 months caused multiple effects, including neurotoxicity, cardiovascular toxicity, hematologic effects, hepatic effects, renal effects, and testicular effects at one or both concentrations. Insufficient details were available for adequately evaluating this study for AEGL derivation.

Two developmental toxicity studies were available. Hughes et al. (1990) found no effects on the fetuses of rat dams exposed to piperidine at concentrations up to 80 ppm (280 mg/m^3) for 6 h/day during organogenesis. Timofievskaya and Silantyeva (1975) reported inconsistent results regarding the effect of piperidine on the fetuses of rat dams exposed at 0.9-30 ppm (3-100 mg/m^3) throughout gestation or on gestation day 9 or at 0.9 or 30 ppm (3 or 100 mg/m^3) on gestation day 4.

No inhalation studies were found on the carcinogenicity of piperidine. In an oral study, carcinogenic activity was not observed in rats administered piperidine at 0.09% in drinking water for 50 weeks (Lijinsky and Taylor 1977). Genotoxicity studies showed that piperidine was not mutagenic in *S. typhimurium* with or without metabolic activation in either the Ames or the host-mediated assay (Riebe et al. 1982). Piperidine also was negative in the *E. coli* recombination assay (Riebe et al. 1982), but was positive in the mouse lymphoma cell assay without metabolic activation (Wangenheim and Bolcsfoldi 1988). Piperidine induced DNA strand breaks in mouse lymphoma cells (Garberg et al. 1988).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

Piperidine is absorbed from the respiratory tract, digestive tract, and skin (Gehring 1983). Piperidine also is synthesized endogenously from lysine, cadaverine, and pipecolic acid. Pipecolic acid is a product of lysine degradation, and homogenates of brain tissue can convert pipecolic acid to piperidine. Radioactive piperidine is recovered from rat brain after intraperitoneal injection of radioactive pipecolic acid. Piperidine has been found in the muscles, liver, heart, kidneys, spleen, testes, small intestine, and lungs of rats and mice at concentrations ranging from 0.115-0.440 nmol/g of tissue. However, the highest endogenous concentrations are found in the brain, where concentrations reported for whole mouse and rat brain ranged from 0.016-3.28 nmol/g depending on the extraction and analysis procedures. The concentration of piperidine in whole human brain was reported to be 1.8 nmol/g. In other species, piperidine was found in the cerebellum of dogs at 3.9-5.18 nmol/g, in mice at 3.07-3.17 nmol/g, in cats at 0.8 nmol/g, and in rats at 0.047 nmol/g. Concentration in other brain regions varied considerably (Giacobini 1976). Perry et al. (1964) reported that piperidine is found in human cerebral spinal fluid at very low concentrations.

Piperidine and its metabolites are excreted in urine. Unchanged piperidine, 3-hydroxypiperidine, 4-hydroxypiperidine, and two unidentified metabolites were found in urine collected over 72 h after intraperitoneal injection of rats with [^{3}H]piperidine (Okano et al. 1978).

von Euler (1945) used a colorimetric method to determine the amount piperidine in the urine of nonsmoking human subjects (eight male and four female medical students). Male subjects had an average urinary piperidine concentration of 0.49 mg/dL and females an average of 0.88 mg/dL in 24-h pooled specimens; the total amount excreted in 24 h was 8.5 mg for males and 7.6 mg for females.

4.2. Mechanism of Toxicity

Piperidine is a very strong alkaline agent with a pK_b of 2.88 at 25°C; consequently, it is severely corrosive to skin producing severe third degree burns in a human after less than 3 min of contact (Linch 1965). Linch (1965) considered piperidine to be more corrosive than "strong primary irritants." Because of its corrosive properties, piperidine is expected to cause irritation to the eyes and respiratory tract. Piperidine is found naturally in the brain and other tissues of vertebrates and invertebrates; it is a biogenic amine and acts as a neuromodulator (Giacobini 1976). Piperidine stimulates and blocks actions on ganglia, chemoreceptors, and neuromuscular junctions. It acts on chemoreceptors, which stimulates respiration; acts on sympathetic ganglia releasing catecholamines, which raises blood pressure; acts on parasympathetic ganglia, which stimulates

contraction of smooth muscle; and acts on end plates, which stimulates contraction of skeletal muscle (Kase and Miyata 1976). Piperidine interacts with cholinergic receptor sites of muscle end plates and with nicotinic receptors on sympathetic and parasympathetic ganglia to cause effects mimicking those of acetylcholine (Giacobini 1976). Piperidine also acts on the CNS where it mimics the nicotinic effects of acetylcholine on synaptic sites in the brain (Kase and Miyata 1976). Piperidine affects CNS responses related to emotional behavior, physiologic processes of sleep, and extrapyramidal motor function (ataxia, head turning, and nystagmus) (Giacobini 1976; Kase and Miyata 1976).

4.3. Structure-Activity Relationships

Pyrrolidine (CAS registry no. 123-75-1) is a five-membered alicyclic secondary amine that is structurally similar to piperidine (Trochimowicz et al. 1994). It produces CNS effects similar to those of piperidine (Giacobini 1976). The 2-h LC_{50} of pyrrolidine in mice is 1,300 mg/m^3; inhalation exposure causes irritation, excitement, and convulsions. The oral LD_{50} (lethal dose, 50% lethality) is 300 mg/kg for rats, 450 mg/kg for mice, and 250 mg/kg for rabbits and guinea pigs. Intravenous administration of pyrrolidine causes increases in blood pressure and respiration in dogs and cats (Trochimowicz et al. 1994). Piperazine (CAS registry no. 110-85-0) is a six-membered alicyclic amine that is also structurally similar to piperidine (Trochimowicz et al. 1994). Piperazine produced signs of respiratory irritation in rats after exposure at 40 mg/L (4,000 mg/m^3) for 2 h (DuPont 1968, as cited in Trochimowicz et al. 1994). Mice showed changes in motor activities and muscle contraction inhalation exposure at 5,400 mg/m^3 for 2 h (Timofievskaya 1979, as cited in Trochimowicz et al. 1994). Oral LD_{50} values range from 2,050 to 3,000 mg/kg for rats and from 600 to 1,900 mg/kg for mice. Piperazine caused an initial fall in blood pressure and heart rate in rats, followed by a transient rise in both parameters (Trochimowicz et al. 1994).

4.4. Other Relevant Information

One case was reported in the literature concerning chemical burns associated with skin contact with piperidine. A worker was sprayed with piperidine when transferring the chemical under room temperature conditions. The worker suffered first degree burns on the face, left ear, and neck; second degree burns on the forearms and abdomen; and third-degree burns on the chest. Contact time with the chemical was less than 3 min (Linch 1965).

Smyth et al. (1962) reported an oral LD_{50} for piperidine of 520 mg/kg for the rat; values reported by Trochimowicz et al. (1994) ranged from 133 to 337 mg/kg. Oral administration of piperidine causes weakness, respiratory distress, and convulsions. van den Heuvel et al. (1990) reported LD_{50} values of 445 mg/kg for male and female rats combined; clinical signs included ptosis, respiratory effects, lethargy, ataxia, tremors, salivation, and lacrimation.

4.4.1. Species Variability

Little information was available to evaluate species variability in response to piperidine vapor. The LC_{50} is 3,480 ppm for a 1-h exposure to the guinea pig, 1,740 ppm for a 2-h exposure to the mouse, and 1,390 ppm for a 4-h exposure to the rat. The linear correlation for concentration vs. time for these three species is -0.96, indicating the response does not vary because of species.

4.4.2. Susceptible Populations

No data were available for determining human variability to piperidine after inhalation exposure.

4.4.3. Concentration-Exposure Duration Relationship

Data from a single species were not available for establishing a concentration-exposure duration relationship for piperidine. However, LC_{50} data were available for three different species that allowed derivation of the value for n, which is used in the equation $C^n \times t = k$ for extrapolating data to the pertinent AEGL time frames. The 1-h LC_{50} for the guinea pig is 3,480 ppm (AIHA 2001); the 2-h LC_{50} for the mouse is 1,740 ppm (BG Chemie 2000; AIHA 2001); and the 4-h LC_{50} for the rat is 1,390 ppm (BASF 1980). The correlation coefficient is -0.96, and the value of n derived from these data is 1.5. Figure 6-1 shows the concentration-exposure duration relationship.

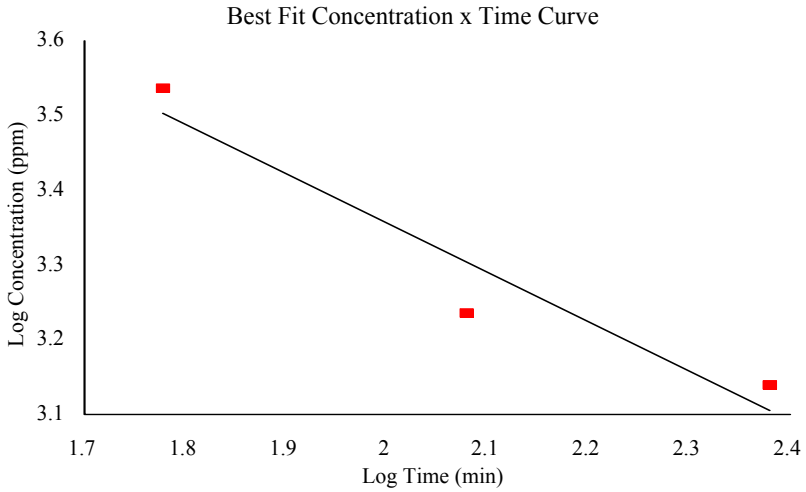

FIGURE 6-1 Concentration-exposure duration relationship for piperidine.

4.4.4. Concurrent Exposure Issues

There are no known concurrent exposure issues related to inhalation of piperidine.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Piperidine has an amine-like pungent (Trochimowicz et al. 1994) or pepper-like odor (Lewis 1993; Trochimowicz et al. 1994). At concentrations of 2-5 ppm, piperidine has an odor reported to be tolerated for only a brief time by unacclimated individuals. The odor threshold for piperidine was reported to be <2 ppm (A.C. Nawakowski, Upjohn Company, unpublished material, 1980, as cited in Trochimowicz et al. 1994) and 0.37 ppm by van Doorn et al. (2002). Bazarova and Migoukina (1975) reported that the irritation threshold for inhalation exposure to piperidine was 90 mg/m^3 (26 ppm). These data are from secondary sources and are not be verified.

5.2. Animal Data Relevant to AEGL-1

Bazarova and Migoukina (1975) reported that the acute inhalation threshold for nervous system response to piperidine was 5.7 ppm for an unidentified species. In a repeat exposure study by Bazarova (1973), no effects were described in rats after the first exposure to piperidine at 0.6 or 3 ppm for 4 h. A concentration-related increase in the severity of nasal irritation (secretions and bloody encrustation) was observed during or after each 6-h exposure at 50-200 ppm for 5 days, and eye lid closure and salivation were observed at 200 ppm (BASF 1990). Nasal irritation also was observed after the second 6-h exposure to piperidine at 100 ppm in a 28-day inhalation study (BASF 1993). No effects were observed after exposure at 5 or 20 ppm. In a developmental toxicity study, Hughes et al. (1990) observed eye closure, increased respiration, hunched posture, piloerection, salivation, a lack of response to a knock on the chamber door after the first exposure at 80 ppm in pregnant rats exposed for 6 h/day during gestation days 6-15. At 20 ppm, dams did not respond to a knock on the chamber door. No clinical signs were observed at 5 ppm. An extensive battery of neurofunctional test showed no treatment-related CNS toxicity after repeated 6-h daily exposures at concentrations up to 100 ppm. Studies by BASF (1990, 1993) and Hughes et al. (1990) appeared to follow standard protocol for repeat exposure studies and were conducted under Good Laboratory Practice.

5.3. Derivation of AEGL-1 Values

Data on odor detection, threshold, or tolerance as well as the data on irritation threshold were obtained from secondary sources, and the primary sources

were not available for verification. Three studies showed nasal secretions, bloody or reddish encrustation or other evidence of upper respiratory tract irritation, ocular irritation, or general discomfort in rats exposed to piperidine at 50-200 ppm (Hughes et al. 1990; BASF 1990, 1993). The lowest concentration causing nasal irritation was 50 ppm for a 6-h exposure in rats (BASF 1990), and no nasal irritation was observed in rats exposed at 20 ppm for 6 h (BASF 1993). A lack of response to a knock was observed in pregnant rats exposed to piperidine at 20 ppm for 6 h, but the toxicologic significance of this observation is uncertain because a functional observation battery showed no treatment-related effects after repeated exposures at 100 ppm for 6 h. A no-effect level for nasal irritation of 20 ppm for 6 h was selected as the end point for deriving AEGL-1 values. An uncertainty factor of 3 for interspecies differences and a factor 3 for intraspecies variability were applied. The rationale for selecting these factors included the following: (1) the irritant effects are mediated by direct contact of piperidine (corrosive agent) with the nasal epithelium without involvement of other regions of the respiratory tract; and (2) the cell composition of the nasal mucosa is similar among species and individuals in the population, although the cell distribution and nasal morphology differ among species. An interspecies factor of 3 is also supported by an analysis of the LC_{50} data for three species exposed for three different time periods. The LC_{50} values are 3,480 ppm for a 1-h exposure to the guinea pig, 1,740 ppm for a 2-h exposure to the mouse, and 1,390 ppm for a 4-h exposure to the rat. The linear correlation coefficient for regression analysis of the LC_{50} values for the three species is −0.96, and the concentration and time relationships for three species do not vary by more than 30%, indicating the response is similar between the species. Therefore, these data support an interspecies factor of 3. After applying a total uncertainty factor of 10, the resulting value of 2 ppm was time scaled based on the equation $C^n \times t = k$, where $n = 1.5$. The value of n was derived from a regression analysis of the LC_{50} values for the mouse, guinea pig, and rat (see section 4.4.3). The 30-min AEGL-1 value was applied to the 10-min exposure, because of the uncertainty in scaling 6-h duration to a 10-min exposure. AEGL-1 values for piperidine are presented in Table 6-5. All AEGL-1 values are below the irritation threshold of 26 ppm reported by Bazarova and Migoukina (1975).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to AEGL-2 end points were found. The irritation threshold for piperidine was reported to be 26 ppm (Bazarova and Migoukina 1975); however, no information was provided on how that value was derived. Secondary sources reported that piperidine can cause sore throat, signs

TABLE 6-5 AEGL-1 Values for Piperidine

10 min	30 min	1 h	4 h	8 h
10 ppm (35 mg/m^3)	10 ppm (35 mg/m^3)	6.6 ppm (23 mg/m^3)	2.6 ppm (9 mg/m^3)	1.7 ppm (6 mg/m^3)

of respiratory tract irritation (coughing, labored breathing), and dizziness (probably CNS related), but exposure concentrations and durations were not specified.

6.2. Animal Data Relevant to AEGL-2

Smyth et al. (1962) observed no deaths among six rats exposed to piperidine at 2,000 ppm for 4 h, and BASF (1980) reported no deaths among 20 rats exposed at 290 ppm for 4 h. Nasal secretions and bloody encrustation were observed after exposure at 50-200 ppm for 6 h (BASF 1990). In addition, closed eyes (possibly indicative of ocular irritation) and salivation (probably from attempted mouth breathing) occurred in rats during each exposure to piperidine at 200 ppm. Severity of nasal and ocular irritation and general discomfort showed a concentration-related increase at piperidine concentrations of 50-200 ppm. Clinical signs observed at 287 ppm included ocular and nasal irritation, spasmodic respiration (probably from attempted mouth breathing because of the pungent odor), and ragged fur; none of these clinical signs were indicative of death. Thus, the clinical signs observed in rats exposed at 290 ppm for 4 h are similar but slightly more severe than those observed in rats exposed to 200 ppm for 4 h. In rats exposed at 10 mg/m^3 (3 ppm) for 4 h/day for 4 months, Bazarova (1973) noted cardiovascular and hematologic effects at the beginning of exposure (not otherwise described), but did not state whether the effects were observed after the first exposure; the results have not been corroborated in another study. Studies by BASF (1980, 1990) appeared to have been conducted using the standard protocols for acute inhalation and repeat exposure studies.

No developmental toxicity was found in rat fetuses after dams were exposed to piperidine at 0.9, 4, or 30 ppm throughout gestation, on gestation day 4, or on gestation day 9 (Timofievskaya and Silantyeva 1975). Developmental toxicity also was not observed after exposure of pregnant rats at 5, 20, or 80 ppm for 6 h/day on gestation days 6-15 (Hughes et al. 1990).

6.3. Derivation of AEGL-2 Values

AEGL-2 values were derived from the study showing nasal irritation but no salivation or eye closure, possibly indicative of ocular irritation, in rats exposed to piperidine at 100 ppm for 6 h (BASF 1990). The uncertainty factors,

justification for the uncertainty factors, and time scaling were the same as those described for AEGL-1 values (see Section 5.3). AEGL-2 values for piperidine are presented in Table 6-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human lethality data on piperidine were found.

7.2. Animal Data Relevant to AEGL-3

Zayeva et al. (1968) reported an LT_{50} of 80 min for piperidine, but an exposure concentration was not specified. Bazarova and Migoukina (1975) reported an LC_{50} of 1,885 ppm (6,500 mg/m^3) for an unknown species exposed for an unknown duration. BASF (1981) reported that two of 12 rats exposed to a saturated piperidine atmosphere at 20 C died after 3 min and three of six rats died after 10 min. The 4-h LC_{50} for rats was 1,390 ppm (4,800 mg/m^3); no rats died at 290 ppm (1,000 mg/m^3) and all 20 rats exposed at 2,190 ppm (7,540 mg/m^3) died (BASF 1980). No deaths occurred in six rats exposed to piperidine at 2,000 ppm (7,000 mg/m^3) for 4 h, but all six rats exposed at 4,000 ppm (14,000 mg/m^3) for 4 h died (Smyth et al. 1962). LC_{50} values of 1,740 ppm (6,000 mg/m^3) were reported for a 2-h exposure to the mouse and 3,480 ppm (12,000 mg/m^3) for a 1-h exposure to the guinea pig. The mouse and guinea pig values were cited from secondary sources; the primary sources could not be located.

7.3. Derivation of AEGL-3 Values

One acute inhalation study showing increased mortality with concentration was available for deriving AEGL-3 values for piperidine. Clinical signs at lethal doses included effects on the eyes, upper and lower respiratory tracts, and the CNS. Dyspnea, tremors, clonic convulsions, and prostration were the most severe signs that appeared to be associated with death. One death occurred among 20 rats exposed at 810 ppm, and dyspnea was the only clinical sign that was potentially related to the death. The 4-h LC_{50} for inhalation exposure to piperidine is 1,390 ppm. The lethality threshold (LC_{01}) for 4 h was estimated by probit analysis to be 448 ppm (NCSS, Version 5.5). The LC_{01} benchmark dose (BMD_{01}) estimated from the probit model using EPA's Benchmark Dose Software, Version 1.3.2 (EPA 2003), was 415 ppm and the lower confidence limit ($BMDL_{05}$) was 474 ppm. AEGL-3 values were derived from the LC_{01} of 448 ppm for a 4-h exposure. That value is below the lowest concentration (810 ppm) that caused one death among 20 rats (5% lethality) and above than the highest

TABLE 6-6 AEGL-2 Values for Piperidine

10 min	30 min	1 h	4 h	8 h
50 ppm (175 mg/m^3)	50 ppm (175 mg/m^3)	33 ppm (116 mg/m^3)	13 ppm (46 mg/m^3)	8.3 ppm (29 mg/m^3)

concentration (290 ppm) that caused no deaths or clinical signs indicative of death. Therefore, the LC_{01} appears to be a good estimate of the threshold for lethality. The uncertainty factors, justification for the uncertainty factors, and time scaling were the same as those described for AEGL-1 values (see Section 5.3). In addition, larger uncertainty factors of 10 for either interspecies differences or intraspecies variability would lower the AEGL-3 values for the 4- and 8-h durations below the irritation threshold of 26 ppm for piperidine (Bazarova and Migoukina 1975). AEGL-3 values for piperidine are summarized in Table 6-7.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Acute Toxicity End Points

No human data were available for deriving any of the AEGL values. AEGL-1 values were derived on the basis of a no-effect level (20 ppm for 6 h) for nasal irritation in rats exposed to piperidine. Uncertainty factors of 3 for interspecies differences and 3 for intraspecies variability were applied, and time scaling was performed using the equation $C^n \times t = k$, with n = 1.5. AEGL-2 values were derived on the basis of the highest concentration (100 ppm for 6 h) that caused nasal irritation but no salivation or eye closure. The basis of AEGL-3 was the LC_{01} derived from a 4-h acute lethality study in rats. The LC_{01} (448 ppm) was lower than the lowest concentration associated with death or clinical signs indicative of death (810 ppm) and greater than the highest concentration that caused no deaths or clinical signs indicative of death (290 ppm). Uncertainty factors and time-scaling methods for AEGL-2 and AEGL-3 values were the same as described for AEGL-1 values. In addition, the interspecies uncertainty factor for AEGL-3 is supported by an analysis of LC_{50} values for three species. AEGL values are summarized in Table 6-8.

8.2. Comparison with Other Standards and Guidelines

The only standards available for piperidine are the workplace environmental exposure level (WEEL) established by the American Industrial Hygiene Association (AIHA) and the United Kingdom Occupational Exposure Level (OEL). The WEEL for piperidine is 1 ppm (8-h time-weighted average), with a skin notation (AIHA 1996, 2001, 2007). AIHA based the WEEL on secondary

TABLE 6-7 AEGL-3 Values for Piperidine

10 min	30 min	1 h	4 h	8 h
370 ppm (1,295 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (385 mg/m^3)	45 ppm (158 mg/m^3)	28 ppm (98 mg/m^3)

TABLE 6-8 AEGL Values for Piperidine

Classification	10 min	30 min	1 h	4h	8h
AEGL-1 (nondisabling)	10 ppm (35 mg/m^3)	10 ppm (35 mg/m^3)	6.6 ppm (23 mg/m^3)	2.6 ppm (9 mg/m^3)	1.7 ppm (6 mg/m^3)
AEGL-2 (disabling)	50 ppm (175 mg/m^3)	50 ppm (175 mg/m^3)	33 ppm (116 mg/m^3)	13 ppm (46 mg/m^3)	8.3 ppm (29 mg/m^3)
AEGL-3 (lethal)	370 ppm (1,295 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (385 mg/m^3)	45 ppm (158 mg/m^3)	28 ppm (98 mg/m^3)

sources and comparison to standards for 2-aminopyridine of 0.5 ppm (2 mg/m^3) set by various organizations and an immediately dangerous to life and health value of 5 ppm (20 mg/m^3). The source documentation for the WEEL (AIHA 2007) cites three dermal LD_{50} values: 275 mg/kg in rats (van den Heuval et al. 1990), 320 mg/kg in rabbits (Royal Society 1987), and 1,000 mg/kg in rabbits (D. Conine, Abbott Laboratories, personal conversation, 1994, as cited in AIHA 1996). The latter value was from an unpublished study. These dermal LD_{50} values are very high, and it is unlikely that such concentrations would occur during an accidental release of piperidine vapors. It appears that the data used to derive AEGL values were not available to the organizations that developed the standards and guidelines for piperidine.

8.3. Data Quality and Research Needs

The studies by Bazarova (1973), Bazarova and Migoukina (1975), Zayeva et al. (1968), and Timofievskaya and Silantyeva (1975) did not provide adequate experimental detail and explanation of results. Studies by BASF (1980, 1990, 1993) and Hughes et al. (1990) were well conducted and useful for deriving the AEGL values. Overall, the BASF and Hughes et al. studies showed an exposure-response continuum from 5 to 2,190 ppm; therefore, the database for piperidine provided sufficient data for deriving AEGLs. Nevertheless, the evaluation and conclusions regarding the acute inhalation toxicity of piperidine vapor and AEGL derivations could be strengthen with definitive data on the odor and irritation threshold in humans and with 1- and 8-h acute inhalation toxicity studies at concentrations in rats that would encompass lethal and nonlethal end points.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PIPERIDINE

Derivation of AEGL-1 Values

Key study:	BASF. 1993. Study on the Inhalation Toxicity of Piperidine as a Vapor in Rats: 28-day Test. Project No. 4610523-89065. BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany.
Toxicity end point:	No-effect level for nasal irritation (20 ppm for 6 h).
Time scaling:	$C^n \times t = k$; n = 1.5 (derived by regression analysis of LC_{50} data for rats, guinea pigs, and mice).
Uncertainty factors:	3 for interspecies differences because the effects are mediated by direct contact with nasal epithelium, which has similar cell composition among species but different cell distribution and nasal morphology; linear correlation for the concentration vs. time relationship for LC_{50} values for three species is -0.96 and the concentration-time relationships are similar, not varying by more than 30%, indicating that the response was similar among the three species 3 for intraspecies variability because the nasal epithelium does not vary among individuals in the population.
Calculations:	C = 20 ppm ÷ 10 (total uncertainty factor) = 2 ppm $C^n \times t = k$; C = 2 ppm, t = 360 minutes, n = 1.5 $k = (2\ ppm)^{1.5} \times 360\ min = 1{,}018.2338\ ppm\text{-}min$
10-min AEGL-1:	Set equal to the 30-min AGEL-1 values

30-min AEGL-1:	$C = (1{,}018.2338 \text{ ppm-min} \div 30 \text{ min})^{1/1.5}$ $C = 10$ ppm
1-h AEGL-1:	$C = (1{,}018.2338 \text{ ppm-min} \div 60 \text{ min})^{1/1.5}$ $C = 6.6$ ppm
4-h AEGL-1:	$C = (1{,}018.2338 \text{ ppm-min} \div 240 \text{ min})^{1/1.5}$ $C = 2.6$ ppm
8-h AEGL-1:	$C = (1{,}018.2338 \text{ ppm-min} \div 480 \text{ min})^{1/1.5}$ $C = 1.7$ ppm

Derivation of AEGL-2 Values

Key study:	BASF. 1990. Range-finding Study on the Inhalation Toxicity of Piperidine as Vapor in Rats: 5-day Study. Project No. 3010523-89017, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany.
Toxicity end point:	Nasal irritation without eye closure or salivation (100 ppm for 6 h).
Time scaling:	$C^n \times t = k$; $n = 1.5$ (derived by regression analysis of LC_{50} data for rats, guinea pigs, and mice).
Uncertainty factors:	3 for interspecies differences because the effects are mediated by direct contact with nasal mucosa, which has similar cell composition among species but different cell distribution and nasal morphology; the data indicate only small variations in LC_{50} values for three different species 3 for intraspecies variability because the nasal epithelium does not vary among individuals in the population.
Calculations:	$C = 100 \text{ ppm} \div 10$ (total uncertainty factor) $= 10$ ppm $C^n \times t = k$; $C = 10$ ppm, $t = 360$ min, $n = 1.5$ $k = 11{,}384.1996$ ppm-min

10-min AEGL-2:	Set equal to the 30-min AGEL-1 values
30-min AEGL-2:	$C = (11{,}384.1996 \text{ ppm-min} \div 30 \text{ min})^{1/1.5}$ C = 50 ppm
1-h AEGL-2:	$C = (11{,}384.1996 \text{ ppm-min} \div 60 \text{ min})^{1/1.5}$ C = 33 ppm
4-h AEGL-2:	$C = (11{,}384.1996 \text{ ppm-min} \div 240 \text{ min})^{1/1.5}$ C = 13 ppm
8-h AEGL-2:	$C = (11{,}384.1996 \text{ ppm-min} \div 480 \text{ min})^{1/1.5}$ C = 8.3 ppm

Derivation of AEGL-3 Values

Key study:	BASF. 1980. Determination of the Acute Inhalation Toxicity LC_{50} of Piperidine as Vapor in Sprague-Dawley Rats After a 4-Hour Exposure. BASF Gewerbehygiene and Toxikologie.
Toxicity end point:	LC_{01} (lethality threshold) of 448 ppm calculated by probit analysis.
Time scaling:	$C^n \times t = k$; n = 1.5 (derived by regression analysis of LC_{50} data for rats, guinea pigs, and mice).
Uncertainty factors:	3 for interspecies differences because the data showed only small variations in LC_{50} values for three species. 3 for intraspecies variability because a factor of 10 produces unusually low values that are not supported by available data.
Calculations:	C = 448 ppm ÷ 10 (total uncertainty factor) = 44.8 ppm $C^n \times t = k$; C = 44.8 ppm, t = 240 min, n = 1.5 k = 71,966.1488 ppm-min

10-min AEGL-3:	$C = (71{,}966.1488 \text{ ppm-min} \div 10 \text{ min})^{1/1.5}$ $C = 370$ ppm
30-min AEGL-3:	$C = (71{,}966.1488 \text{ ppm-min} \div 30 \text{ min})^{1/1.5}$ $C = 180$ ppm
1-h AEGL-3:	$C = (71{,}966.1488 \text{ ppm-min} \div 60 \text{ min})^{1/1.5}$ $C = 110$ ppm
4-h AEGL-3:	$C = (71{,}966.1488 \text{ ppm-min} \div 240 \text{ min})^{1/1.5}$ $C = 45$ ppm
8-h AEGL-3:	$C = (71{,}966.1488 \text{ ppm-min} \div 480 \text{ min})^{1/1.5}$ $C = 28$ ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR PIPERIDINE

Derivation Summary for Piperidine

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
10 ppm (35 mg/m^3)	10 ppm (35 mg/m^3)	6.6 ppm (32 mg/m^3)	2.6 ppm (9 mg/m^3)	1.7 ppm (6 mg/m^3)

Reference: BASF. 1993. Study on the Inhalation Toxicity of Piperidine as a Vapor in Rats: 28-day Test. Project No. 4610523-89065. BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany.

Test species/Strain/Number: Rat, Wistar, five of each sex

Exposure route/Concentration/Durations: Inhalation; 0, 20, and 100 ppm; 6 h/day for 28 days

Effects: Nasal irritation (red crusts on nasal edge) at 100 ppm starting on day 2; no effect at 20 ppm.

End point/Concentration/Rationale: No-effect level for nasal irritation at 100 ppm for 6 h

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the effects are mediated by direct contact with nasal epithelium, which has similar cell composition among species, although cell distribution and nasal morphology differ; the linear correlation coefficient for the concentration vs. time relationship for LC_{50} values for three species is -0.96 and the concentration-time relationships are similar, not varying by more than 30%, indicating the response is similar among the three species
Intraspecies: 3, because the nasal epithelium does not vary among individuals in the population

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$; n = 1.5 based on regression analysis of LC_{50} values for the rat exposed for 4 h, the mouse exposed for 2 h, and the guinea pig exposed for 1 h.

Confidence and support of AEGL values: Time scaling was based on LC_{50} values of three different species. The key study was a 28-day study in which the animals were observed daily for clinical signs. The exposure concentration from which the AEGL values were derived was a no-effect level for nasal irritation in a well-conducted study; concentrations ≤50 ppm of piperidine vapor caused exposure-related effects on the upper respiratory tract and eyes. The AEGL values are below the reported irritation threshold of 26 ppm.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
50 ppm (175 mg/m^3)	50 ppm (175 mg/m^3)	33 ppm (116 mg/m^3)	13 ppm (46 mg/m^3)	8.3 ppm (29 mg/m^3)

Reference: BASF. 1990. Range-finding Study on the Inhalation Toxicity of Piperidine as Vapor in Rats: 5-day Study. Project No. 3010523-89017, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany.

Test species/Strain/Number: Rat, Wistar, five of each sex

Exposure route/Concentration/Durations: Inhalation; 0, 50, 100, and 200 ppm; 6 h/day for 5 days

Effects: Nasal irritation at all concentrations (severity increased with concentration and time); "stretched respiration posture," eye closure, and salivation at 200 ppm.

End point/Concentration/Rationale: 100 ppm for 6 h was the highest concentration at which nasal irritation (reddish crusts on the nasal edge) was observed without eye closure or salivation. Severity of nasal irritation in the rat increased with increasing exposure concentration, but there was no involvement of other regions of the respiratory tract.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the effects are mediated by direct contact with nasal epithelium, which has similar cellular composition among species, although cell distribution and morphology differ; the linear correlation coefficient for the concentration vs. time relationship for LC_{50} values for three species is -0.96 and the concentration-time relationships are similar, not varying by more than 30%, indicating the response is similar among the three species.
Intraspecies: 3, because the nasal epithelium does not vary among individuals in the population.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$; n = 1.5 based on regression analysis of LC_{50} values for the rat exposed for 4 h, the mouse exposed for 2 h, and the guinea pig exposed for 1 h.

Confidence and support of AEGL values: Time scaling was based on LC_{50} values of three different species. The key study used for deriving AEGL-2 values was conducted according to standard protocol. The resulting AEGL-2 values for 10-60 min are greater than the reported irritation threshold for humans. Nasal irritation was the most sensitive end point in rats. The concentration of piperidine at which nasal irritation occurred and from which AEGL-2 values were derived caused no respiratory effects that extended beyond the nasal region and did not cause eye closure or salivation. The experimental concentration did not cause CNS toxicity. Therefore, the AEGL-2 values are well within the limits that would protect against long-term or irreversible effects of piperidine vapor.

AEGL-3 VALUES FOR PIPERIDINE

10 min	30 min	1 h	4 h	8 h
370 ppm (1,295 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (385 mg/m^3)	45 ppm (158 mg/m^3)	28 ppm (98 mg/m^3)

Reference: BASF. 1980. Determination of the Acute Inhalation Toxicity LC_{50} of Piperidine as Vapor in Sprague-Dawley Rats After a 4-h Exposure. BASF Gewerbehygiene und Toxikologie.

Test species/Strain/Number: Rats, Sprague-Dawley, 10 of each sex

Exposure route/Concentration/Durations: Inhalation; 290, 810, 1,190, 1,540, and 2,190 ppm; 4 h (single exposure)

Effects:
290 ppm: No deaths; nasal and ocular irritation.

810 ppm: One of 20 rats died; nasal and ocular irritation, corrosion around the nose (1 rat), and dyspnea.

1,190 ppm: 10 of 20 rats died; nasal and ocular irritation, corneal damage, corrosion around the nose, dyspnea, and CNS toxicity.

1,540 ppm: seven of 20 rats died; prostration and same effects noted at 1,190 ppm

2,190 ppm: 20 of 20 rats died; effects same as at 1,540 ppm

End point/Concentration/Rationale: Lethality threshold (LC_{01}) for piperidine is 448 ppm. That concentration is lower than the lowest concentration (810 ppm) where one of 20 rats died and had signs of dyspnea, which could be associated with death, and is greater than the highest concentration (290 ppm) that caused no deaths or clinical moribund signs.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the linear correlation coefficient for the concentration vs. time relationship for LC_{50} values for three species is -0.96 and the concentration-time relationships are similar, not varying by more than 30%, indicating the response is similar among the three species.
Intraspecies: 3, because a factor of 10 would produce AEGL values for the 4- and 8-h durations that are lower than the irritation threshold.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$; n = 1.5 based on regression analysis of LC_{50} values for the rat exposed for 4 h, the mouse exposed for 2 h, and the guinea pig exposed for 1 h.

Confidence and support of AEGL values: Time scaling was based on LC_{50} values of three different species. The acute inhalation study was conducted according to standard protocol and showed a reasonable concentration-response relationship for lethality and a clear concentration-response relationship for severity of clinical signs. The LC_{01} was a good approximation of the lethality threshold; therefore, the AEGL-3 values should be within the limits that would protect humans from lethal exposure to piperidine vapor.

APPENDIX C

CATEGORY PLOT FOR PIPERIDINE

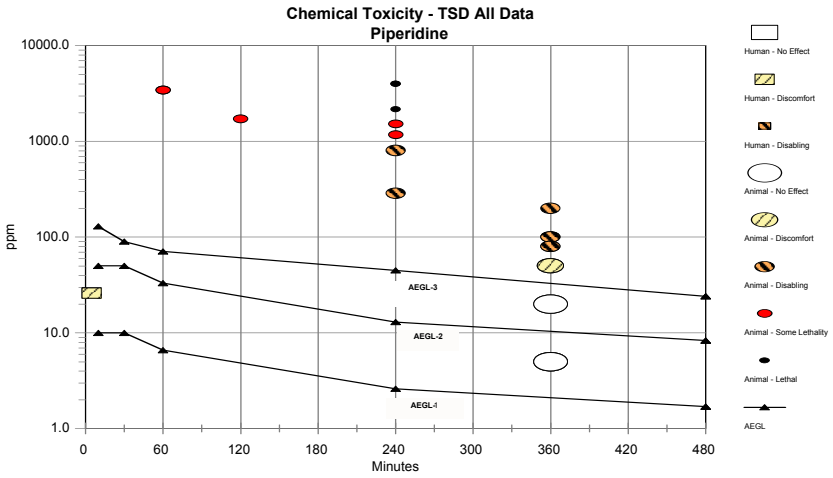

FIGURE C-1 Category plot of animal and human toxicity data in relation to AEGL values for piperidine.

7

Trimethoxysilane and Tetramethoxysilane[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Dana Glass (Oak Ridge National Laboratory), Mark Follansbee and Julie Klotzbach (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).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

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

SUMMARY

Trimethoxysilane and tetramethoxysilane are colorless liquids with ester-like odors. They are structural analogs and are in the organic silane family. Both chemicals have similar toxicologic effects in the lung and eye. Little relevant data on the toxicity of the chemicals in either humans or laboratory animals are available.

AEGL-1 values were not recommended for trimethoxysilane because of inadequate data. Data were also inadequate to derive AEGL-2 values, so values were derived by taking one-third of the AEGL-3 values. The Standing Operating Procedure for determining AEGL values (NRC 2001) specifies that AEGL-2 values can be derived by this method when a chemical has a steep dose-response curve. AEGL-3 values for trimethoxysilane were determined on the basis of mortality data from 1- and 4-h LC_{50} (lethal concentration, 50% lethality) inhalation studies in rats (Nachreiner and Dodd 1988). Points of departure were the calculated LC_{01} (lethal concentration, 1% lethality) values of 263 ppm for 10 min, 123 ppm for 30 min, 76.3 ppm for 1 h, 29.3 ppm for 4 h, and 18.2 ppm for 8 h. A total uncertainty factor of 30 was used. A factor of 3 was applied for interspecies differences, because similar effects were observed in rats, mice, and hamsters exposed at the same concentration in a 5-day inhalation study (Dow Corning Corp. 1981). The default value of 10 was used for intraspecies variabil-

ity, because no data were available to estimate human variability and it was not clear that trimethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001). Time scaling was performed using the concentration-time relationship equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 1.45 was calculated for trimethoxysilane. AEGL values for trimethoxysilane are presented in Table 7-1.

AEGL-1 values were not recommended for tetramethoxysilane because of inadequate data. AEGL-2 values for tetramethoxysilane were derived from an inhalation study in which rats were exposed to tetramethoxysilane at concentrations up to 45 ppm for 6 h/day, 5 days/week for 28 days (Kolesar et al. 1989). No deaths or effects on the respiratory or ocular epithelium were observed at 0, 5, and 10 ppm. At 15 ppm, nasal changes indicative of minimal acute inflammation were found in two of 20 rats and acute keratitis of cornea was observed in four of 20 rats, indicating a no-effect level for irreversible effects. At 30 and 45 ppm, lesions more severe than defined by AEGL-2 and deaths were observed, respectively. Therefore, 15 ppm was used as the point of departure for calculating AEGL-2 values. Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to 30 min, 1 h, and 4 h, and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because extrapolating from durations of more than 4 h to 10 min is not recommended (NRC 2001). A total uncertainty factor of 30 was used. A factor of 3 was applied for interspecies differences because in a 5-day inhalation study with trimethoxysilane, a structural analog, effects were similar in rats, mice, and hamsters (Dow Corning Corp. 1981). A default value of 10 was used for the intraspecies variability because there were no data to estimate human variability and it was not clear that tetramethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001).

AEGL-3 values for tetramethoxysilane were derived from a 4-h LC_{50} inhalation study in rats (Dow Corning Corp. 1992). The data were analyzed with EPA's Benchmark Dose Calculation Software, version 1.3.2 (EPA 2005), and values were calculated using log-probit analysis. A $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 26 ppm was used as the basis for determining AEGL-3 values. For completeness, a BMC_{01} (benchmark concentration with 1% response) of 30 ppm was also derived, but the lower $BMCL_{05}$ value was used. Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to 30 min and 1 h and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001). A total uncertainty factor of 30 was used. An uncertainty factor of 3 was used for interspecies differences because in a 5-day inhalation study with trimethoxysilane, a structural analog of tetramethoxysilane, effects were similar in rats, mice, and hamsters (Dow Corning Corp. 1981). A default value of 10 was used for intraspecies variability because there were no data to estimate human variability and it was not clear that tetramethox-

ysilane acts as a simple chemical irritant in the lungs (NRC 2001). The AEGL values for tetramethoxysilane are presented in 7-2.

1. INTRODUCTION

Trimethoxysilane and tetramethoxysilane are organosilanes (silicon esters). Silicon esters are silicon compounds that contain an oxygen bridge from silicon to an organic group (Si-OR). These compounds are classified according to whether the Si-OR bond is expected to remain intact or hydrolyzed in the final application. Trimethoxysilane and tetramethoxysilane are both alkoxysilanes and generally have sweet-fruity odors that become less apparent as the molecular weight increases. Both chemicals can be absorbed into the corneal tissue and cause eye damage (Arkles 2000). Tetramethoxysilane is used in the ceramic industry for closing pores, for coating metal surfaces, and as a bonding agent in paints and lacquers. Trimethoxysilane is used as an intermediate for producing silane. Whereas inorganic silanes are oxidized spontaneously on contact with oxygen and air, the organosilanes are more stable.

TABLE 7-1 Summary of AEGL Values for Trimethoxysilane

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (disabling)	2.9 ppm (15 mg/m^3)	1.4 ppm (7.0 mg/m^3)	0.83 ppm (4.2 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.20 ppm (1.0 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethality)	8.8 ppm (44 mg/m^3)	4.1 ppm (21 mg/m^3)	2.5 ppm (13 mg/m^3)	0.98 ppm (5.0 mg/m^3)	0.61 ppm (3.1 mg/m^3)	LC_{01} values (Nachreiner and Dodd 1988)

Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.

TABLE 7-2 Summary of AEGL Values for Tetramethoxysilane

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (disabling)	1.1 ppm (6.8 mg/m^3)	1.1 ppm (6.8 mg/m^3)	0.91 ppm (5.6 mg/m^3)	0.57 ppm (3.5 mg/m^3)	0.38 ppm (2.4 mg/m^3)	No-effect level for irreversible effects (Kolesar et al. 1989)
AEGL-3 (lethality)	1.7 ppm (11 mg/m^3)	1.7 ppm (11 mg/m^3)	1.4 ppm (8.7 mg/m^3)	0.87 ppm (5.4 mg/m^3)	0.43 ppm (2.7 mg/m^3)	Threshold for lethality (Dow Corning Corp. 1992)

Abbreviations: NR, not recommended

Selected chemical and physical properties for trimethoxysilane and tetramethoxysilane are presented in Table 7-3.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available on the acute lethality of trimethoxysilane or tetramethoxysilane in humans.

2.2. Nonlethal Toxicity

No data were available on the toxicity of trimethoxysilane or tetramethoxysilane in humans.

TABLE 7-3 Physical and Chemical Properties of Trimethoxysilane and Tetramethoxysilane

Parameter	Trimethoxysilane (AIHA 1997)	Tetramethoxysilane (AIHA 1998)
Synonyms	TMS	Methyl silicate; tetramethoxyorthosilicate; TMOS
CAS registry no.	2487-90-3	681-84-5
Chemical formula	$C_3H_{10}O_3Si$	$C_4H_{12}O_4Si$
Molecular weight	122.22	152.22
Physical state	Colorless liquid	Clear, colorless liquid
Odor	Ester odor	Faint, ester-like
Melting point	-114°C	5°C
Boiling point	84°C	122°C
Flash point	7.2°C (closed cup)	20°C (closed cup)
Density (air = 1)	4.2	5.3
Solubility (in water)	Reacts slowly; reacts with water liberating methanol	Reacts, generating methanol
Vapor pressure	57 mm Hg at 20°C	10.1 mm Hg at 20°C
Specific gravity	0.95 at 20°C	1.03 g/cc at 20°C
Explosive limits (volume % in air)	Lower limit: 4.3% at 34°C Upper limit: 40.1% at 62°C	No data available
Conversion factors	1 ppm = 5.0 mg/m^3 1 mg/m^3 = 0.2 ppm	1 ppm = 6.2 mg/m^3 1 mg/m^3 = 0.16 ppm

2.2.1. Odor Threshold

Inadequate data were available to calculate an odor threshold for trimethoxysilane or tetramethoxysilane.

2.2.2. Experimental Studies

No data were available on experimental studies in humans with trimethoxysilane or tetramethoxysilane.

2.2.3. Epidemiologic Studies/Occupational Exposures

Secondary sources indicate that both trimethoxysilane (AIHA 1997) and tetramethoxysilane (BIBRA 1988) cause ocular irritation; however, primary sources describing such effects were not available.

2.2.4. Clinical Studies

No data were available on clinical studies of trimethoxysilane or tetramethoxysilane.

2.3. Neurotoxicity

No data were available on the neurotoxicity of trimethoxysilane or tetramethoxysilane in humans.

2.4. Developmental and Reproductive Toxicity

No data were available on the developmental and reproductive toxicity of trimethoxysilane or tetramethoxysilane in humans.

2.5. Genotoxicity

No data were available on the genotoxicity of trimethoxysilane or tetramethoxysilane in humans.

2.6. Carcinogenicity

No data were available on the chronic toxicity or carcinogenicity of trimethoxysilane or tetramethoxysilane in humans.

2.7. Summary

Very little data were available on human exposure to trimethoxysilane or tetramethoxysilane.

3. ANIMAL TOXICITY DATA: TRIMETHOXYSILANE

3.1. Acute Lethality

An LC_{50} study was conducted using Good Laboratory Practices (GLP) by Union Carbide (Nachreiner and Dodd 1988). Five male and five female Sprague-Dawley rats were exposed to trimethoxysilane at concentrations of 19, 39, 71, or 166 ppm for 4 h or at 68, 155, 342, or 643 ppm for 1 h. Liquid trimethoxysilane was metered from a syringe pump into a heated evaporator and the resulting vapor was carried into the chamber by an inlet air stream. A gas chromatograph equipped with a flame-ionization detector was used to measure chamber concentrations of the trimethoxysilane. Because methanol can be produced from the breakdown of trimethoxysilane with moisture, methanol concentrations also were measured. The highest methanol vapor concentration was 173 ppm in the 1-h study and 66 ppm in the 4-h study. Methanol production was controlled by limiting the relative humidity of the chamber. The 4-h LC_{50} (with 95% confidence level) for trimethoxysilane was 81 ppm for males, 42 ppm for females, and 60 ppm for both sexes. The 1-h LC_{50} (with 95% confidence level) was 161 ppm for males, 146 ppm for females, and 154 ppm for both sexes. Those values were determined by a modified method of Finney (1964) using probit analysis. Mortalities were observed at all of the concentrations except 19 ppm in the 4-h group and 68 ppm in the 1-h group, with all deaths occurring during the 14-day post-exposure observation period. Mortality data are presented in Table 7-4.

Clinical signs were observed on the day of exposure in all groups, except for the 68-ppm (1 h) and 19-ppm (4 h) groups, and included: hyperactivity followed by hypoactivity; respiratory irritation; ocular irritation; and ataxia and slow righting reflex (71 ppm only). The following clinical signs were observed post exposure mostly beginning about day 5: unkempt fur, perinasal encrustation, decreased respiratory rate, body weight loss, and audible respiration. These effects were observed in all groups except for the 68-ppm group (1 h), which only had unkempt hair the last week of the post exposure period and the rats in the 19-ppm group (4 h), which had no clinical signs. The primary gross lesion identified in the animals that died was a red discoloration of the lungs. Rats in the 643-ppm group (1 h) or 166-ppm group (4 h) also had dark purple discoloration of the liver and fluid in the trachea. No gross lesions were observed in the animals that died in the 39- or 71-ppm groups. Microscopic examination of the lungs showed lesions that increased in severity and incidence with increasing

TABLE 7-4 Summary of Mortality in Rats Exposed to Trimethoxysilane by Inhalation

Concentration (ppm)	Sex	Mortality	Day of death (post exposure)
1-h exposure			
68	Male	0/5	Not applicable
	Female	0/5	Not applicable
155	Male	2/5	Days 5 and 9
	Female	3/5	Two deaths on day 7, one on day 8
342	Male	5/5	One on day 7, and twp on days 8 and 9
	Female	5/5	One on day 6, 7, and 9; two on day 10
643	Male	5/5	1 on days 1, 2, and 9 and 2 on day 8
	Females	5/5	1 on days 7, 9, and 13 and 2 on day 8
4-h exposure			
19	Male	0/5	Not applicable
	Female	0/5	Not applicable
39	Male	0/5	0/5
	Female	1/5	One on day 14
71	Male	2/5	One on days 13 and 14
	Female	5/5	One on days 6, 7, 9; two on day 13
166	Male	5/5	One on days 5, 7, and 10; two on day 6
	Female	5/5	One on days 6, 8, and 10; two on day 7

Source: Nachreiner and Dodd 1988.

concentration and exposure duration; however, statistical analysis was not performed. The study author and the pathologist for the study both concluded that pulmonary lesions increased in severity with increasing concentration and exposure duration with animal death caused by lung dysfunction.

Pathologic findings in the lungs of the rats exposed to trimethoxysilane for 1 h included:

- 643 ppm: four males and four females; marked to severe necrotic bronchiolitis in all lungs, squamous metaplasia of bronchiolar epithelium in three lungs, and marked to severe vascular changes (congestion, edema) in all lungs.
- 342 ppm: one male and three females; vascular changes in all lungs, and some degree of bronchial epithelial changes and submucosal fibrosis in all lungs.

- 155 ppm: four males and three females; necrotic bronchiolitis in some lungs, severe atelectasis in one lung, and most vascular and inflammatory lesions were of at least moderate severity.
- 68 ppm: three males and three females; all survived; mild to moderate vascular and inflammatory changes, and considerable variation in severity of lung reaction.

Pathologic findings in the lungs of rats exposed to trimethoxysilane for 4 h included:

- 166 ppm: three males and four females; marked to severe necrotic bronchiolitis in all lungs, and moderate to marked vascular/inflammatory changes in all lungs.
- 71 ppm: one male; necrotic bronchiolitis, congestion, and edema.
- 39 ppm: three males and three females; all rats survived until day 14; necrotic bronchiolitis in four lungs, atelectasis in two lungs, and considerable variability in vascular/inflammatory lesions.
- 19 ppm: three males and three females; all survived; two females had mild inflammatory cells; two males had moderate bronchiolar epithelial cell degeneration.

In this same study, Nachreiner and Dodd (1988) conducted static exposures. Five rats per sex were exposed for 10 or 60 min to a near saturated vapor atmosphere of trimethoxysilane. In the 1-h static exposure, the chamber concentration of trimethoxysilane decreased from 60,000 ppm to 3,000 ppm within the first 22 min while the methanol concentration increased to 111,000 ppm. During the 10-min static exposure, the concentration of trimethoxysilane decreased from 56,000 ppm to 47,000 ppm, and methanol increased to 69,000 ppm. All animals died during or within 2 h post exposure. Clinical signs in these animals included tremors and respiratory difficulty; gross examination showed red discoloration of the lungs and fluid in the trachea.

3.2. Acute Nonlethal

Ocular and dermal irritation studies of trimethoxysilane were conducted in rabbits (Union Carbide 1988). A 4-h application of 0.5 mL of trimethoxysilane to occluded rabbit skin caused moderate to severe erythema, severe edema, and necrosis in all six rabbits tested. Edema was gone by day 14 and erythema by day 7; however, the chemical was given an overall rating of severe irritant because ulceration, scabs, and alopecia remained through day 14. Two of the rabbits were found dead at day 12 but it was unclear if their deaths were related to treatment.

Trimethoxysilane (0.1 mL) placed in the eyes of six rabbits resulted in corneal opacity in three rabbits and iritis and moderate to severe conjunctival

irritation in all rabbits. All lesions resolved by day 7. After 0.01 mL of trimethoxysilane was placed in the eye, five of six rabbits had minor to moderate corneal opacity, and all rabbits had iritis and moderate to severe conjunctival irritation. No corneal lesions were reported when 0.005 mL was tested, but irisitis was observed in four of six rabbits.

3.3. Repeat Exposure Studies

3.3.1. Rats

In a study using GLP, 10 Sprague-Dawley rats per sex were exposed 7 h/day, 5 days/week for 4 weeks to trimethoxysilane at concentrations of 0.5, 5.0, or 10.0 ppm (Breckenridge et al. 1980). Animals were exposed whole body in four 400-L volume chambers. Air flow through the chambers was maintained at 45 L/min. Rats were not provided food or water during exposure. Chamber temperature, humidity, and concentration were measured continually during the exposure. The chamber concentrations were measured hourly by an infrared-gas analyzer. The concentrations were achieved after a 30-min equilibration period. Controls were exposed to filtered room air. During weeks 2 and 3 of treatment, 60% of the high-concentration animals died and 40% of the mid-concentration animals died by the end of the fourth week. No mortalities occurred in the control- or low-concentration groups. Exposure in the high-concentration group was terminated at day 21 and the survivors immediately sacrificed due to the high mortality rate. High- and mid-concentration animals exhibited lung congestion, generalized weakness, and a statistically significant decrease in body weight and food consumption. The low-concentration group was comparable to controls and showed no clinical signs. Histopathologic examination was performed on the control, low-concentration, and high-concentration animals only. All 20 rats in the 10-ppm group had bronchitis and bronchiolitis, whereas none of the rats in the 0.5-ppm and control groups exhibited these effects. Hematology results showed a concentration-dependent increase in red blood cells, hemoglobin, and hematocrit in the mid- and high-concentration animals and a concentration-dependent decrease in the white blood cells in most of the treated animals.

In a study by Union Carbide (1991), Fisher 344 rats were exposed to trimethoxysilane vapor at 0 (control), 0.2 ± 0.05 (standard deviation), 0.9 ± 0.12 (1 ppm), or 4.9 ± 0.34 (5 ppm) for 6 h/day. The rats were exposed for a total of nine exposures over an 11-day period. Ten rats of each sex were tested in the 0.2- and 1-ppm groups, and 15 of each sex in the control- and 5-ppm group. The additional five animals in the latter two groups were to be kept for a post-exposure recovery period; however, mortality was too high in the 5-ppm group (14/15 males and 12/15 females died between days 8 and 12) to allow for a post-exposure observation period. Table 7-5 presents observations at each concentration.

3.3.2. Rats, Mice, Hamsters, and Rabbits

In a repeat exposure study, Sprague-Dawley (BR) rats, (ICR) BR mice, LVG (SYR) hamsters, and New Zealand White rabbits were exposed to trimethoxysilane at concentrations of 0, 10, 25, or 50 ppm for 7 h/day for 5 consecutive days, with a 14-day observation period post exposure (Dow Corning Corp. 1981). Five animals per sex were used in the studies with rats, mice, and hamsters, and two animals per sex were used in the study with rabbits. Table 7-6 presents the mortality data for this study. The investigators calculated 5-day LC_{50} values of 13, 14, 72, and 1 ppm for the rats, mice, hamsters, and rabbits, respectively. The report stated that the rabbits could have had a preexisting viral condition that was exacerbated under study conditions, thus resulting in high mortality. The laboratory had experienced this scenario in other studies with rabbits from the same supplier.

All animals had similar clinical signs of gasping, depression, and nasal discharge (see Table 7-7). In the animals that died, lung congestion, atelectosis, and hemorrhage were observed; however, raw data were not provided. The study author reported that the animals killed at the end of the observation period had the same effects, but they were less severe.

TABLE 7-5 Observations in the Union Carbide (1991) Study of Rats Exposed to Trimethoxysilane

0	0.2 ppm	1 ppm	5 ppm
No clinical signs	Laryngitis in 1/10 males, 2/10 females	Weight loss; increased lung weight; bronchopneumonia (10/10 males; 10/10 females); lymphoid tissue depletion (lymph nodes)	87% mortality; severe irritation (labored breathing, gasping); weight loss; decreased organ weight (spleen, liver, kidney); increased erythrocytes, hemoglobin,, and hematocrit; lymphocytopenia; lymphoid depletion; bronchopneumonia (1/1 male and 2/3 female survivors; 11/14 males and 12/12 females that died)

TABLE 7-6 Mortality Results in Dow Corning Corp. (1981) Study of Trimethoxysilane

Concentration (ppm)	Rats	Mice	Hamsters	Rabbits
0	0/10	0/10	0/10	0/2
10	3/10	5/10	0/10	2/2
25	9/10	4/10	3/10	2/2
50	10/10	10/10	3/10	2/2

TABLE 7-7 Clinical Signs in Dow Corning Corp. (1981) Study of Trimethoxysilane

Concentration (ppm)	Rats	Mice	Hamsters	Rabbits
0	None	None	None	None
10	Depression + Nasal discharge +	Depression + Nasal discharge +	Depression + Nasal discharge +	Depression + Nasal discharge ++
25	Depression + Nasal discharge + Gasping NS	Depression + Nasal discharge + Gasping +	Depression ++ Nasal discharge + Gasping +	Depression ++ Nasal discharge ++ Gasping ++
50	Depression + Nasal discharge + Gasping +	Depression + Nasal discharge + Gasping +	Depression ++ Nasal discharge + Gasping +	Depression ++ Nasal discharge +++ Gasping +++

3.4. Neurotoxicity

No data were available on neurotoxicity of trimethoxysilane.

3.5. Developmental and Reproductive Toxicity

No data were available on the developmental and reproductive toxicity of trimethoxysilane.

3.6. Genotoxicity

Trimethoxysilane was tested for mutagenicity in *Salmonella typhimurium* (TA1535, TA1537, TA98, and TA100) and *Escherichia coli* (wP2) in a reverse mutation assay with and without metabolic activation (Isquith et al. 1987). Positive controls were used. No evidence of mutagenic potential was observed in any assay, and positive controls produced appropriate responses.

3.7. Chronic Toxicity and Carcinogenicity

No chronic toxicity or carcinogenicity studies on trimethoxysilane were available.

3.8. Summary

The data on trimethoxysilane were limited. Rats exposed to trimethoxysilane had 1- and 4-h LC_{50}s of 154 ppm and 60 ppm, respectively (Nachreiner and Dodd 1988). Mortality was observed at concentration of 155 ppm and greater in the 1-h study and at 39 ppm and greater in the 4-h study. Ocular and dermal irri-

tation were present in rabbits when trimethoxysilane was placed in the eyes or occluded on the skin for 4 h (Union Carbide 1988). Repeat exposure studies resulted in mortality at concentrations of 5 ppm or greater in rats after nine exposures over 11 days (Union Carbide 1991) or when exposed for up to 4 weeks (Breckenridge et al. 1980). In another repeat exposure study, hamsters, mice, and rats had similar clinical signs following exposure to trimethoxysilane for 5 days and mortality occurred at 10 ppm or greater in the mice and rats (Dow Corning Corp. 1981). Trimethoxysilane demonstrated no mutagenic potential in a reverse bacterial mutation assay with or without metabolic activation (Isquith et al. 1987).

4. ANIMAL TOXICITY DATA: TETRAMETHOXYSILANE

4.1. Acute Lethality

Groups of 10 male Sprague-Dawley rats were exposed nose-only to tetramethoxysilane at 31, 50, or 88 ppm for 4 h (Dow Corning Corp. 1992). Vapor was generated by bubbling clean dry air through the test material. Rats were exposed nose-only in a chamber designed to contain 10 rats in a radial pattern on two planes of five rats each. Concentration was monitored continuously by long-path gas infrared spectroscopy. Animals were observed for abnormalities several times during the study and during the 2-week recovery period. Body weight was also recorded.

Mortality occurred at 50 and 88 ppm. Nine rats in the 88-ppm group and three in the 50-ppm group died within 7 days post exposure. An LC_{50} of 63 ppm (95% confidence limits 51-78 ppm) was determined by probit analysis. Gasping and coughing were observed in all animals of the 50- and 88-ppm groups during the post-exposure observation period. However, these effects abated within 2 weeks. All of the animals in the 31-ppm group exhibited weight gain by the end of the recovery period. Rats in the 50-ppm group showed initial weight loss but those that survived gained weight by the end of the recovery period. The only survivor in the 88-ppm group also had weight gain after initial weight loss. Necropsy revealed dose-related lung damage that ranged from involvement of small areas of the lobe (five of 10 rats in the 31-ppm group and three of three rats in the 50-ppm group) to involvement of entire lung lobes (5/10 at 31-ppm group and 10/10 at 88-ppm group). Severity and microscopic lesions were not described. The report did not mention any use of control rats.

4.2. Acute Nonlethal

No acute studies were identified that showed nonlethal effects for tetramethoxysilane.

4.3. Repeat Exposure Studies

4.3.1. Rats

Groups of 10 Sprague-Dawley rats per sex were exposed to tetramethoxysilane by inhalation for 6 h/day, 5 days/week for 28 days at vapor concentrations of 0, 1, 5, or 10 ppm (Phase 1) and 0, 15, 30, or 45 ppm (Phase 2) (Kolesar et al. 1989). Exposures were conducted in a 450-L chamber operated under dynamic conditions. Air flow was maintained at approximately 120 L/min, and tetramethoxysilane vapors were created using the glass J-tube method of Miller et al. (1980). Chamber concentration was measured once an hour with a gas chromatograph equipped with a flame-ionization detector. Clinical observations were made daily, body weight was measured twice a week, and food consumption was measured weekly. Blood for hematology and clinical chemistry was collected at the study's termination; however, data were not collected on rats in the 45-ppm group.

All animals exposed at 45 ppm either died or were killed during the 28-day study. No effects were observed in any rats exposed at 0, 1, 5, or 10 ppm. A statistically significant difference was observed in food consumption, body weight, and clinical parameters in rats exposed at 30 ppm. Males exposed at 15 ppm had only a decrease in total protein. No microscopic lesions were found in the respiratory tract or eyes of rats exposed at 1, 5, or 10 ppm. However, at 15 ppm or greater, tetramethoxysilane-related ocular and respiratory tract changes were observed. Changes were most severe in the upper respiratory tract. The lesions included ulceration, desquamation, and inflammation of the respiratory epithelium, with a large amount of exudate in the nasal cavity. Ocular lesions were observed at 15, 30, and 45 ppm. At 30 and 45 ppm, ocular lesions included desquamation of the central corneal epithelium. While effects appeared to be more severe in the 30-ppm group than the 45-ppm group, this was likely a result of the longer duration of exposure experienced by the 30-ppm group due to the high mortality in the 45-ppm group. At 15 ppm, four of 20 rats had minimal acute keratitis with no epithelial desquamation. These lesions were severe at 45 ppm, moderate to severe at 30 ppm, minimal at 15 ppm, and not seen at 10 ppm.

4.4. Neurotoxicity

No data were available on neurotoxicity of tetramethoxysilane in laboratory animals.

4.5. Developmental and Reproductive Toxicity

No data were available on developmental and reproductive toxicity of tetramethoxysilane in laboratory animals.

4.6. Genotoxicity

No data were available on genotoxicity of tetramethoxysilane in laboratory animals.

4.7. Chronic Toxicity and Carcinogenicity

No data were available on chronic toxicity or carcinogenicity of tetramethoxysilane in laboratory animals.

4.8. Summary

There were few animal studies of tetramethoxysilane. Lethality was reported in a study of rats exposed nose-only to tetramethoxysilane at 50 ppm. The only other study was a repeat exposure study in which rats were exposed to tetramethoxysilane at concentrations up to 45 ppm for 28 days. No effects were noted at 10 ppm or less, and minimal effects were observed at 15 ppm indicating a steep dose-response curve.

5. SPECIAL CONSIDERATIONS

5.1. Metabolism and Disposition

No metabolism or disposition studies were available for trimethoxysilane or tetramethoxysilane.

5.2. Mechanism of Toxicity

The exact mechanism of toxicity is not known for trimethoxysilane or tetramethoxysilane. Epithelial tissue is the target tissue for these chemicals, especially in the eye and respiratory tract. Both chemicals appear to have the same toxicologic effects and have similar LC_{50} values in rats.

5.3. Structure-Activity Relationships

Trimethoxysilane and tetramethoxysilane are both organic silanes and are classified as silane esters. They are both used as intermediates in the production of silicone and are structural analogs.

5.4. Other Relevant Information

No additional relevant information was available.

5.4.1. Species Variability

Trimethoxysilane was tested in an inhalation study comparing effects on hamster, rats, mice, and rabbits (Dow Corning Corp. 1981). Rats, mice, and hamsters had similar clinical effects. LC_{50} values in rats and mice exposed to trimethoxysilane for 5 days were also similar; however, the results are questionable because of the validity of having LC_{50} values in a 5-day study. Rabbits exhibited high mortality but it appeared to be from a secondary infection within the population. Little species variability also is expected for tetramethoxysilane because the two chemicals are structural analogs and have similar rat 4-h LC_{50} values (60 ppm for trimethoxysilane and 63 ppm for tetramethoxysilane).

5.4.2. Susceptible Populations

Little human data are available on trimethoxysilane or tetramethoxysilane. Secondary sources indicate that the chemicals are strong ocular irritants in humans, and animal data supports those reports. Animal data also show that both chemicals can cause lung damage; therefore, anyone with compromised lung function would be considered more at risk from exposure to trimethoxysilane or tetramethoxysilane.

5.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). For trimethoxysilane, the value of n was 1.45. That value was derived using the ten Berge formula and the rat mortality data from the acute rat inhalation studies by Nachreiner and Dodd (1988).

The available data on tetramethoxysilane were inadequate to derive an empirical value for n. In the absence of chemical specific data, the default values of n = 3 was applied to extrapolate to shorter durations and n = 1 was applied to extrapolate to longer durations, to provide AEGL values that are protective of human health (NRC 2001).

6. DATA ANALYSIS FOR AEGL-1

6.1. Summary of Human Data Relevant to AEGL-1

No human data were available to determine AEGL-1 values for either trimethoxysilane or tetramethoxysilane.

6.2. Summary of Animal Data Relevant to AEGL-1

Insufficient animal data were available for determining AEGL-1 values for either trimethoxysilane or tetramethoxysilane.

6.3. Derivation of AEGL-1 Values

AEGL-1 values were not derived for trimethoxysilane or tetramethoxysilane because of insufficient data. Although consideration was given to using data from repeat exposure studies to determine AEGL-1 values, both chemicals lack good warning properties based on odor and the values derived would be very low for trimethoxysilane and very similar to AEGL-2 values for tetramethoxysilane.

7. DATA ANALYSIS FOR AEGL-2

7.1. Summary of Human Data Relevant to AEGL-2

No human data were available to determine AEGL-2 values for trimethoxysilane or tetramethoxysilane.

7.2. Summary of Animal Data Relevant to AEGL-2

Only one acute inhalation study on trimethoxysilane was found (Nachreiner and Dodd 1988). Thus, the available data were inadequate for determining AEGL-2 values for trimethoxysilane.

For tetramethoxysilane, the data most relevant to AEGL-2 values was a repeat exposure study in rats (Kolesar et al. 1989). Rats were exposed to tetramethoxysilane at 0, 1, 5, 10, 15, 30, or 45 ppm for 6 h/day, 5 days/week for 28 days. Deaths occurred at 45 ppm. At 30 ppm, nasal cavity ulceration was found in 18 of 20 animals, metaplasia of the lungs in 15 of 20 animals, and bilateral desquamation of the central corneal epithelium. These effects were more severe than the definition of AEGL-2. At 15 ppm, lung lesions, acute inflammation of the nasal epithelium, and acute keratitis were minimal.

7.3. Derivation of AEGL-2 Values

In the absence of sufficient animal data, AEGL-2 values for trimethoxysilane were obtained by taking one-third of the AEGL-3 values. This approach was used in accordance with the Standing Operating Procedures for determining AEGL values (NRC 2001) for chemicals with a steep dose-response curve when data are inadequate for calculating AEGL-2 values.

AEGL-2 values for tetramethoxysilane were based on data from a repeat exposure study in rats (Kolesar et al. 1989). In that study, 15 ppm was the no-effect level for irreversible effects. Time scaling to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to 30 min, 1 h, and 4 h and n = 1 for extrapolation to 8 h. The 30-min value was adopted as the 10-min value because extrapolating from an exposure of 4 h or more to 10-min exposure is not recommended (NRC 2001). A total uncertainty factor of 30 was applied. A factor of 3 was used for interspecies differences rather than 10 because: (1) there are no human data to compare with the animal data; (2) comparative studies of trimethoxysilane (a structural and toxicologic analog of tetramethoxysilane) found similar effects over the same exposure concentration range (10-50 ppm) in rats, mice, and hamsters, suggesting that variability in response did not exceed a factor of 3; (3) the effects observed in animals included ocular irritation and lesions which have been observed in humans, suggesting a similar mode of action across species; and (4) the point of departure was based on a repeated-exposure study. A default value of 10 (NRC 2001) was used for intraspecies variability because there were no data to estimate human variability and it was not clear that tetramethoxysilane acts as a simple chemical irritant in the lungs. AEGL-2 values for trimethoxysilane and tetramethoxysilane are presented in Table 7-8.

8. DATA ANALYSIS FOR AEGL-3

8.1. Summary of Human Data Relevant to AEGL-3

No human data were available to determine AEGL-3 values.

8.2. Summary of Animal Data Relevant to AEGL-3

Rat inhalation studies were used to derive AEGL-3 values for both trimethoxysilane and tetramethoxysilane. For trimethoxysilane, LC_{50} data were available from an inhalation study of rats exposed to trimethoxysilane at concentrations of 19, 39, 71, or 166 ppm for 4 h or at 68, 155, 342, or 643 ppm for 1 h (Nachreiner and Dodd 1988). For tetramethoxysilane, LC_{50} data were available from a study in rats exposed nose-only to tetramethoxysilane at concentrations of 31, 50 or 88 ppm for 4 h (Dow Corning Corp. 1992).

8.3. Derivation of AEGL-3 Values

8.3.1. AEGL-3 Values for Trimethoxysilane

AEGL-3 values for trimethoxysilane were derived from the 1-h and 4-h LC_{50} data from the study by Nachreiner and Dodd (1988). Time scaling to dif-

ferent exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Mortality data for male and female rats were combined and the ten Berge formula was used to calculate an n value of 1.45 (ten Berge et al. 1986). Points of departure were the calculated LC_{01} values (lethal concentration, 1% lethality) of 263 ppm for 10 min, 123 ppm for 30 min, 76.3 ppm for 1 h, 29.3 ppm for 4 h, and 18.2 ppm for 8 h. A total uncertainty factor of 30 was used. A factor of 3 was used for interspecies differences because similar effects were observed in rats, mice, and hamsters exposed at the same concentrations in a 5-day inhalation study (Dow Corning Corp. 1981). A default value of 10 was used for intraspecies variability because there were no data to estimate human variability and was not clear that trimethoxysilane is acts as a simple chemical irritant in the lungs (NRC 2001). AEGL-3 values for trimethoxysilane are presented in Table 7-9.

8.3.2. AEGL-3 Values for Tetramethoxysilane

AEGL-3 values for tetramethoxysilane were derived from a study in rats exposed nose-only to tetramethoxysilane concentrations of 31, 50 or 88 ppm for 4 h (Dow Corning Corp. 1992). The calculated LC_{50} was 63 ppm. The data were analyzed using the EPA Benchmark Dose Calculation Software (EPA 2005) to determine a $BMCL_{05}$ of 26 ppm. A BMC_{01} of 30 ppm also was calculated, but was not used because it was greater than the $BMCL_{05}$. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). The default values of n = 3 for extrapolation to 30 min and 1 h and n = 1 for

TABLE 7-8 AEGL-2 Values for Trimethoxysilane and Tetramethoxysilane

10 min	30 min	1 h	4 h	8 h
Trimethoxysilane				
2.9 ppm (15 mg/m^3)	1.4 ppm (7.0 mg/m^3)	0.83 ppm (4.2 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.20 ppm (1.0 mg/m^3)
Tetramethoxysilane				
1.1 ppm (6.8 mg/m^3)	1.1 ppm (6.8 mg/m^3)	0.91 ppm (5.6 mg/m^3)	0.57 ppm (3.5 mg/m^3)	0.38 ppm (2.4 mg/m^3)

TABLE 7-9 AEGL-3 Values for Trimethoxysilane and Tetramethoxysilane

10 min	30 min	1 h	4 h	8 h
Trimethoxysilane				
8.8 ppm (44 mg/m^3)	4.1 ppm (21 mg/m^3)	2.5 ppm (13 mg/m^3)	0.98 ppm (5.0 mg/m^3)	0.61 ppm (3.1 mg/m^3)
Tetramethoxysilane				
1.7 ppm (11 mg/m^3)	1.7 ppm (11 mg/m^3)	1.4 ppm (8.7 mg/m^3)	0.87 ppm (5.7 mg/m^3)	0.43 ppm (2.7 mg/m^3)

extrapolation to 8 h were used because of insufficient data to calculate an empirical value. The 30-min value was adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001). A total uncertainty factor of 30 was used. A factor 3 was used for interspecies differences because: (1) there are no human data to compare with the animal data; (2) comparative studies of trimethoxysilane (a structural and toxicologic analog of tetramethoxysilane) found similar effects over the same exposure concentration range (10-50 ppm) in rats, mice, and hamsters, suggesting that variability in response did not exceed a factor of 3; (3) the effects observed in animals included ocular irritation and lesions which have been observed in humans, suggesting a similar mode of action across species; and (4) the point of departure was based on a repeated exposure study. A default value of 10 was used for intraspecies variability because there were no data to estimate human variability and it was not clear that tetramethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001). AEGL-3 values for tetramethoxysilane are presented in Table 7-9.

9. SUMMARY OF AEGLS

9.1. AEGL Values and Toxicity End Points

AEGL values for trimethoxysilane and tetramethoxysilane are provided in Table 7-10. Data on both chemicals were insufficient for deriving AEGL-1 values. The data on trimethoxysilane were also insufficient for deriving AEGL-2, so values were calculated by taking one-third of the AEGL-3 values. AEGL-3 values for trimethoxysilane were derived from LC_{01} values calculated from a rat inhalation study (Nachreiner and Dodd 1988).

AEGL-2 values for tetramethoxysilane were derived from a repeat exposure study (Kolesar et al. 1989), in which 15 ppm was the no-effect level for irreversible effects. AEGL-3 values for tetramethoxysilane were derived from estimates of a $BMCL_{05}$ on the basis of 4-h LC_{50} data (Dow Corning Corp. 1992).

9.2. Comparisons with Other Standards and Guidelines

Few standards have been established for either trimethoxysilane or tetramethoxysilane (see Tables 7-11 and 7-12). Emergency Response Planning Guidelines established by the American Industrial Hygiene Association (AIHA) are available for both chemicals (AIHA 2005), but documentation from all the sources used to develop those guidelines could not be obtained to understand the basis for those values. Trimethoxysilane has a Workplace Environmental Exposure Level (WEEL) of 0.05 ppm (AIHA 2005). That value was developed using animal data from longer term studies. The no-observed-effect level was reported to be 0.2 ppm in a 9-day exposure study in rats (Union Carbide 1991), and it was noted that 0.5 ppm resulted in decreased food consumption and weight gain in a 4-week study (Breckenridge et al.. 1980). AIHA concluded a WEEL of 0.05 ppm would be adopted as an 8-h time-weighted average (TWA).

TABLE 7-10 AEGL Values for Trimethoxysilane and Tetramethoxysilane

Classification	10 min	30 min	1 h	4 h	8 h
Trimethoxysilane					
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	2.9 ppm (15 mg/m^3)	1.4 ppm (7.0 mg/m^3)	0.83 ppm (4.2 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.20 ppm (1.0 mg/m^3)
AEGL-3 (lethality)	8.8 ppm (44 mg/m^3)	4.1 ppm (21 mg/m^3)	2.5 ppm (13 mg/m^3)	0.98 ppm (5.0 mg/m^3)	0.61 ppm (3.1 mg/m^3)
Tetramethoxysilane					
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	1.1 ppm (6.8 mg/m^3)	1.1 ppm (6.8 mg/m^3)	0.91 ppm (5.6 mg/m^3)	0.57 ppm (3.5 mg/m^3)	0.38 ppm (2.4 mg/m^3)
AEGL-3 (lethality)	1.7 ppm (11 mg/m^3)	1.7 ppm (11 mg/m^3)	1.4 ppm (8.7 mg/m^3)	0.87 ppm (5.4 mg/m^3)	0.43 ppm (2.7 mg/m^3)

Abbreviations: NR, not recommended

TABLE 7-11 Extant Standards and Guidelines for Trimethoxysilane

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.9 ppm (15 mg/m^3)	1.4 ppm (7.0 mg/m^3)	0.83 ppm (4.2 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.20 ppm (1.0 mg/m^3)
AEGL-3	8.8 ppm (44 mg/m^3)	4.1 ppm (21 mg/m^3)	2.5 ppm (13 mg/m^3)	0.98 ppm (5.0 mg/m^3)	0.61 ppm (3.1 mg/m^3)
ERPG-1 (AIHA)[a]			0.5 ppm (2.5 mg/m^3)		
ERPG-2 (AIHA)			2.0 ppm (10 mg/m^3)		
ERPG-3 (AIHA)			5.0 ppm (25 mg/m^3)		
WEEL (AIHA)[b]					0.05 ppm (0.25 mg/m^3)

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AHIA 2005]).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

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

[b]WEEL (workplace environmental exposure level, American Industrial Hygiene Association [AIHA 2005] is the 8-h time-weighted average concentration allowed in a normal 8-h workday.

TABLE 7-12 Extant Standards and Guidelines for Tetramethoxysilane

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.1 ppm (6.8 mg/m^3)	1.1 ppm (6.8 mg/m^3)	0.91 ppm (5.6 mg/m^3)	0.57 ppm (3.5 mg/m^3)	0.38 ppm (2.4 mg/m^3)
AEGL-3	1.7 ppm (11 mg/m^3)	1.7 ppm (11 mg/m^3)	1.4 ppm (8.7 mg/m^3)	0.87 ppm (5.4 mg/m^3)	0.43 ppm (2.7 mg/m^3)
ERPG-1 (AHIA)[a]			N/A		
ERPG-2 (AHIA)			10 ppm (63 mg/m^3)		
ERPG-3 (AHIA)			20 ppm (125 mg/m^3)		
TLV-TWA (ACGIH)[b]					1 ppm (6 mg/m^3)
REL-TWA (NIOSH)[c]					1 ppm (6 mg/m^3)
MAC (The Netherlands)[d]					1 ppm (6 mg/m^3)

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association [AHIA 2005]).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

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

[b]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2005]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]REL-TWA (recommended exposure limit - time weighted average, National Institute for Occupational Safety and Health [NIOSH 2010]) is defined analogous to the ACGIH TLV-TWA.

[d]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Ministry of Social Affairs and Employment, The Hague, The Netherlands [MSZW 2004]) is defined analogous to the ACGIH TLV-TWA.

For tetramethoxysilane, 1 ppm was established by the National Institute for Occupational Safety and Health (NIOSH) as the recommended exposure limit (REL-TWA) (NIOSH 2010), by the American Conference of Governmental Industrial Hygienists (ACGIH) as the threshold limit value (TLV-TWA) (ACGIH 2005), and as the Dutch maximum acceptable concentration (MAC) (MSZW 2004). The ACGIH TLV-TWA was recommended in 1981 and was based on an undated, unpublished report (Frant et al.) available in the Netherlands and the accepted value is currently under review by the ACGIH TLV committee. NIOSH indicated that a concentration of 1 ppm would reduce risks of severe ocular effects. No information was obtained on how the Dutch MAC was derived.

9.3. Data Adequacy and Research Needs

Many data gaps were identified for both trimethoxysilane and tetramethoxysilane. Inadequate data exists for genotoxicity, reproductive and developmental toxicity, chronic toxicity, and carcinogenicity. Because of similar modes of action and similar LC_{50} values, testing just one of the chemicals and applying the data to both could possibly reduce the number of animal studies required.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR TRIMETHOXYSILANE

Derivation of AEGL-1 Values

Inadequate data exist for deriving AEGL-1 values for trimethoxysilane.

Derivation of AEGL-2 Values

The available data were inadequate for deriving AEGL-2 values. Because of the steep dose response curve in the acute LC_{50} study (Nachreiner and Dodd 1988), AEGL-2 values were determined by reducing the AEGL-3 values by one-third (NRC 2001).

10-min AEGL-2: 8.8 ppm ÷ 3 = 2.9 ppm (15 mg/m^3)

30-min AEGL-2: 4.1 ppm ÷ 3 = 1.4 ppm (7.0 mg/m^3)

1-h AEGL-2: 2.5 ppm ÷ 3 = 0.83 ppm (4.2 mg/m^3)

4-h AEGL-2: 0.98 ppm ÷ 3 = 0.33 ppm (1.7 mg/m^3)

8-h AEGL-2: 0.61 ppm ÷ 3 = 0.20 ppm (1.0 mg/m^3)

Derivation of AEGL-3 Values

Key study: Nachreiner, D.J., and D.E. Dodd. 1988. Trimethoxysilane: Acute Vapor Inhalation Toxicity Study in Rats. Project Report No. 50-147. Union Carbide, Bushy Run Research Center.

Toxicity end point: Calculated LC_{01} values from rat 1-h and 4-h data (sexes combined)

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986)
n = 1.45 (0.99-1.91)

	10 min	30 min	1 h	4 h	8 h
LC_{01}	263 ppm	123 ppm	76.3 ppm	29.3 ppm	18.2 ppm
LC_{50}	533 ppm	250 ppm	155 ppm	59.4 ppm	36.8 ppm

Uncertainty factors:	3 for interspecies differences 10 for intraspecies variability
10-min AEGL-3:	263 ppm ÷ 30 = 8.8 ppm (44 mg/m^3)
30-min AEGL-3:	123 ppm ÷ 30 = 4.1 ppm (21 mg/m^3)
1-h AEGL-3:	76.3 ppm ÷ 30 = 2.5 ppm (13 mg/m^3)
4-h AEGL-3:	29.3 ppm ÷ 30 = 0.98 ppm (5.0 mg/m^3)
8-h AEGL-3:	18.2 ppm ÷ 30 = 0.61 ppm (3.1 mg/m^3)

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR TRIMETHOXYSILANE

Derivation Summary for Trimethoxysilane

AEGL-1 VALUES

Inadequate data exist for deriving AEGL-1 values for trimethoxysilane. Absence of AEGL-1 values does not indicate that exposure below AEGL-2 levels is safe.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
2.9 ppm	1.4 ppm	0.83 ppm	0.33 ppm	0.20 ppm

Data adequacy: The available data were inadequate for deriving AEGL-2 values. Because of the steep dose response curve in the acute LC_{50} study (Nachreiner and Dodd 1988), AEGL-2 values were determined by reducing the AEGL-3 values by one-third (NRC 2001).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
8.8 ppm	4.1 ppm	2.5 ppm	0.98 ppm	0.61 ppm

Key Reference: Nachreiner, D.J., and D.E. Dodd. 1988. Trimethoxysilane: Acute Vapor Inhalation Toxicity Study in Rats. Project Report No. 50-147. Union Carbide, Bushy Run Research Center, Export,PA.

Test Species/Strain/Number: Rat, Sprague-Dawley, 5 males and 5 females per concentration

Exposure route/Concentrations/Durations: Inhalation; 19, 39, 71, or 166 ppm for 4 h and 68, 155, 342, or 643 for 1 h

Effects:

19 ppm: no deaths or clinical signs; lung lesions ranged from mild infiltrate of inflammatory cells to congestion and edema.

39 ppm: 1/10 deaths; atelectasis in two lungs; bronchial lesions ranging from fibrosis to necrosis.

71 ppm: 7/10 deaths; necrotic bronchiolitis, congestion, edema, and hemorrhage in lungs.

166 ppm: 10/10 deaths; marked to severe necrotic bronchiolitis; moderate to marked vascular and inflammatory changes in all lungs.

(Continued)

AEGL-3 VALUES Continued

End point/Concentration/Rationale: Calculated LC_{01} values
Uncertainty factors/Rationale: Interspecies: 3, rats, mice, and hamsters had similar clinical signs and the rate of mortality was similar among rats and mice in a subchronic study (Dow Corning Corp. 1981). Intraspecies: 10, no data were available to estimate human variability and it was not clear that trimethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001).
Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: $C^n \times t = k$ (ten Berge et al. 1986), where n = 1.45
Data adequacy: Adequate for deriving AEGL-3 values

APPENDIX C

DERIVATION OF AEGL VALUES FOR TETRAMETHOXYSILANE

Derivation of AEGL-1 Values

Inadequate data exist for deriving AEGL-1 values for tetramethoxysilane.

Derivation of AEGL-2 Values

Key study:	Kolesar, G.B., W.H. Siddiqui, R.G. Geil, R.M. Malczewski, and E.J. Hobbs. 1989. Subchronic inhalation toxicity of tetramethoxysilane in rats. Fundam. Appl. Toxicol. 13(2):285-295.
Toxicity end point:	No-effect level for irreversible effects of 15 ppm
Time scaling:	$C^n \times t = k$ n = 3 for extrapolating to 30 min, 1 h, and 4 h $(15 \text{ ppm})^3 \times 6 \text{ h} = 20{,}250 \text{ ppm}$ n = 1 for extrapolating to 8-h $(15 \text{ ppm})^1 \times 6 \text{ h} = 90 \text{ ppm}$
Uncertainty factors:	3 for interspecies differences 10 for intraspecies variability
10-min AEGL-2:	1.1 ppm (6.8 mg/m^3) Set equivalent to 30-min AEGL-2 value because extrapolating from 4 h to 10 min is not recommended (NRC 2001)
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 20{,}250 \text{ ppm-h}$ $C^3 = 40{,}500 \text{ ppm}$ C = 34.34 34.34 ÷ 30 = 1.1 ppm (6.8 mg/m^3)
1-h AEGL-2:	$C^3 \times 1 \text{ h} = 20{,}250 \text{ ppm-h}$ $C^3 = 20{,}250 \text{ ppm}$ C = 27.26 ppm 27.26 ppm ÷ 30 = 0.91 ppm (5.6 mg/m^3)

4-h AEGL-2:	$C^3 \times 4$ h = 20,250 ppm-h C^3 = 5,062.5 ppm C = 17.17 17.17 ppm ÷ 30 = 0.57 ppm (3.5 mg/m^3)
8-h AEGL-2:	$C^1 \times 8$ h = 90 ppm-h C^1 = 11.25 ppm 11.25 ppm ÷ 30 = 0.38 ppm (2.4 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Dow Corning Corp. 1992. Initial Submission: The Acute Vapor Inhalation Toxicity of Tetramethoxysilane and Trimethoxysilane with Rats (Final Report) with Cover Letter Dated 040992. Document ID No. 88920001842; Microfiche No. OTS0539103.
Toxicity end point:	4-h LC_{50} rat data; a $BMCL_{05}$ of 26 ppm was used as the point of departure for AEGL-3 values (EPA Benchmark Calculation Dose Software, Version 1.3.2)
Time scaling:	$C^n \times t = k$ n = 3 for extrapolating to 30-min and 1-h $(26 \text{ ppm})^3 \times 4$ h = 70,000 ppm n = 1 for extrapolating to 8-h $(26 \text{ ppm})^1 \times 4$ h = 104 ppm
Uncertainty factors:	3 for interspecies differences 10 for intraspecies variability
10-min AEGL-3:	1.7 ppm (11 mg/m^3) Set equivalent to 30-min AEGL-3 value because extrapolating from 4 h to 10 min is not recommended (NRC 2001)
30-min AEGL-3:	$C^3 \times 0.5$ h = 70,000 ppm-h C^3 = 140,000 ppm C = 52 52 ÷ 30 = 1.7 ppm (11 mg/m^3)

1-h AEGL-3:	$C^3 \times 1$ h = 70,000 ppm-h C^3 = 70,000 ppm C = 41 ppm 41 ppm ÷ 30 = 1.4 ppm (8.7 mg/m^3)
4-h AEGL-3:	C = 26 ppm 26 ppm ÷ 30 = 0.87 ppm (5.4 mg/m^3)
8-h AEGL-3:	$C^1 \times 8$ h = 104 ppm-h C^1 = 13 ppm C = 13 ppm 13 ppm ÷ 30 = 0.43 ppm (2.7 mg/m^3)

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR TETRAMETHOXYSILANE

Derivation Summary for Tetramethoxysilane

AEGL-1 VALUES

Inadequate data exist for deriving AEGL-1 values for tetramethoxysilane. Absence of AEGL-1 values does not indicate that exposure below AEGL-2 values is safe.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.1 ppm	1.1 ppm	0.91 ppm	0.57 ppm	0.38 ppm

Key reference: Kolesar, G.B., W.H. Siddiqui, R.G. Geil, R.M. Malczewski, and E.J. Hobbs. 1989. Subchronic inhalation toxicity of tetramethoxysilane in rats. Fundam. Appl. Toxicol. 13(2):285-295.

Test species/Strain/Number: Rat, Sprague-Dawley, 10 males and 10 females per concentration

Exposure route/Concentrations/Durations: Inhalation; 0, 1, 5, or 10 ppm (Phase 1) and 0, 15, 30, or 45 ppm (Phase 2); 6 h/day, 5 days/week for 28 days

Effects:
45 ppm: mortality (20/20)
30 ppm: ulceration in nasal cavity (18/20), squamous lung metaplasia (15/20), bilateral corneal desquamation of epithelium.
15 ppm: no lung lesions, minimal acute keratitis in corneal epithelium.
≤ 10 ppm: no lesions.

End point/Concentration/Rationale: 15 ppm was the no-effect level for irreversible effects

Uncertainty factors/Rationale:

Interspecies: 3, rats, mice, and hamsters had similar clinical signs and the rate of mortality was similar among rats and mice in a subchronic study of trimethoxysilane, a structural analog of tetramethoxysilane (Dow Corning Corp. 1981).

Intraspecies: 10, no data were available to estimate human variability and it was not clear that tetramethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to 30 min, 1 h, and 4 h and n = 1 for extrapolation to 8 h. The 30-min AEGL-2 value was adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001).

Data adequacy: Adequate for deriving AEGL-2 values

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.7 ppm	1.7 ppm	1.4 ppm	0.87 ppm	0.43 ppm

Key reference: Dow Corning Corp. 1992. Initial Submission: The Acute Vapor Inhalation Toxicity of Tetramethoxysilane and Trimethoxysilane with Rats (Final Report) with Cover Letter Dated 040992. Document ID No. 88-920001842; Microfiche No. OTS0539103.

Test species/Strain/Number: Rat; Sprague-Dawley; 10 males per concentration

Exposure route/Concentrations/Durations: Inhalation; 31, 50, or 88 ppm for 4 h

Effects:
31 ppm: no deaths or no clinical signs.
50 ppm: 3/10 deaths, gasping/coughing post exposure, lung damage.
88 ppm: 9/10 deaths, gasping/coughing post exposure, more wide-spread lung damage.

End point/Concentration/Rationale: Lethality; $BMCL_{05}$ of 26 ppm determined using EPA Benchmark Database Software

Uncertainty factors/Rationale:

Interspecies: 3, rats, mice, and hamsters had similar clinical signs and the rate of mortality was similar among rats and mice in a subchronic study of trimethoxysilane, a structural analog of tetramethoxysilane (Dow Corning Corp. 1981).

Intraspecies: 10, no data were available to estimate human variability and it was not clear that tetramethoxysilane acts as a simple chemical irritant in the lungs (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986), where n = 3 for extrapolation to 30 min and 1 h and n = 1 for extrapolation to 8 h. The 30-min AEGL-3 value is adopted as the 10-min value because extrapolating from 4 h to 10 min is not recommended (NRC 2001).

Data adequacy: Adequate for deriving AEGL-3 values

APPENDIX E

TIME SCALING FOR TRIMETHOXYSILANE

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and its toxicologic and pharmacologic properties. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC 1993) or Haber's Rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). According to this concept, exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is dependent equally on the concentration and the exposure duration.

However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. The relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific, and even a toxic-end-point specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship

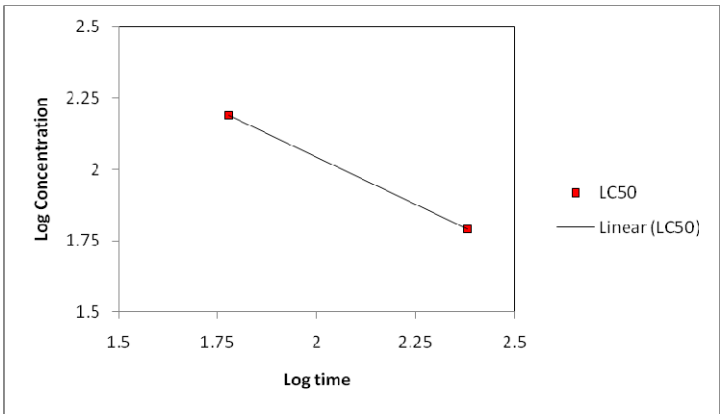


FIGURE E-1 Regression Plot of LC_{50} Values in Rats from Study by Nachreiner and Dodd (1988).

between exposure concentration and exposure duration for a given chemical and for a specific health-effect end point. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of C vs. t yields a progressive decrease in the slope of the curve.

To calculate n for trimethoxysilane, a regression plot of LC_{50} values was derived using the concentration specific 60- and 240-min LC_{50} values in rats reported by Nachreiner and Dodd (1988). The LC_{50} values were analyzed using a linear regression analysis of the log-log transformation of a plot of C vs. t to derive a value of n for trimethoxysilane (see Figure E-1). The value of n for trimethoxysilane is 1.45.

APPENDIX F

CATEGORY PLOTS FOR TRIMETHOXYSILANE AND TETRAMETHOXYSILANE

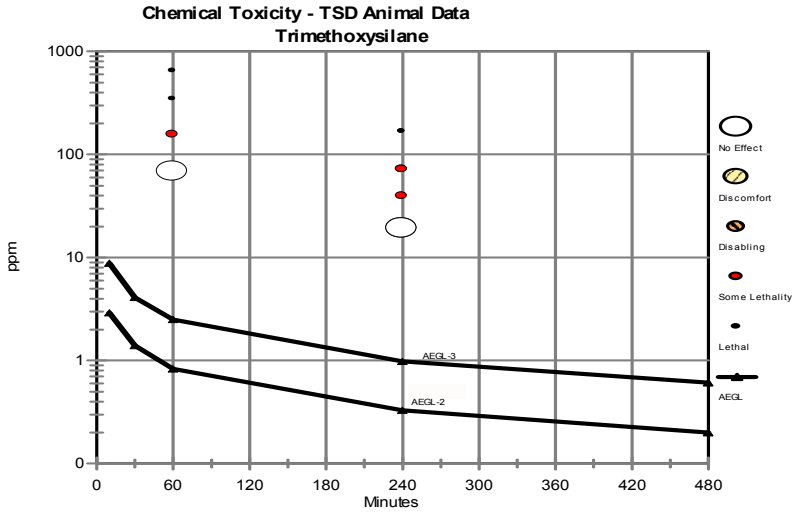


FIGURE F-1 Category plot of toxicity data and AEGL values for trimethoxysilane.

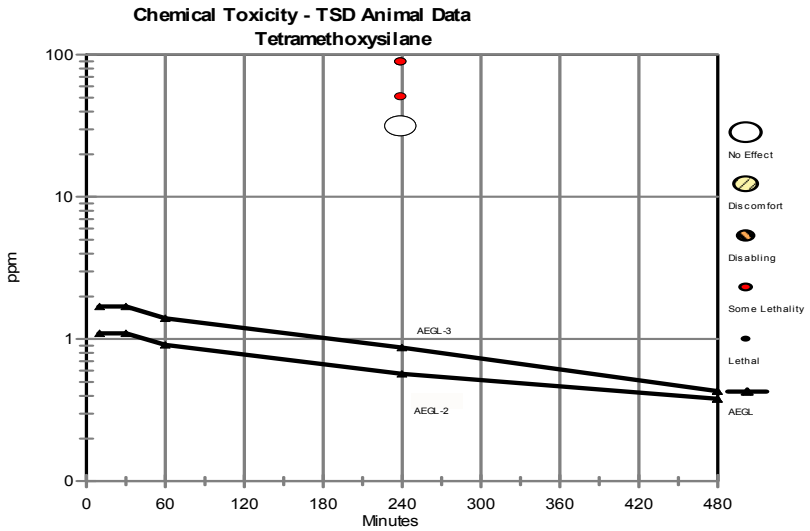


FIGURE F-2 Category plot of toxicity data and AEGL values for tetramethoxysilane.

APPENDIX G

BENCHMARK CALCULATIONS FOR TETRAMETHOXYSILANE

The benchmark calculations for tetramethoxysilane are based on a 4-h acute LC_{50} inhalation study (Dow Corning Corp. 1992). For the derivation of AEGL-3, the $BMCL_{05}$ of 26 ppm was used.

$BMCL_{05}$ = 26 ppm
BMC_{01} = 30 ppm

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\DATA\TETRAMETHOXYSILANE.(d)
Gnuplot Plotting File: C:\BMDS\DATA\TETRAMETHOXYSILANE.plt
Thu Jan 12 10:41:03 2006

BMDS MODEL RUN

The form of the probability function is:

P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose))

where, CumNorm(.) is the cumulative normal distribution function

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -11.5792
Slope = 2.85911

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

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

Parameter Estimates

Variable	Estimate	Standard error
Background	0	NA
Intercept	-14.29	4.18256
Slope	3.49447	1.02457

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	-9.35947			
Fitted model	-9.50533	0.291706	1	0.5891
Reduced model	-20.1904	21.6618	2	<0.0001

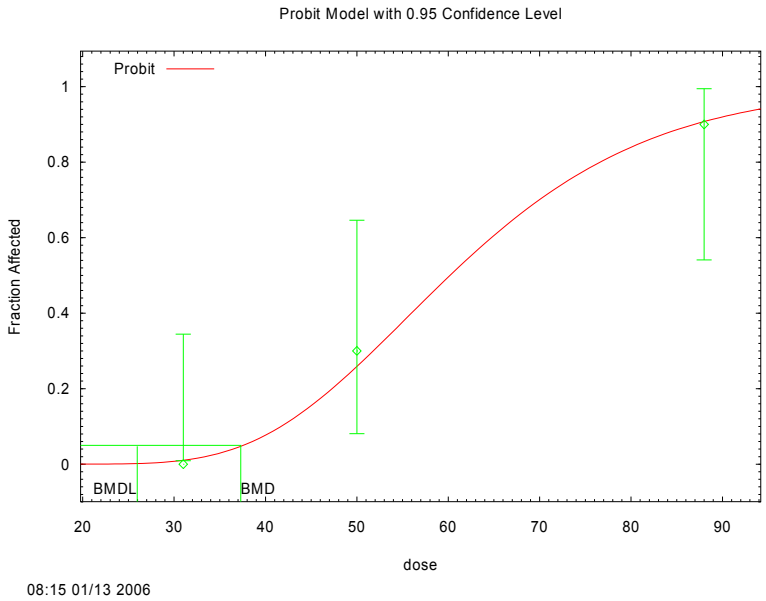
AIC: 23.0107

Goodness of Fit

		Scaled			
Dose	Estimated probability	Expected	Observed	Size	Residual
31.0000	0.0110	0.110	0	10	-0.3337
50.0000	0.2678	2.678	3	10	0.23
88.0000	0.9124	9.124	9	10	-0.1392

Chi-square = 0.18; DF = 1; P-value = 0.6683

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 37.2855
BMDL = 25.9763



8

Trimethylbenzenes[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 Carol Wood (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Manager John P. Hinz (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

Trimethylbenzene (TMB) isomers, including 1,3,5-, 1,2,4-, and 1,2,3-TMB, are common components of fuels and mixed hydrocarbon solvents (Delic et al. 1992). Together with other compounds of the same empirical formula, these flammable and explosive hydrocarbons are referred to as the C_9 aromatics. TMB isomers are clear, colorless liquids that are insoluble in water (O'Neil et al. 2001). Little difference in toxicity has been observed between the TMB isomers. Because occupational exposures are likely to involve more than one isomer, regulatory standards are for the individual isomers and any mixture thereof.

For derivation of AEGL values, all available data on the individual TMB isomers were considered. The most appropriate end point was used as the point of departure for deriving values for each AEGL tier. Therefore, even though the point of departure might be based on data from an individual isomer, the resulting AEGL values are considered applicable to all three TMB isomers.

Human data were not available for derivation of AGEL values. No symptoms were reported at the concentrations tested in pharmacokinetic studies, and no case reports of human intoxication with the pure materials were found.

The most appropriate animal data for deriving AEGL-1 values were from neurotoxicity studies in rats exposed to 1,2,4-, 1,3,5-, or 1,2,3-TMB for 4 h (Korsak et al. 1995; Korsak and Rydzyński 1996). The effective concentration (EC_{50}) values calculated on the basis of decrements in rotarod performance were 954, 963, and 768 ppm, respectively, indicating little difference in the effect level between the isomers. The average EC_{50} of 900 ppm for mild neurologic effects for the three isomers was chosen as the point of departure. A total uncer-

tainty factor of 10 was used. A factor of 3 for interspecies differences was used because the mechanism of action for hydrocarbon narcosis is not expected to differ between rats and humans, and a factor of 3 was applied for intraspecies variability because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (NRC 2001). Because the point of departure is based on a systemic effect, values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-min and 1-h durations and n = 1 for the 8-h duration. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-min values should not be scaled from experimental exposure durations of 4 h or longer. Therefore, the 30-min AEGL-1 value was adopted as the 10-min value.

Few data were available for deriving AEGL-2 values. Rats repeatedly exposed to 1,2,4-TMB at 2,000 ppm for 6 h exhibited irritation, respiratory difficulty, lethargy, and tremors (Gage 1970); therefore, 2,000 ppm was chosen as the basis for deriving the AEGL-2 values. That point of departure also is supported by the weight of evidence on neurologic deficits measured at this concentration (Korsak et al. 1995; Korsak and Rydzyński 1996). The point of departure might not be a no-effect-level for AEGL-2 values, because the effects could lead to an impaired ability to escape. However, because the study involved repeated exposures, 2,000 ppm was considered a conservative estimate of effects for a single exposure. A total uncertainty factor of 10 was applied, which included a factor 3 for interspecies differences and 3 for intraspecies variability. Use of larger uncertainty factors was unnecessary because the mechanisms for irritation and narcosis are not expected to differ between humans and animals. Values were scaled using the same method used to derive AEGL-1 values, and the 30-min AEGL-2 value was adopted as the 10-min value.

Data were insufficient to derive AEGL-3 values for TMB. AEGL values for TMB are presented in Table 8-1.

1. INTRODUCTION

Trimethylbenzene (TMB) isomers include 1,3,5-, 1,2,4-, and 1,2,3-TMB, which are common components of motor vehicle and aviation fuels and mixed hydrocarbon solvents (Delic et al. 1992). Together with other compounds of the same empirical formula, these substances are referred to as the C_9 aromatics. The primary hazards associated with these compounds are fire and explosion. TMB isomers are clear, colorless liquids that are insoluble in water (O'Neil et al. 2001). 1,2,4-TMB is purified by superfractionation and is used as a component of liquid scintillation cocktails (Earhart and Komin 2000). The 1,3,5- and 1,2,3-TMB isomers are produced synthetically and the derivatives are used in specialty solvents (Delic et al. 1992; Earhart and Komin 2000).

TABLE 8-1 AEGL Values for Trimethylbenzenes

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	180 ppm (890 mg/m^3)	180 ppm (890 mg/m^3)	140 ppm (690 mg/m^3)	90 ppm (440 mg/m^3)	45 ppm (220 mg/m^3)	Average ED_{50} for rotarod performance after 4 h (Korsak et al. 1995; Korsak and Rydzyński 1996).
AEGL-2 (disabling)	460 ppm (2,300 mg/m^3)	460 ppm (2,300 mg/m^3)	360 ppm (1,800 mg/m^3)	230 ppm (1,100 mg/m^3)	150 ppm (740 mg/m^3)	Ocular and nasal irritation and lethargy in rats exposed at 2,000 ppm for 6 h (Gage 1970).
AEGL-3 (lethal)	NR	NR	NR	NR	NR	

Abbreviations: NR = not recommended

Chemical and physical properties of the TMB isomers are presented in Table 8-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human fatalities or acute poisoning from TMB were found.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Awareness

AIHA (1995) reported odor detection levels or "concentrations" of 2.4 ppm for 1,2,4-TMB and 2.2 ppm for 1,3,5-TMB from acceptable sources after a critique of the data. No odor threshold value for 1,2,3-TMB was found.

2.2.2. Case Reports

No reports of injury or illness from accidental or intentional exposure to TMB isomers were found.

TABLE 8-2 Chemical and Physical Properties of Trimethylbenzenes

Parameter	1,3,5-TMB	1,2,4-TMB	1,2,3-TMB	Reference
Synonyms	Mesitylene	Pseudocumene	Hemimellitene	Delic et al. 1992
CAS registry no.	108-67-8	95-63-6	526-73-8	
Chemical formula	C_9H_{12}	C_9H_{12}	C_9H_{12}	Delic et al. 1992
Molecular weight	120.19	120.19	120.19	Earhart and Komin 2000
Physical state	Liquid	Liquid	Liquid	Delic et al. 1992
Melting point	-44.8°C	-43.78°C	—	O'Neil et al. 2001
Boiling point	164°C	169°C	176°C	Delic et al. 1992
Density Vapor (air =1) Liquid (water =1)	 -0.8651 g/cm^3 at 20°C	 4.15 0.8758 g/cm^3 at 20°C	 4.1 0.8944 g/cm^3 at 20°C	 Delic et al. 1992 Earhart and Komin 2000
Solubility in water	Practically insoluble	Practically insoluble	—	O'Neil et al. 2001
Vapor pressure	1.5 mm Hg 25°C	2.03 mm Hg 25°C	2.5 mm Hg 25°C	EPA 1987
Flash point	43.0°C	46.0°C	51.0°C	Earhart and Komin 2000
Flammability limits (% in air)	0.88	0.88	0.88	Henderson 2001
Conversion factors	1 ppm = 4.92 mg/m^3 1 mg/m^3 = 0.203 ppm	1 ppm = 4.92 mg/m^3 1 mg/m^3 = 0.203 ppm	1 ppm = 4.92 mg/m^3 1 mg/m^3 = 0.203 ppm	Delic et al. 1992

2.2.3. Epidemiologic Studies and Occupational Exposures

No epidemiologic data specifically on TMB exposure were found. Occupational exposures usually involve a complex mixture of hydrocarbons including dozens of related aromatic and aliphatic organic chemicals.

Concentrations of a variety of compounds were measured in six areas of an offset printing shop to estimate emission of volatile organic compounds (Wadden et al. 1995). Concentrations of 1,3,5-, 1,2,4-, and 1,2,3-TMB ranged from 1.63-3.68 mg/m^3 (0.33-0.75 ppm), 2.27-5.07 mg/m^3 (0.46-1.03 ppm), and 0.23-0.53 mg/m^3 (0.05-0.11 ppm), respectively. No attempt was made to correlate these area measurements with breathing zone concentrations. In a similar workplace monitoring study, workers were exposed to concentrations ranging from none detected to 25.3 ppm (total of all three isomers) as an 8-h time weighted average (Jones et al. 2006). TMB concentrations in breath and urinary metabolite concentrations were positively correlated with personal and ambient air samples, but no symptoms were reported.

Concentrations of combined 1,2,4- and 1,2,3-TMB measured in the breathing zone of a painter were 0.4-4.6 mg/m^3 (0.08-0.93 ppm). The painter used paint diluted with white spirit (C_9 aromatics) and worked for 11-21 min (van der Wal and Moerkerken 1984).

Exposure to organic compounds was monitored and complaints recorded over several days in asphalt workers involved in road repair and construction (Norseth et al. 1991). Organic compounds were collected by personal samplers and measured by gas chromatography. Fatigue, reduced appetite, laryngeal and pharyngeal irritation, cough, and ocular irritation were found more often in asphalt workers than in a reference group. When symptoms were converted to a numeric scale for calculation of a "symptom sum," a positive correlation was found between symptom sum and concentration of 1,2,4-TMB ($r = 0.31$). Mean concentrations of the 1,2,4-, 1,3,5-, and 1,2,3-TMB isomers were 1.50, 0.14, and 0.38 ppm, respectively. The most prevalent compounds were *m*- and *p*-xylene (12.4 ppm) and the C_9-C_{13} aliphatics (39.6 ppm).

Bättig et al. (1956) reported on the health status of workers in a painting workshop. A total of 27 individuals with average ages of 48-55, depending on job type, had worked with the solvent "Fleet-X" for an average of 7 years. "Fleet-X" contains 50% 1,2,4-TMB, 30% 1,3,5-TMB, and 20% other solvents. Concentrations of total hydrocarbons in workshop air were 10-60 ppm. Up to 80% of the exposed workers complained of nervousness, tension, and anxiety and 70% had asthmatic bronchitis. Hematology showed a tendency to hyperchromic anemia and coagulation disorders. Gerarde (1960) subsequently noted that the hematology changes reported by Bättig et al. (1956) might have been due to trace amounts of benzene. Hematopoietic toxicity has not been reported in animal studies with pure TMB (Gage 1970).

2.2.4. Experimental Studies

In pharmacokinetic studies with all three TMB isomers, no irritation or central nervous system effects were reported in volunteers exposed at up to 25 ppm for 2 h (Järnberg et al. 1996) or 4 h (Jones et al. 2006) or at up to 30 ppm for 8 h (Kostrzewski et al. 1997).

2.3. Neurotoxicity

No information was found regarding the potential neurotoxicity of pure TMB in humans.

2.4. Developmental and Reproductive Toxicity

No information was found regarding the potential reproductive or developmental toxicity of pure TMB in humans.

2.5. Genotoxicity

No information was found regarding the potential genotoxicity of pure TMB in humans.

2.6. Carcinogenicity

No information was found regarding the potential carcinogenicity of pure TMB in humans. None of the TMB isomers have been classified by U.S. Environmental Protection Agency or the International Agency for Research on Cancer.

2.7. Summary

Very little information is available concerning human exposure to pure TMB isomers despite the wide use of these materials. No deaths have been reported from exposure to TMB. Occupational studies involved exposure to mixtures of hydrocarbon solvents.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Adult male and female Wistar rats (number per sex not specified) were exposed in whole body inhalation chambers to 1,3,5-TMB (purity not reported)

(Cameron et al. 1938). Atmospheres were generated by bubbling air through a saturation unit, and the chamber atmospheres were described as being accurate during a continuous run. Four of 16 rats exposed continuously to 1,3,5-TMB at 2,240 ppm for 24 h died. Narcosis developed and the animals died of respiratory failure; pulmonary congestion was observed at necropsy.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of six male Wistar rats were exposed to 1,3,5-TMB at 0, 61, 305, 609, or 1,218 ppm for 6 h. No details were provided on the purity of 1,3,5-TMB, exposure apparatus, atmosphere generation, or monitoring (Wiglusz et al. 1975a,b). Blood was collected at various times after exposure for analyses of hematology and serum enzyme activity. No changes were found in hemoglobin concentration, erythrocyte and leukocyte count, or the activity of aspartate aminotransferase, alanine amino transferase, or glutamate dehydrogenase. However, a concentration-related slight increase in the percentage of segmented neutrophils and a slight reduction in the percentage of lymphocytes were observed immediately after exposure, and alkaline phosphatase activity was significantly higher on day 7 post exposure (at 609 ppm only). Clinical findings and body weight were not mentioned.

Male and female Wistar rats (number per sex not specified) were exposed in whole body inhalation chambers (Cameron et al. 1938). Atmospheres were generated by bubbling air through a saturation unit, and the chamber atmospheres were described as being accurate during a continuous run. No adverse clinical signs, deaths, or necropsy findings occurred in animals (n = 4-8) exposed to 1,2,4-TMB at 1,800-2,000 ppm for up to 48 h or for 8 h/day for 14 days. No animals died in groups (n = 10) exposed at 560 ppm for 24 h or for 8 h/day for 14 days.

3.2.2. Mice

The RD_{50} values (concentrations of a substance that reduces the respiratory rate by 50%) for 1,2,4-, 1,3,5-, and 1,2,3-TMB (purities of >97, 99, and 90-95%, respectively) in male Balb/C mice were 578, 519, and 541 ppm, respectively (Korsak et al. 1995, 1997). Groups of animals (n = 8-10) were exposed at 253-1,928 ppm for 6 min, followed by a 6-min recovery period. Each animal was placed in a plethysmograph for measurement of respiratory pattern. Chamber atmospheres were generated by heating the liquid solvent in washers and diluting with air to the desired concentration. Concentration was monitored by a gas chromatograph with a flame-ionization detector. The maximum reduction in respiratory rate occurred during the first 2 min of exposure with each isomer. Clinical signs were not mentioned.

Male and female mice (strain and number per sex not specified) were exposed in whole body inhalation chambers to 1,2,4- or 1,3,5-TMB (Cameron et al. 1938). Atmospheres were generated by bubbling air through a saturation unit, and the chamber atmospheres were described as being accurate during a continuous run as measured by "chemical analysis." No adverse clinical signs, deaths, or necropsy findings occurred in animals (n = 10) exposed to 1,3,5-TMB at 560 ppm for 24 h or for 8 h/day for 14 days. Likewise, no effects were seen in animals (n = 10) exposed to1,2,4-TMB at 1,800-2,000 ppm for 12 h.

Lazarew (1929) exposed white mice (strain and number per sex not specified) to 1,2,4- or 1,3,5-TMB in whole body inhalation chambers for 2 h. Details of atmosphere generation were not provided. Mice exposed to 1,2,4-TMB at 8,100 ppm or to 1,3,5-TMB at 5,000-7,000 ppm exhibited lateral position during exposure. Slightly higher concentrations of 8,100-9,100 ppm and 7,000-9,000 ppm for 1,2,4- and 1,3,5-TMB, respectively, resulted in loss of reflexes.

3.3. Neurotoxicity

Groups of 10 male Wistar rats were exposed in whole-body chambers to 1,2,4-, 1,3,5-, or 1,2,3-TMB at 250-2,000 ppm for 4 h (purity >97, 100, and 90-95%, respectively) (Korsak et al. 1995; Korsak and Rydzyński 1996). Chamber atmospheres were generated by heating the liquid and diluting it with air to the desired concentration. Chamber concentrations were monitored by a gas chromatograph equipped with a flame-ionization detector. Immediately after exposure each animal was tested either for rotarod performance or hot-plate reaction. Clinical signs were not mentioned; all animals survived the exposures, but no observations other than results of neurotoxicity testing were mentioned. A concentration-dependent increase in the number of failures in rotarod performance and decrease in pain sensitivity (measured as latency to the paw-lick response) occurred. Following exposure to either 1,2,4-, 1,3,5- or 1,2,3-TMB, the effective concentration for a 50% response (EC_{50}) for rotarod performance were calculated to be 954 (95% confidence interval [CI]: 791-1,113), 963 (95% CI: 750-1,113), and 768 (95% CI: 578-942) ppm, respectively. EC_{50} values for pain sensitivity were 1,155 (95% CI: 552-1,544), 1,212 (95% CI: 1,086-1,329), and 848 (95% CI: 694-982) ppm, respectively. EC_{50} values were calculated from a graph of exposure concentration versus either probit of the number of failures (rotarod) or percent over controls in latency (pain sensitivity).

Male Wistar rats were exposed for 6 h/day, 5 days/week in whole-body chambers to 1,2,4- or 1,2,3-TMB at 25, 100, or 250 ppm for 28 days (Gralewicz et al. 1997a; Wiaderna et al. 1998) or 90 days (Korsak and Rydzyński, 1996; Korsak et al. 1997). In a follow-up study, male Wistar rats were exposed to the same isomers at 100 ppm for 28 days (Gralewicz and Wiaderna 2001). Chamber atmospheres were generated by heating the liquid solvent in washers and diluting it with air to the desired concentration. Concentrations were monitored by a gas chromatograph equipped with a flame-ionization detector. No treatment-

related clinical signs of toxicity were observed and all animals survived. Body weight was not affected by exposure to any TMB isomer.

In the 28-day exposure studies, a series of neurotoxicity tests was conducted (n = 10-15/group) 14-61 days after exposure ended to assess residual effects (Gralewicz et al. 1997a; Wiaderna et al. 1998; Gralewicz and Wiaderna 2001). No effects from any of the TMB isomers were noted in the radial maze or pain sensitivity assays. Passive avoidance learning was delayed and the foot-shock-induced increase in latency of the paw-lick response persisted in rats exposed to 1,2,4-TMB at 100 and 250 ppm, to 1,2,3-TMB at 25 and 100 ppm, and to 1,3,5-TMB at 100 ppm. When observed in the open field, grooming and locomotor activity were increased in rats exposed to 1,2,4- and 1,3,5- TMB at 100 ppm. Acquisition of the active avoidance response was impaired in rats exposed to the three isomers at 100 ppm. Electroencephalogram recordings were made on an additional group of rats exposed to 1,24-TMB at 0, 25, 100, or 250 ppm for 28 days (Gralewicz et al. 1997b). The spike-wave discharge activity in the control and 25-ppm groups progressively increased during a 4-month post-exposure period, and decreased in the 100- and 250-ppm groups.

In the 90-day exposure studies, only rotarod performance and pain sensitivity (hot plate behavior) were evaluated (n = 6-7/group) (Korsak and Rydzyński 1996; Korsak et al. 1997). A concentration-dependent increase in the number of failures in rotarod performance was observed throughout the study with 1,2,4-TMB at 250 ppm and 1,2,3-TMB at 100 and 250 ppm. Recovery of rotarod performance was not evident in rats 2 weeks they were exposed at the highest concentration of either isomer. Similarly, a concentration-dependent reduction in pain sensitivity was observed with 1,2,4-TMB at 100 and 250 ppm and at all concentrations of 1,2,3-TMB. However, there was complete recovery of pain sensitivity 2 weeks after exposure (Korsak and Rydzyński 1996). In an additional experiment, pulmonary lavage fluid was collected and analyzed 24 h after the last exposure to 1,2,4-TMB. The total number of cells in the bronchoalveolar lavage fluid was increased in all TMB-exposed groups due to an increase in macrophages, polymorphonuclear leucocytes, and lymphocytes. Lactate dehydrogenase and acid phosphatase activities in the lavage fluid were increased in all groups (Korsak et al. 1997).

Male Mol:WIST rats (n = 5) exposed to white spirit (constituent composition not described) at 0, 400, or 800 ppm for 6 h/day, 5 days/week for 3 weeks had concentration-related increases in whole brain levels of noradrenaline, dopamine, and 5-hydroxytryptamine; brain weight, protein concentration, and acetyl- and butyryl-cholinesterase activities were unaffected (Lam et al. 1992). Clinical signs of toxicity were not described.

Groups of four male Wistar rats and eight female H strain mice were exposed by whole body for 4 or 2 h, respectively, to a range of concentrations of each TMB isomer ("analytical purity") (Frantík et al. 1994). Details of atmosphere generation and monitoring were not included and the exact concentrations were not provided. Within 1 min of removal from the chamber, each animal was measured for inhibition of propagation and maintenance of the electrically

evoked seizure discharge. An electrical impulse was applied through ear electrodes and the duration of tonic extension of the hindlimbs was recorded; control values were subtracted from values recorded after exposure with inhibition considered a measure of neurotoxicity. Concentrations of 1,2,4-, 1,3,5-, and 1,2,3-TMB that resulted in 30% depression in rats were 636, 440, and 489 ppm, respectively, and in mice were 391, 611, and 416 ppm, respectively. No other information was provided.

3.4. Developmental and Reproductive Toxicity

Female Sprague-Dawley rats (n = 24) were exposed whole body to 1,3,5-TMB at 100-1,200 ppm or to 1,2,4-TMB at 100-900 ppm (purity was 99% for both isomers) for 6 h/day on gestation days 6-20 (Saillenfait et al. 2005). Test atmospheres were generated by passing air flow through the fritted disk of a heated bubbler containing the test chemical. Vaporized compound was carried into the main air inlet pipe and concentration was adjusted by varying the airflow passing through the bubbler. Atmospheres were monitored by gas a chromatograph equipped with a flame-ionization detector. Mean measured concentrations differed by less than 2% of nominal concentrations. Maternal toxicity was evident as decreased body weight gain and reduced food consumption with 1,3,5-TMB at concentrations of 300 ppm and greater and with 1,2,4-TMB at concentrations of 600 ppm and greater. All dams survived, and no clinical signs of toxicity were observed. Fetal body weight was decreased with both isomers at concentrations of 600 ppm and greater. No external, visceral, or skeletal malformations were observed with either isomer.

Groups of 30 female CD-1 mice were exposed whole body to C_9 aromatic hydrocarbons at concentrations of 0, 100, 500, or 1,500 ppm for 6 h/day on gestation days 6-15 (IRDC 1988a; McKee et al. 1990). Mean analytically-determined concentrations during the study were within 2% of nominal concentrations. The composition of the test material contained 8.37% 1,3,5-TMB, 40.5% 1,2,4-TMB, and 6.18% 1,2,3-TMB. The remainder of the mixture was comprised of *o*-xylene, cumene, *n*-propyl benzene, and 4-, 3-, and 2-ethyltoluene. No treatment-related mortality, clinical signs of toxicity, or changes in food consumption were observed at 100 or 500 ppm. A total of 12 animals exposed at 1,500 ppm died between gestation days 8-16. Clinical signs of toxicity at 1,500 ppm included abnormal gait (18 animals), labored breathing, hunched posture, weakness, inadequate grooming, circling, and ataxia (7-9 animals). Most of these signs were observed after one or two days of exposure. Body weight gain by the 500- and 1,500-ppm groups was 88 and 63%, respectively, of the control group during exposure. Food consumption by the 1,500-ppm group was 65-77% of the control group. Hematologic analysis on gestation day 15 revealed significantly reduced hematocrit and mean corpuscular volume and increased mean corpuscular hemoglobin concentration in mice exposed at 1,500 ppm compared with controls. Maternal necropsy was unremarkable. At

cesarean section on gestation day 18, dams in the 1,500-ppm group had significantly fewer live fetuses/dam because of an increase in post-implantation loss compared with controls. Fetal body weight in the mid- and high-concentration groups was significantly reduced compared to that of controls (1.16 and 0.82 g, respectively, vs. 1.25 g for controls). Cleft palate was found in 14 fetuses from seven high-concentration litters compared with one control fetus, and reduced ossification of the skull was found in 18 fetuses from six high-concentration litters compared with none in the controls.

In a range-finding developmental toxicity study, groups of five female CD-1 mice were exposed whole body to C_9 aromatic hydrocarbons at concentrations of 0, 100, 250, 500, 1,000, or 1,500 ppm for 6 h/day on gestation days 6-15 (IRDC 1988b). Composition of the test article was as described by McKee et al. (1990). Two dams in the 1,500-ppm group were sacrificed moribund on gestation day 6. All remaining animals survived. Clinical signs in high-concentration animals were similar to those described by McKee et al. (1990). During the treatment interval, body weight gain was reduced at 1,000 and greater, and food consumption was reduced at 1,500 ppm compared with controls. Fetal body weight was reduced at 500 ppm or greater. No treatment-related external fetal malformations were observed. Fetuses were not examined viscerally or skeletally.

In a three-generation reproduction study, groups of 30 or 40 male and 30 or 40 female Charles River COBS CD rats were exposed whole body to C_9 aromatic hydrocarbons at concentrations of 0, 100, 500, or 1,500 ppm for 6 h/day, 5 days/week for 10 weeks prior to mating and during a 2-week mating interval. After mating, the males were killed. Females continued to be exposed for 6 h/day, 7 days/week on gestation days 0-20, and exposure was resumed on lactation days 5-21 (McKee et al. 1990). Mean analytically-determined concentrations during the study were within 2% of nominal concentrations. The composition of the test material contained 8.37% 1,3,5-TMB, 40.5% 1,2,4-TMB, and 6.18% 1,2,3-TMB. The remainder of the mixture was comprised of *o*-xylene, cumene, *n*-propyl benzene, and 4-, 3-, and 2-ethyltoluene.

All F_0 and F_1 parental males survived the exposure. In the 1,500-ppm groups, a total of seven of 30 F_0 females, six of 30 F_1 females, 36 of /40 F_2 males, and 34 of 40 F_2 females died or were sacrificed. Clinical signs of toxicity of ataxia and reduced motor activity were described in the F_1 parental animals. During premating, males and females of all generations exposed at 500 and 1,500 ppm and the F_2 animals exposed at100 ppm had reduced body weight and body weight gain. Body weight reductions were more pronounced in each successive generation. Food consumption was similar between the treated and control groups throughout the study and gross necropsy of the adults was unremarkable (McKee et al. 1990).

The precoital interval was increased at 1,500 ppm for all generations. Mating, gestation, and fertility indices were not affected in the F_0 or F_2 generations, although only six F_3 litters were produced due to deaths of the F_2 animals. At 1,500 ppm, F_1 parental animals had decreased male fertility index and decreased

live litter size at birth. F_2 offspring in the 1,500-ppm group had reduced live birth index (85.1% vs 97.5% in controls) and reduced survival to postnatal day 4 (87.4% vs 95.4% for controls). Body weight of F_1, F_2, and F_3 pups exposed at 1,500 ppm was significantly less than that of controls beginning on lactation day 7. In addition, body weights of the F_3 pups in the 1,500-ppm group were lower than that of controls at birth, and in the 500-ppm group were lower starting on lactation day 14 (McKee et al. 1990).

3.5. Genotoxicity

The three TMB isomers were evaluated for mutagenicity using *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA102, for micronucleus formation, and for induction of sister chromatid exchange in male and female mice (Janik-Spiechowicz et al. 1998). Only 1,2,3-TMB increased both base-pair substitutions and frameshift mutations in the absence of metabolic activation. The 1,2,4- and 1,3,5-TMB isomers were negative for mutagenicity, and all three were negative for micronucleus formation. The isomers were cytotoxic at 20-40 µL/plate, and the highest doses in mice (>2,900 mg/kg) caused overt hematopoietic toxicity and death of several animals. Positive results for sister chromatid exchange induction were found with all isomers at nonlethal doses.

3.6. Subchronic Toxicity, Chronic Toxicity, and Carcinogenicity

Alderley Park rats (n = 4/sex) were exposed whole body in dynamic chambers to 1,2,4-TMB (purity not reported) for 6 h/day, for 5 days/week; exposures were either at nearly saturated vapor for a total of 12 exposures or at 1,000 ppm for a total of 15 exposures (Gage 1970). Nearly saturated atmospheres of 2,000 ppm (estimated by weighing the sample before and after the day's exposure) were obtained by passing air through the liquid contained in a bubbler with a sintered glass air-distributor disc. The 1,000-ppm atmosphere was generated by injecting liquid at a known rate into a metered stream of air by means of a controlled fluid-feed atomizer. Rats exposed to the saturated atmosphere displayed nasal irritation, described as sneezing that progressed in severity to nasal discharge and bloody exudates; ocular irritation, described as eyes closed that progressed in severity to lachrymation; respiratory difficulty, such as rapid, shallow breathing that progressed to labored and slow breathing; lethargy, which included decreased activity; a lower response to noise; tremors; and decreased weight gain over the course of the experiment. Exposure at 1,000 ppm resulted in initial signs of slight ocular and nasal irritation. Onset and progression of clinical signs was not further described. All animals survived and no hematology changes or gross or histopathologic lesions were noted after exposure at either concentration.

Groups of male Wistar rats (n = 6) were exposed to 1,3,5-TMB at 0 or 609 ppm for 6 h/day, 6 days/week for 5 weeks; no details were provided on the pu-

rity of the test article, exposure apparatus, atmosphere generation, or monitoring (Wiglusz et al. 1975a,b). Blood was collected at various times after exposure for analysis of hematology and serum enzyme activity. No changes in hematology were found, but aspartate aminotransferase activity was slightly elevated on day 14 postexposure. Clinical findings and body weight were not mentioned.

Male and female Wistar rats (n = 20/sex/group) were exposed to 1,2,3-TMB (>97% pure) at 0, 25, 100, or 250 ppm for 6 h/day, 5 days/week for 3 months (Korsak et al. 2000). Chamber atmospheres were generated by heating the liquid and diluting with air to the desired concentration. Concentration was monitored by a gas chromatograph equipped with a flame-ionization detector. All animals survived to scheduled necropsy and no treatment-related clinical signs of toxicity were observed. Body weight gain and food consumption were not affected by treatment. Animals exposed at 250 ppm exhibited increased liver weight relative to body weight (males), decreased erythrocyte counts (males), increased reticulocyte counts (males), decreased neutrophil counts (both sexes), increased lymphocyte counts (both sexes), increased serum sorbitol dehydrogenase (males), and increased serum alkaline phosphatase (females). Microscopic examination of the respiratory tract revealed an increased number of goblet cells in females of the 100- and 250-ppm groups, and interstitial lymphocytic infiltration in males of the 250-ppm group.

No adverse effects were observed in rats exposed at 1,700 ppm of an isomeric mixture of TMB for 10-21 days; the isomer composition was not described (Rossi and Grandjean 1957). Decreased weight gain, lymphopenia, neutrophilia, and marked central nervous system depression were seen when animals were exposed at the same concentration for 4 months (Bättig et al. 1958). Hematotoxicity observed in these older studies may have been due to benzene in the solvents (ACGIH 1992).

3.7. Summary

Animal data are summarized in Table 8-3. Clinical signs of irritation were observed in laboratory animals at concentrations >1,000 ppm in some studies but not in others. Lethargy or narcosis in animals correlated with neurotoxicity measured in rats. Alterations in hematology observed in some studies were not confirmed in other studies. TMB is not a selective developmental toxicant. Results from a three-generation reproductive toxicity study suggest cumulative systemic toxicity in both male and female rats over successive generations.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

TMB is readily absorbed, accumulates in adipose tissue, and metabolites are excreted in the urine in both humans and rats exposed by inhalation. 1,2,4-

TMB was detected in the serum of a laboratory technician 2 h after handling a liquid scintillation cocktail; it was assumed that inhalation was the main route of exposure and a duration was not specified (Kenndler et al. 1989).

TABLE 8-3 Summary of Animal Studies of Trimethylbenzenes

Species (sex)	Concentration (ppm)	Duration	Effects	Reference
Rat (M/F)	2,240	24 h	4/16 died	Cameron et al. 1938
Rat (M/F)	560	24 h or 8 h/d for 14 d	None	
	1,800-2,000	48 h or 8 h/day for 14 d	None	
Rat (M)	768-1,212	4 h	Calculated EC_{50} for mild neurotoxic effects	Korsak et al. 1995; Korsak and Rydzyński 1996
Rat (M/F)	1,000	6 h, 15 times	Ocular and nasal irritation	Gage 1970
	2,000	6 h, 12 times	Severe irritation, lethargy	
Mouse (M)	519-578	6 min	RD_{50}	Korsak et al. 1995, 1997
Mouse (M/F)	560	24 h or 8 h/d for 14 d	None	Cameron et al. 1938
	1,800-2,000	12 h	None	
Mouse	5,000-8,100		Lateral position	Lazarew 1929
	7,000-9,000	2 h	Loss of reflexes	
Rat (M)	25, 100, 250	6 h/d, 5 d/wk, 28 or 90 d	Mild neurotoxicity at 100 and 250 ppm	Korsak and Rydzyński 1996; Gralewicz et al. 1997a; Korsak et al. 1997; Wiaderna et al. 1998; Gralewicz and Wiaderna 2001
Rat (M/F)	25, 100, 250	6 h/d, 5 d/wk, 90 d	Hematology and clinical chemistry changes at 250 ppm, lesions in respiratory tract at 100 and 250 ppm	Korsak et al. 2000

Järnberg et al. (1996, 1997a,b, 1998) studied the kinetics of inhaled 1,2,4-, 1,2,3-, or 1,3,5-TMB (purity of >99, 90-95, and 99%, respectively) in healthy male volunteers (ages 26-48 years). Subjects were exposed in a chamber to 25 ppm of each isomer or 2 ppm of 1,2,4-TMB for 2 h at a work load of 50 W. Relative respiratory uptake was 56-64% and exhalation after exposure accounted for 30-37% of the absorbed dose. Large volumes of distribution and terminal half-lives in blood of 78-120 h indicated accumulation in a deep compartment, most likely adipose tissue (Järnberg et al. 1996). Between 3-18% of the absorbed dose of each isomer was recovered in the urine as dimethylhippuric acid after 24 h and only about 3% of the absorbed dose was excreted as the unconjugated dimethylbenzoic acid (Järnberg et al. 1997a). When subjects were exposed concurrently to 1,2,4-TMB at 2 ppm and white spirit (16% aromatics) at 61 ppm, both blood concentrations of 1,2,4-TMB and excretion rates of dimethylhippuric acid were increased compared with exposure to 1,2,4-TMB alone (Järnberg et al. 1997b, 1998).

In a similar experiment, volunteers (ages 20-39 years) were exposed at rest in a chamber with each TMB isomer at 1-30 ppm for 4 or 8 h (Kostrzewski and Wiaderna-Brycht 1995; Kostrzewski et al. 1997). Retention by the lungs was 67-71% of the inhaled concentration, and elimination from the blood followed a three-compartment model. Urinary excretion of dimethylbenzoic acid was greatest 2 h before the end of exposure until 2 h after exposure ended.

Jones et al. (2006) exposed two male and two female volunteers (ages not specified) in a chamber to 1,3,5-TMB at 25 ppm for 4 h. TMB was measured in blood and breath during and after exposure and urinary dimethylbenzoic acids were measured after exposure. Blood concentrations reached steady-state after 1-2 h of exposure, with the mean concentration 0.85 μmol/L; blood concentrations remained constant through the last sampling time of 1 h postexposure. Breath concentrations of TMB peaked rapidly after initiation of exposure, and concentrations ranged from 114 to 160 nmol/L during exposure. Biphasic elimination was observed after exposure with a mean half-life of 60 min for the rapid phase and 600 min for the slow phase. 3,5-Dimethylbenzoic acid was measured in the urine, with a peak mean concentration of 40 mmol/mol creatinine at 4-8 h postexposure. Urinary elimination was biphasic with an initial mean half-life of 13 h and a secondary half-life of 60 h.

1,3,5-TMB was measured in the blood of rats after a 2 h whole-body exposure at 120-720 ppm; blood concentrations ranged from 15.7 to 143.5 μmol/L in a concentration-related manner (Römer et al. 1986; Freundt et al. 1989). Concentrations of all three isomers were measured in the whole brains of rats exposed to white spirit (Stoddard solvent) at 400 or 800 ppm for 6 h/day, 5 days/week for 3 weeks (Lam et al. 1992). 1,3,5-TMB was found at 0.10 and 0.08 mg/kg of brain (wet weight) after exposure at 400 and 800 ppm, respectively; the 1,2,4- and 1,2,3-TMB isomers were not detected in rats exposed at 400 ppm, but were measured at 0.40 and 0.07 mg/kg, respectively, in rats exposed at 800 ppm. Although the total white spirit concentration increased in the brain with

increasing concentration, the accumulation was mainly from the aliphatic components and not the aromatic components (Lam et al. 1992).

Zahlsen et al. (1992) measured tissue concentrations in rats exposed whole-body to 1,2,4-TMB at 100 ppm for 12 h/day for 3 days. After each day of exposure, low concentrations of the isomer were found in the blood, brain, liver, and kidneys, with little difference in concentration after successive days of exposure suggesting no accumulation. In fat, the concentration decreased with each day. Only trace amounts were detected in the tissues 12 h after the last exposure. These investigators also exposed rats to 1,2,4-TMB at 1,000 ppm for 12 h/day for up to 14 days (Zahlsen et al. 1990). With the exception of fat, steady state was established between days 3 and 7. The highest concentration of 1,2,4-TMB in the fat was measured on day 1, with a significantly lower steady state level found on days 3-14. The brain-blood and fat-blood ratios were 2.0 and 63, respectively.

Similar tissue distribution was found in rats after an oral dose of ^{14}C-1,2,4-TMB (Huo et al. 1989). Small amounts of radioactivity were found throughout the body, with the greatest amount (up to 28% of the dose) in the adipose tissue 3 h after dosing. Tissue concentrations declined rapidly within 24 h, and more than 99% of the radioactivity recovered in the urine during this period.

Induction of microsomal enzymes follows exposure to TMB. Rats exposed to 1,2,4-TMB at 0.2 or 2 ppm for 4 h had increased cytochrome P-450 content in the liver, lungs, and kidneys (Shakirov et al. 1999). Cytochrome P-450 content was increased in the liver and decreased in the lungs of male Sprague-Dawley rats after a single intraperitoneal injection of each of the TMB isomers (Pyykkö et al. 1987). Concurrently, 7-ethoxycoumarin *O*-deethylase activity was increased in the liver and decreased in the lung, 7-ethoxyresorufin *O*-deethylase activity was increased in both tissues, and aryl hydrocarbon hydroxylase activity was increased in the liver. Cytochrome b_5 content and NADPH-cytochrome c-reductase activity were unchanged in the lungs and liver (Pyykkö et al. 1987).

Urinary metabolites in rats were measured after oral administration of each TMB isomer at 1.2 g/kg (Mikulski and Wiglusz 1975). With 1,3,5-TMB, 20.7-28.2% of the dose was recovered as 3,5-dimethylhippuric acid. That metabolite was not found with either 1,2,4- or 1,2,3-TMB. Both the 1,3,5- and 1,2,4-TMB isomers were mainly excreted as glycine conjugates with smaller amounts excreted as glucuronic and sulfuric acid conjugates. In contrast, sulphate conjugates were predominate metabolites with 1,2,3-TMB. Approximately 73, 37, and 33% of the dose was excreted in urine within 48 h after administration of 1,3,5-, 1,2,4-, and 1,2,3-TMB, respectively. Pretreatment with phenobarbital increased excretion of glucuronic and sulfate conjugates and decreased excretion of glycine conjugates for all three isomers (Mikulski and Wiglusz 1975). In a similar study, approximately 30.2% of an oral dose of 1,2,4-TMB was recovered in the urine of rats as dimethylhippuric acid (Huo et al. 1989).

A similar metabolic profile was found in male rabbits. Following oral administration of 1,2,4-TMB, the major urinary metabolites were 2,4-dimethylbenzoic acid and 3,4-dimethylhippuric acid (Cerf et al. 1980). Like-

wise, following oral administration of 1,3,5-TMB, 9.0% of the dose was excreted in the urine as 3,5-dimethylbenzoic acid and 68.5% was recovered as the glycine conjugate 3,5-dimethylhippuric acid (Laham and Potvin 1989).

Urinary 3,4-dimethylhippuric acid concentrations have been used to determine worker or occupational exposure to 1,2,4-TMB (Ichiba et al. 1992; Fukaya et al. 1994). This metabolite correlates with workplace atmospheric concentration, and has been found at higher concentration postshift compared with preshift concentrations.

Minor metabolic pathways include production of mercapturic acid and hydroxylation. About 5% of an intraperitoneal dose of 1,2,3-TMB to rats was excreted in the urine as 2,3-dimethylbenzyl mercapturic acid (Tsujimoto et al. 1999). After an oral dose of either 1,2,4-TMB or 1,2,5-TMB at 100 mg/kg, only 0.05 and 0.4% of the dose, respectively, were recovered in the urine of rats as phenolic metabolites (Bakke and Scheline 1970).

4.2. Mechanism of Toxicity

Little is known about the mechanism of TMB toxicity. At higher concentrations, direct irritation of mucous membranes and narcosis was apparent in some of the animal studies (Lazarew 1929; Cameron et al. 1938; Gage 1970). Hematologic evaluations were highly variable among studies, and some investigators believe benzene might have contaminated some preparations and affected results (Gerarde 1960). This is particularly true of older studies.

4.3. Structure Activity Relationships

Little difference in toxicity has been observed between the TMB isomers. Calculated ED_{50} values for neurologic deficits in rats were similar for the three isomers. Likewise, RD_{50} values in mice did not differ. Since occupational exposures are likely to involve more than one isomer, regulatory standards are for the individual isomers and any mixture thereof. In the monitoring studies described in Section 2.2.3, the most abundant isomer was 1,2,4-TMB.

For derivation of AEGL values, all available data on the individual TMB isomers were considered. The most appropriate end point for each AEGL category was used as the point of departure for deriving AEGL values. Therefore, even though the point of departure might be based on data from an individual isomer, the AEGL values are considered applicable to all three TMB isomers.

4.4. Other Relevant Information

4.4.1. Species Variability

Rats appear to be slightly more sensitive than mice to the toxic effects of the TMB isomers. However, differences in results might be due to the methods of atmosphere generation and concentration measurement, not due to the animal

response. Mild clinical signs were reported in male and female rats exposed repeatedly to TMB at 1,000 ppm for 6 h (Gage 1970), but not in mice exposed at up to 2,000 ppm for 12 h (Cameron et al. 1938). Lethality was reported in rats exposed at 2,240 ppm for 24 h (Cameron et al. 1938), but no mortality data on mice were found. Marked central nervous system depression was noted in mice exposed to TMB at 5,000 ppm for 2 h (Lazarew 1929). Thus, differences in analytic techniques between the older and more recent literature might explain the differences in species responses.

4.4.2. Susceptible Populations

Limited data suggest that the pregnant mouse is most susceptible to alkyl benzene toxicity. Exposure of mice for 6 h/day on gestation days 8-16 to a mixture of TMB isomers and other alkyl benzenes resulted in maternal and developmental toxicity at 500 and 1,500 ppm (IRDC 1988a; McKee et al. 1990). In contrast, no adverse effects were reported in female mice exposed to 1,2,4-TMB at 2,000 ppm for 12 h (Cameron et al. 1938). However, differences in response might have been due to total absorbed dose as a consequence of repeated versus single exposure.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for substances like TMB can 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 a chemical-specific data to empirically derive an exponent, a default value of n = 1 can be used when extrapolating to longer durations and a default value of n = 3 can be used when extrapolating to shorter durations (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were found. In occupational studies, exposures were not correlated with symptoms, and exposures involved a mixture of hydrocarbon compounds. In pharmacokinetic studies with all three TMB isomers, no irritation or other adverse effects were reported in volunteers exposed at up to 25 ppm for 2 h (Järnberg et al. 1996) or at up to 30 ppm for 8 h (Kostrzewski et al. 1997).

5.2. Summary of Animal Data Relevant to AEGL-1

The most appropriate animal data for derivation of AEGL-1 values are neurotoxicity studies (Korsak et al. 1995; Korsak and Rydzyński 1996). In a

study of rats exposed to the three TMB for 4 h, the calculated EC_{50} values for rotarod performance were 954, 963, and 768 ppm, indicating little difference in the effect level between isomers.

Exposure of male and female rats to 1,2,4-TMB at 1,000 ppm for 6 h resulted in signs of slight ocular and nasal irritation (Gage et al. 1970). Although the exposures were repeated 15 times, the onset of clinical signs was not reported. All animals survived and no changes in hematology or gross lesions were noted.

Maternal toxicity was not evident in rats exposed to 1,3,5-TMB at 100 ppm or to 1,2,4-TMB at 300 ppm for 6 h/day on gestation days 6-20 (Saillenfait et al. 2005).

No adverse effects were reported in mice after exposure to 1,2,4-TMB at 1,800-2,000 ppm for 12 h (Cameron et al. 1938).

5.3. Derivation of AEGL-1 Values

Few studies were available on which to base AEGL-1 values. A concentration of 900 ppm for 4 h, calculated as the average EC_{50} for mild neurologic effects for the three TMB isomers, was chosen as the point of departure. The EC_{50} is considered a threshold consistent with the AEGL-1 definition as a no-effect level for asymptomatic nonclinical effects. A slightly higher concentration resulted in signs of irritation. A total uncertainty factor of 10 was used. A factor 3 for intraspecies variability was applied because the threshold for narcosis differs by no more than 2- or 3-fold among the general population (NRC 2001), and a factor of 3 for interspecies differences was used because the mechanism of action for narcosis is not expected to differ between rats and humans. Because the point of departure is a systemic effect, values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-min and 1-h durations and n = 1 for the 8-h duration. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-min values should not to be scaled from an experimental duration of 4 h or longer. Therefore, the 30-min AEGL-1 value was adopted as the 10-min value. AEGL-1 values for TMB are presented in Table 8-4.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values were found.

TABLE 8-4 AELG-1 Values for Trimethylbenzenes

10 min	30 min	1 h	4 h	8 h
180 ppm (890 mg/m^3)	180 ppm (890 mg/m^3)	140 ppm (690 mg/m^3)	90 ppm (440 mg/m^3)	45 ppm (220 mg/m^3)

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data relevant to derivation of AEGL-2 values are those of Gage (1970). Exposure of male and female rats to 1,2,4-TMB at 2,000 ppm for 6 h resulted in signs of nasal and ocular irritation, respiratory difficulty, lethargy, tremors, and reduced weight gain over the course of the experiment. Although the exposure was repeated 12 times, the onset of clinical signs was not reported. All animals survived and no hematologic changes or gross lesions were noted.

In a study evaluating neurotoxicity, rats were exposed to each TMB isomer at concentrations up to 2,000 ppm for 4 h (Korsak et al. 1995; Korsak and Rydzyński 1996). A concentration-dependent increase in the number of failures in rotarod performance and decrease in pain sensitivity (measured as latency to the paw-lick response) occurred in exposed animals. Clinical signs were not mentioned and all animals survived.

6.3. Derivation of AEGL-2 values

Rats exposed to 1,2,4-TMB at 2,000 ppm for 6 h exhibited irritation, respiratory difficulty, lethargy, and tremors; therefore, 2,000 ppm was chosen as the basis for deriving AEGL-2 values. The weight of evidence supports that point of departure, with neurologic deficits also measured at 2,000 ppm (Korsak et al. 1995; Korsak and Rydzyński 1996). Furthermore, no adverse effects were reported in rats exposed to a mixture of TMBs at 1,700 ppm for 10-21 days (Rossi and Grandjean 1957), no effects were reported in mice exposed to 1,2,4-TMB at 1,800-2,000 ppm for 12 h (Cameron et al. 1938), and cumulative effects on body weight and reproductive parameters were found over successive generations of rats exposed to a mixture TMB isomers and other alkyl benzenes at 1,500 ppm (McKee et al. 1990). The point of departure might not be a no-effect-level for AEGL-2 values, because the effects could lead to an impaired ability to escape. However, because the key study involved repeated exposures, 2,000 ppm was considered a conservative estimate of effects from a single exposure. A total uncertainty factor of 10 was used. A factor of 3 for intraspecies variability was applied because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (NRC 2001), and a factor 3 for interspecies differences was used because the mechanisms for irritation and narcosis are not expected to differ between animals and humans. Values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the

absence of an empirically derived, chemical-specific exponent, scaling was performed using a default of n = 3 for extrapolating to the 30-min, 1-, and 4-h durations and n = 1 for the 8-h duration. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-min values should not to be scaled from an experimental exposure duration of 4 h or longer. Therefore, the 30-min AEGL-2 value was adopted as the 10-min value. AEGL-2 values are presented in Table 8-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human data relevant to deriving AEGL-3 values for TMBs were not available.

7.2. Summary of Animal Data Relevant to AEGL-3

The only available lethality data on TMB was a study in rats that were exposed continuously to 1,3,5-TMB for 24 h, but concentration-response data were not reported (Cameron et al. 1938). In another study, white mice were exposed to 1,2,4- or 1,3,5-TMB in whole body inhalation chambers for 2 h (Lazarew 1929). The lowest concentration of either isomer that resulted in lateral position of the animals was 5,000 ppm. At slightly higher concentrations, the animals had loss of reflexes. Although the narcosis causing lateral position in mice could possibly lead to respiratory failure if the exposure duration was extended or the concentration was increased, data supporting this premise are lacking.

7.3. Derivation of AEGL-3 Values

Insufficient data were available to derive AEGL-3 values for TMB. Thus, AEGL-3 values were not recommended.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for TMB are presented in Table 8-6. AEGL-1 values were based on slight neurotoxicity in rats, and AEGL-2 values were based on irritation and neurotoxicity in rats. AEGL-3 values were not recommended.

TABLE 8-5 AEGL-2 Values for Trimethylbenzenes

10 min	30 min	1 h	4 h	8 h
460 ppm (2,300 mg/m^3)	460 ppm (2,300 mg/m^3)	360 ppm (1,800 mg/m^3)	230 ppm (1,100 mg/m^3)	150 ppm (740 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are presented in Table 8-7. These standards have been established for the individual TMB isomers and any mixture thereof. The time-weighted average exposure concentration for workers is 25 ppm in the United States and Sweden. An Immediately Dangerous to Life or Health (IDLH) concentration has not been established by National Institute for Occupational Safety and Health. The occupational exposure limit from The Netherlands and Germany is 20 ppm. The short-term exposure limit in Sweden (OEL-STEL) for a 15-min exposure (35 ppm) is lower than the AEGL-1 value for 10 or 30 min (180 ppm). Information describing the basis of the OEL-STEL value was not available for comparison to the AEGL-1 derivation.

8.3. Data Adequacy and Research Needs

Few relevant human and animal data were available despite the widespread use of these TMB in common fuels and hydrocarbon solvents in commerce. Thus, a clear concentration-response was difficult to assess for both nonlethal and lethal concentrations. Some discrepancies also were noted in the available data, which might be due to differences in analytic techniques used in the older studies compared with more studies.

TABLE 8-6 AEGL Values for Trimethylbenzenes

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	180 ppm (890 mg/m^3)	180 ppm (890 mg/m^3)	140 ppm (690 mg/m^3)	90 ppm (440 mg/m^3)	45 ppm (220 mg/m^3)
AEGL-2 (disabling)	460 ppm (2,300 mg/m^3)	460 ppm (2,300 mg/m^3)	360 ppm (1,800 mg/m^3)	230 ppm (1,100 mg/m^3)	150 ppm (740 mg/m^3)
AEGL-3 (lethal)	NR	NR	NR	NR	NR

Abbreviations: NR, not recommended.

TABLE 8-7 Extant Standard and Guidelines for Trimethylbenzenes

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	180 ppm	180 ppm	140 ppm	90 ppm	45 ppm
AEGL-2	460 ppm	460 ppm	360 ppm	230 ppm	150 ppm
AEGL-3	NR	NR	NR	NR	NR

(Continued)

TABLE 8-7 Continued

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
TLV-TWA (ACGIH)[a]					25 ppm
REL-TWA (NIOSH)[b]					25 ppm
MAK (Germany)[c]					20 ppm (II)
MAC (The Netherlands)[d]					20 ppm
OEL-LLV (Sweden)[e]					25 ppm
OEL-STV (Sweden)[f]	35 ppm				

[a]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2005) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. TMB isomers have a sensitizer notation.

[b]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.

[c]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft - German Research Association] (DFG 2005) is defined analogous to the ACGIH TLV-TWA. Category II is for substances with systemic effects: excursion factor = 2; duration = 15 min, average value; 4/shift with 1 h interval.

[d]MAC (maximaal aanvaarde concentratie [maximal accepted concentration]) (Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

[e]OEL-LLV (occupational exposure limit - level limit value) (Swedish Work Environment Authority 2005) is an occupational exposure limit value for exposure during one working day.

[f]OEL-STV (occupational exposure limit - short-term value) (Swedish Work Environment Authority 2005) is an occupational exposure limit value for exposure during a reference period of 15 min.

Abbreviations: NR, not recommended.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR TRIMETHYLBENZENES

Derivation of AEGL-1 Values

Key studies:	Korsak et al. 1995; Korsak and Rydzyński 1996
Toxicity end point:	Average ED_{50} for decrements in rotarod performance in rats exposed to 1,2,4-, 1,3,5-, or 1,2,3-TMB at 900 ppm for 4 h (954 ppm + 963 ppm + 768 ppm) ÷ 3 = 900 ppm
Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986), default values of n = 3 for extrapolating to the 30-min and 1-h durations and n = 1 for extrapolating to the 8-h duration $(900 \text{ ppm} \div 10)^3 \times 4 \text{ h} = 2.9 \times 10^6$ ppm-h $(900 \text{ ppm} \div 10)^1 \times 4 \text{ h} = 360$ ppm-h
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-1:	Set equal to the 30-min value of 180 ppm
30-min AEGL-1:	$(2.9 \times 10^6 \text{ ppm-h} \div 0.5 \text{ h})^{1/3} = 180$ ppm
1-h AEGL-1:	$(2.9 \times 10^6 \text{ ppm-h} \div 1 \text{ h})^{1/3} = 140$ ppm
4-h AEGL-1:	900 ppm ÷ 10 = 90 ppm
8-h AEGL-1:	360 ppm-h ÷ 8 h = 45 ppm

Derivation of AEGL-2 Values

Key study:	Gage 1970
Toxicity end point:	Nasal and ocular irritation, respiratory difficulty, lethargy, tremors, and decreased weight gain over the course of the experiment in rats exposed 12 times to 1,2,4-TMB at 2,000 ppm for 6 h.
Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986), default values of n = 3 for extrapolating to the 30-min and 1- and 4-h durations and n = 1 for extrapolating to the 8-h duration $(2{,}000 \text{ ppm} \div 10)^3 \times 6 \text{ h} = 4.8 \times 10^7 \text{ ppm-h}$ $(2{,}000 \text{ ppm} \div 10)^1 \times 6 \text{ h} = 1{,}200 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-2:	Set equal to the 30-min value of 460 ppm
30-min AEGL-2:	$(4.8 \times 10^7 \text{ ppm-h} \div 0.5 \text{ h})^{1/3} = 460 \text{ ppm}$
1-h AEGL-2:	$(4.8 \times 10^7 \text{ ppm-h} \div 1 \text{ h})^{1/3} = 360 \text{ ppm}$
4-h AEGL-2:	$(4.8 \times 10^7 \text{ ppm-h} \div 4 \text{ h})^{1/3} = 230 \text{ ppm}$
8-h AEGL-2:	$1{,}200 \text{ ppm-h} \div 8 \text{ h} = 150 \text{ ppm}$

Derivation of AEGL-3 Values

Insufficient data were available to derive AEGL-3 values for TMBs. Thus, AEGL-3 values were not recommended.

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR TRIMETHYLBENZENES

Derivation Summary for Trimethylbenzenes

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
180 ppm	180 ppm	140 ppm	90 ppm	45 ppm

Key references: Korsak, Z., R. Świercz, and K. Rydzyński. 1995. Toxic effects of acute inhalation exposure to 1,2,4-trimethylbenzene (pseudocumene) in experimental animals. Int. J. Occup. Med. Environ. Health 8(4):331-337.
Korsak, Z., and K. Rydzyński. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health 9(4):341-349.

Test species/Strain/Number: Rat, Wistar,10 males

Exposure route/Concentrations/Durations: Inhalation, 250-2,000 ppm of each isomer, 4 h.

Effects:
Calculated ED_{50} for decrements in rotarod performance:
1,2,4-TMB: 954 ppm
1,3,5-TMB: 963 ppm
1,2,3-TMB: 768 ppm

End point/Concentration/Rationale: Average of EC_{50} values = 900 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of action for narcosis is not expected to differ between rats and humans.
Intraspecies: 3, because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (NRC 2001).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-min and 1-h durations and n = 1 for the 8-h duration. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-min values are not to be scaled from an experimental exposure duration of 4 h or more. Therefore, the 30-min AEGL-1 value was adopted as the 10-min value.

Data adequacy: Limited data which meet the definition of AEGL-1.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
460 ppm	460 ppm	360 ppm	230 ppm	150 ppm

Key Reference: Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27(1):1-18.

Test species/Strain/Number: Rat, Alderley Park, 4 per sex

Exposure route/Concentrations/Durations: Inhalation, 1,2,4-TMB at 1,000 or 2,000 ppm for 6 h repeated 15 or 12 times, respectively.

Effects:
1,000 ppm: slight ocular and nasal irritation.
2,000 ppm: nasal and ocular irritation, respiratory difficulty, lethargy, tremors, and decreased weight gain over the course of the experiment.

End point/Concentration/Rationale: Severe irritation and narcosis in rats exposed at 2,000 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanisms of action for irritation and narcosis are not expected to differ between humans and rats.
Intraspecies: 3, because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (NRC 2001).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-min, 1-, and 4-h durations and n = 1 for the 8-h duration. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-min values should not to be scaled from an experimental exposure duration of 4 h or more. Therefore, the 30-min AEGL-2 value was adopted as the 10-min value.

Data adequacy: Limited data which meet the definition of AEGL-2.

AEGL-3 VALUES

Insufficient data were available to derive AEGL-3 values for TMBs. Thus, AEGL-3 values were not recommended.

APPENDIX C
CATEGORY PLOT FOR TRIMETHYLBENZENES

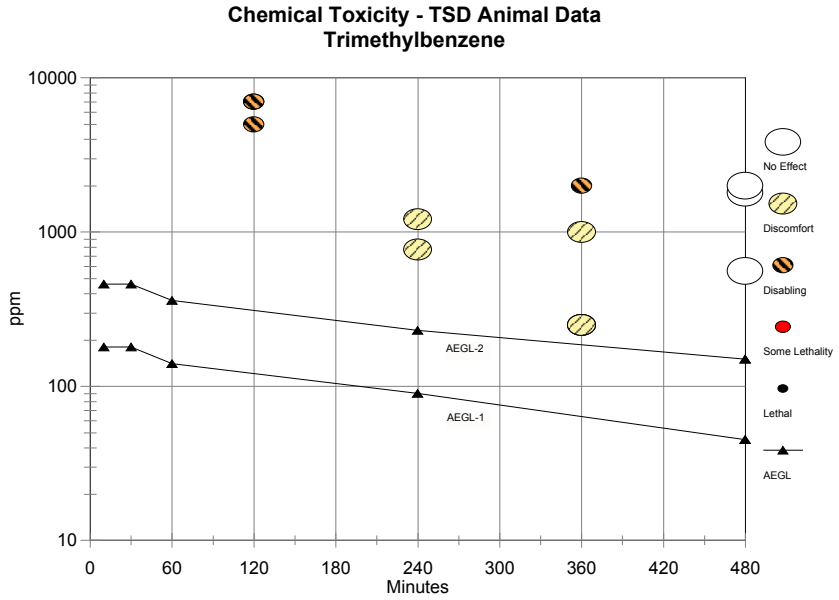

FIGURE C-1 Category plot of toxicity data and AEGL values for trimethylbenzenes.