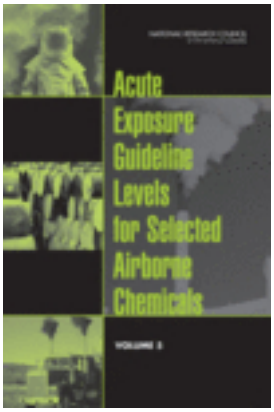

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 5

Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 5

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical indus-

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

try, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 185 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 the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the fifth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for chlorine dioxide, chlorine trifluoride, cyclohexylamine, ethylenediamine, hydrofluoroether-7100 (HFE-7100), and tetranitromethane for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft 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 this report: Sidney Green, Jr., Howard University; Loren Koller, Independent Consultant; Ramesh Gupta, Murray State University; Harihara Mehendale, University of Louisana at Monroe; and Deepak Bhalla, Wayne State 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 the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory), Aida Neel (project associate),

and Radiah Rose (senior editorial assistant). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we 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

William E. Halperin, *Chair*
Committee on Toxicology

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 5

Introduction

This report is the fifth 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, and what steps to take in case of 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 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 (IDLH) values developed by the National Institute for Occupational Safety and Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), 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 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 Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). 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 for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] 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.

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[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The roster of NAC is shown on page 9.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public, including susceptible subpopulations and are applicable to emergency exposures ranging from 10 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:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m3 [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 non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening 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, pregnant women, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in the Guidelines for Developing Community Emer-

gency Exposure Levels for Hazardous Substances (NRC 1993) and the NAC guidelines report Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances (NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on a chemical. 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 from 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, the data from the most sensitive animal species are used to set AEGLs. 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 ($1 \times 10\text{-}4$), 1 in 100,000 ($1 \times 10\text{-}5$), and 1 in 1,000,000 ($1 \times 10\text{-}6$) 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; NRC, 2001). 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 are initially prepared by ad hoc AEGL Development Teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the Federal Register for public comment. The reports are 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, 2001). 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 the AEGL reports, the NRC committee cannot verify all the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

Thus far, the committee has prepared four reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2000, 2002, 2003, 2004). This report is the fifth volume in that series. AEGL documents for chlorine dioxide, chlorine trifluoride, cyclohexylamine, ethylenediamine, hydrofluoroether (HFE 7100), and tetranitromethane are published as an appendix to this report. The committee concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports (NRC 1993, NRC 2001).

AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

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Chlorine Dioxide[1]

Acute Exposure Guideline Levels (AEGLs)

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 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 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:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain

[1]This document was prepared by AEGL Development Team member Cheryl Bast of Oak Ridge National Laboratory along with Robert Benson (Chemical Manager), Bill Bress and Mark McClanahan (Chemical Reviewers) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC).

asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Chlorine dioxide (ClO_2) is a yellow to reddish-yellow gas at room temperature. It has an unpleasant odor, similar to the odor of chlorine and reminiscent of nitric acid. It is a respiratory irritant. Pure chlorine dioxide is stable in the dark and unstable in light. Inhaled (airborne) chlorine dioxide acts primarily as a respiratory tract and ocular irritant. In air, chlorine dioxide readily dissociates both thermally and photochemically and may form chlorine, oxygen, hydrogen chloride, $HClO_3$, $HClO_4$.ClO, chlorine peroxide, and/or chlorine trioxide, dependent on temperature and humidity. Chlorine dioxide dissociates in water into chlorite and chloride, and to a lesser extent into chlorate (Budavari et al. 1996). The major use of chlorine dioxide is that of chemical pulp bleaching. Other uses include drinking water disinfection, the bleaching of textiles, flour, cellulose, leather, fats, oils, and beeswax; taste and odor control of water; as an oxidizing agent; and the in manufacture of chlorite salts (ACGIH

2001). In 2001, chlorine dioxide was used to decontaminate public buildings in the United States after the release of anthrax spores (ATSDR 2002). The acute inhalation database for chlorine dioxide is quite sparse for both human and animal exposures.

The AEGL-1 was based on slight salivation, slight lacrimation, and slight chromodacryorrhea in rats exposed to 3 ppm chlorine dioxide for 6 h (DuPont 1955). A modifying factor of 2 was applied to account for the sparse data base. Interspecies and intraspecies uncertainty factors of 3 each were applied because chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty/modifying factor is 20. Using the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-1 values that are not supported by the total data set by yielding a value of 0.05 ppm, which is considered excessively low in light of the fact that no irritation was noted in rats exposed to 0.1 ppm chlorine dioxide 5 h/day for 10 weeks (Dalhamn 1957) and no irritation was noted in rats exposed at 5 ppm for 15 min, 2 or 4 times/day for 1 month (Paulet and Desbrousses 1974). The AEGL-1 value was held constant across all time points because minor irritation is not likely to be time dependent.

The AEGL-2 was based on lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm chlorine dioxide for 6 h (DuPont 1955). Interspecies and intraspecies uncertainty factors of 3 each were applied because chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. A modifying factor of 2 was also applied to account for the sparse data base. Thus, the total uncertainty/modifying factor is 20. Using the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-2 values that are not supported by the total data set by yielding a 4-h AEGL-2 value of 0.23 ppm, yet rats repeatedly exposed to 3 ppm chlorine dioxide (Dupont 1955), 6 h/day for 10 days showed only minor irritation (slight salivation, slight lacrimation, and slight red ocular discharge on the first day of the study). This comparison shows that a combined uncertainty/modifying factor of 60 is excessively large. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al.

1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points (30 min, 1 h, and 4 h) and $n = 1$ (8 h) when extrapolating to longer time points using the $C^n \times t = k$ equation. The 30-min AEGL-2 value was also adopted as the 10-min AEGL-2 value due to the added uncertainty of extrapolating from a 6-h time point to 10-min.

The AEGL-3 was based on a study showing no deaths in rats exposed to 26 ppm chlorine dioxide for 6 h (DuPont 1955). Chlorine dioxide is highly reactive and causes serious adverse effects in the lung, including congestion and pulmonary edema. These effects are presumed to be the cause of death and are likely caused by a direct chemical effect on the tissue in the lung. As this effect is not expected to vary greatly among individuals or between species, intraspecies and interspecies uncertainty factors of 3 each were applied. A modifying factor of 2 was applied to account for the relatively sparse data base. Thus, the total uncertainty/ modifying factor is 20. Using the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-3 values that are not supported by the total data set by yielding a 4-h AEGL-3 value of 0.50 ppm. The value of 0.50 ppm is too low because it is below the 4-h AEGL-2 value of 0.69 ppm which was shown to be a reasonable lower limit of the disabling AEGL-2 value (see rationale above). The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points (30 min, 1 h, and 4 h) and $n = 1$ (8 h) when extrapolating to longer time points using the $C^n \times t = k$ equation. The 30-min AEGL-3 value was also adopted as the 10-min AEGL-3 value due to the added uncertainty of extrapolating from a 6-h time point to 10 min. The proposed values appear in Table 1-1.

I. INTRODUCTION

Chlorine dioxide (ClO_2) is a yellow to reddish-yellow gas at room temperature. It has an unpleasant odor, similar to the odor of chlorine and reminiscent of nitric acid. It is very reactive and a strong oxidizing agent. Pure chlorine dioxide is stable in the dark and unstable in light (Budavari

TABLE 1-1 Summary Table of AEGL Values for Chlorine Dioxide (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	Slight salivation, slight lacrimation, and slight chromodacryorrhea in rats exposed to 3 ppm for 6 h (DuPont 1955)
AEGL-2 (Disabling)	1.4 (3.9)	1.4 (3.9)	1.1 (3.0)	0.69 (1.9)	0.45 (1.2)	Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm for 6 h (DuPont 1955)
AEGL-3 (Lethal)	3.0 (8.3)	3.0 (8.3)	2.4 (6.6)	1.5 (4.1)	0.98 (2.7)	No lethality in rats exposed to 26 ppm for 6 h (DuPont 1955)

et al. 1996). Inhaled (airborne) chlorine dioxide acts primarily as a respiratory tract and ocular irritant. In air chlorine dioxide gas readily decomposes both thermally and photochemically. Thermal decomposition is characterized by a slow induction period followed by a rapid autocatalytic phase that may be explosive if the initial concentration is above a partial pressure of 76 mm Hg. Unstable chlorine oxide may be formed as an intermediate, and the presence of water vapor is hypothesized to extend the duration of the induction period by reacting with the chlorine oxide intermediate. When water vapor concentrations are high, explosivity is minimized and all decomposition occurs in the induction phase; the water vapor inhibits the autocatalytic phase. The products of thermal decomposition of gaseous chlorine dioxide include chlorine, oxygen, hydrogen chloride, $HClO_3$, and $HClO_4$. The proportions of products formed depend on the ambient temperature and concentration of water vapor (Kaczur and Cawfield 1993). Photochemical decomposition of gaseous chlorine dioxide initially involves homolytic scission of the chlorine oxygen bond to form ClO and O. These products then generate secondary products including chlorine peroxide, chlorine, oxygen, and chlo-

rine trioxide (Griese et al. 1992; Kaczur and Cawfield 1993). The chlorite ion does not persist in the atmosphere either in ionic form or as chlorite salt and is not likely to be inhaled.

In aqueous media, chlorine dioxide is relatively unstable and dissociates in water into chlorite and chloride, and to a lesser extent into chlorate (Budavari et al. 1994. Chlorine dioxide is prepared from chlorine and sodium chlorite or potassium chlorate and sulfuric acid (Budavari et al. 1996). Chlorine dioxide is always made at the place where it is used because of the risk of rapid decomposition. The production volume of chlorine dioxide was estimated from the total sodium chlorate consumption for chemical pulp bleaching, as this use accounts for > 95% of all chlorine dioxide production. The annual production of chlorine dioxide in the United States was estimated to be 79, 81, 146, 226, and 361 kilotons for the years 1970, 1975, 1980, 1985, and 1990, respectively (ATSDR 2002). As stated above, the major use of chlorine dioxide is for chemical pulp bleaching. Other uses include drinking water disinfection and the bleaching of textiles, flour, cellulose, leather, fats, oils, and beeswax; taste and odor control of water; as an oxidizing agent; and in the manufacture of chlorite salts (ACGIH 2001). In 2001, chlorine dioxide was used to decontaminate public buildings in the United States after the release of anthrax spores (ATSDR 2002). Chemical and physical properties are listed in Table 1-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

A bleach tank worker died after exposure to 19 ppm chlorine dioxide for an undetermined duration; whereas, another worker exposed at the same time survived (Elkins 1959). No other details were reported.

2.2. Nonlethal Toxicity

Elkins (1959) reported that 5 ppm chlorine dioxide was “definitely” irritating to humans. No other details were reported.

Three odor thresholds have been reported for chlorine dioxide: 0.1 ppm (Ellenhorn and Barceloux 1988), 9.4 ppm (Amoore and Hautala 1983), and 15 ppm (Vincent et al. 1946). However, there are no reliable data to support these values.

TABLE 1-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Chlorine peroxide; Chlorine oxide; Chlorine (IV) oxide	IPCS, 1993
Molecular formula	ClO_2	Budavari et al. 1996
Molecular weight	67.45	Budavari et al. 1996
CAS Registry Number	10049-04-4	ACGIH, 2001
Physical state	Gas	Budavari et al. 1996
Color	Yellow to reddish-yellow gas bluish-white liquid	Budavari et al. 1996
Solubility in water	3.01 g/l at 25°C and 34 mmHg (decompose)	Budavari et al. 1996
Vapor pressure	760 torr at 20°C	ACGIH, 2001
Vapor density (air = 1)	2.3	ACGIH, 2001
Specific gravity	1.642 at 0°C (liquid)	ACGIH, 2001
Melting point	−59°C	ACGIH, 2001
Boiling point	11°C	ACGIH, 2001
Odor	Unpleasant-similar to chlorine	Budavari et al. 1996
Conversion factors	1 ppm = 2.76 mg/m^3	

Bronchitis and emphysema were reported in a 53-year-old chemist repeatedly exposed to low concentrations of chlorine dioxide over a period of several years and to higher concentrations in conjunction with three explosions (Petry 1954). Dyspnea of increasing severity and asthmatic bronchitis were reported apparently after cessation of the exposures. No exposure concentration was reported.

A 49-year-old woman was exposed to an unknown concentration of chlorine dioxide accidentally generated while bleaching dried flowers (Exner-Friesfeld et al. 1986). She initially noticed a sharp, pungent smell and experienced coughing, pharyngeal irritation, and headache. Seven hours after exposure, she was hospitalized due to a worsening cough and dyspnea. Clinical findings included tachypnea, tachycardia, and rales on asculation. Clinical chemistry revealed marked leukocytosis. The chest x-ray was normal. The vital capacity and forced expiratory volume in 1 sec were decreased, to 73% and 70% of normal, respectively, and airway resistance was correspondingly increased. Blood gas examination revealed hypoxia despite alveolar hyperventilation. Symptoms resolved with corticosteroid treatment, and a follow-up examination two years post-exposure showed normal pulmonary function.

In another case report, Meggs et al. (1995; 1996) evaluated 13 adults (12 females and 1 male) 5 years after an occupational exposure to chlorine dioxide associated with a leak in a water purification system pipe. No exposure concentration or duration data were presented. Observed long-term effects included sensitivity to respiratory irritants (13 people), disability accompanied by loss of employment (11 people), chronic fatigue (11 people), and nasal abnormalities, including talangectasia, paleness, edema, and thick mucous (13 people). Nasal biopsies from the exposed workers showed chronic inflammation with lymphocytes and plasma cells in 11 of the 13 people. This inflammation was described as mild in two persons, moderate in eight persons, and severe in one person. Nasal biopsies of three control subjects showed mild inflammation in one subject. The number of nerve fibers in biopsies from the exposed workers was greater than in biopsies from the control group.

Gloemme and Lundgren (1957) studied 12 male employees who reported symptoms after they began work with chlorine dioxide at a sulfite-cellulose production factory. Spot samples of chlorine and chlorine dioxide during normal operations were generally <0.1 ppm. Occasional leaks from faulty vacuum lines would result in "high" levels of chlorine, chlorine dioxide, and/or sulfur dioxide. Chronic bronchitis was diagnosed in 7 of the 12 workers. The workers reported breathlessness, wheezing, irritant cough, and ocular discomfort associated with the leakages.

Ferris et al. (1967) examined 147 men employed at a pulp mill; the length of employment was not reported. The workers were exposed to sulfur dioxide or chlorine and chlorine dioxide, with average chlorine dioxide concentrations ranging from 0 to 0.25 ppm and average chlorine concentrations ranging from 0 to 7.4 ppm. (Peak chlorine dioxide concentrations reached 2 ppm, and peak chlorine concentrations reached 64 ppm.) Shortness of breath, excess phlegm, and bronchitis were noted in the workers, with workers exposed to chlorine or chlorine dioxide exhibiting more severe symptoms than those exposed only to sulfur dioxide.

Kennedy et al. (1991) compared health effects in 321 pulp mill workers exposed to chlorine dioxide and chlorine with 237 control workers at a rail yard. Personal time weighted average concentrations at the pulp mill were 5 to 14 ppm chlorine and <0.1 ppm chlorine dioxide. No air monitoring data from the rail yard were provided. Additionally, chlorine or chlorine dioxide "gassing" exposures from accidental releases were reported by 60% of the pulp mill workers. There were increased incidences of wheezing and breathlessness reported by pulp mill workers

compared to the rail yard workers; however, pulmonary function tests did not reveal any significant differences between the pulp mill workers and the rail yard controls. Airflow obstruction, as measured by FEV_1, was increased ($p < 0.05$) in the pulp mill workers experiencing "gassing" incidents compared with those not experiencing "gassing" incidents.

2.3. Developmental/Reproductive Effects

No data concerning developmental or reproductive effects of chlorine dioxide inhalation in humans were identified in the available literature; however, epidemiological studies of populations consuming chlorine dioxide- treated drinking water were located. A retrospective study was conducted using 1940s birth records from Chicopee, Massachusetts; this community utilized "relatively high" levels of chlorine dioxide for water disinfection (Tuthill et al. 1982). The morbidity and mortality experience of infants born in Chicopee was compared to that of infants born in Holyoke, Massachusetts, a geographically contiguous community that utilized traditional chlorination practices. There was no difference in fetal, neonatal, or infant mortality; or in birthweight, sex ratio or birth condition between infants born in the two communities. There was an apparent increase ($p < 0.05$) in the number of infants judged as premature by physician assessment in the chlorine-dioxide-exposed population (7.8%) compared with the control community (5.8%). However, there was no increase in prematurity when data were evaluated controlling for the age of the mother.

In another study, Kanitz et al. (1996) conducted an epidemiological study comparing 548 infants born to mothers (Genoa, Italy) who had consumed water disinfected with chlorine dioxide (<0.3 mg/mL) and/or sodium hypochlorite with 128 infants born to mothers (Chiavari, Italy) who had consumed primarily untreated well water. There was a higher frequency of infants with small (≤49.5 cm) body length in mothers exposed to chlorinated water (chlorine dioxide adjusted odds ratio [OR] = 2.0 [95% CI = 1.2-3.3]; sodium hypochlorite OR = 2.3 [95% CI = 1.3-4.2]) compared with those exposed to well water. There was also a higher frequency of infants with small (≤35 cm) cranial circumference in mothers exposed to chlorinated water (chlorine dioxide adjusted OR = 2.2 [95% CI = 1.4-3.9]; sodium hypochlorite OR = 3.5 [95% CI = 2.1-8.5]) compared with those exposed to well water. There was also an approximate doubling of cases of neonatal jaundice in infants of mothers who consumed the disinfected water. The conclusions that can be drawn

from this study are confounded by lack of quantitative exposure information, possible exposure to other chemicals in the water, and lack of consideration of nutritional and smoking habits and maternal age distribution between the two populations.

2.4. Genotoxicity

No data concerning the genotoxicity of chlorine dioxide in humans were identified in the available literature.

2.5. Carcinogenicity

No data concerning the carcinogenicity of chlorine dioxide in humans were identified in the available literature.

2.6. Summary

Deaths from chlorine dioxide exposure have occurred but exposure concentrations are unknown. Exposures that failed to result in mortality suggest that chlorine dioxide is a respiratory irritant causing wheezing, cough, dyspnea, decreased pulmonary function, and nasal pathology. Specific exposure levels and/or durations for specific symptoms were not available and were confounded by concurrent exposures to other chemicals. Information on developmental/ reproductive effects was available only for the oral route of exposure from disinfected drinking water and these studies contain many confounding variables, making it impossible to definitively attribute the effects to chlorine dioxide. No genotoxicity or carcinogenicity data were located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data are limited. A series of experiments in rats reports both lethal and nonlethal effects (DuPont 1955; Dalhamn 1957). Other lethality studies in guinea pigs, rabbits, mice, and rats are not well described. The limited data are summarized in Table 1-3.

TABLE 1-3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Clinical Signs/Comment	Reference
Rat	54	1 h	Death during exposure	Cyanosis, dyspnea, salivation, lacrimation, chromodacryorrhea	DuPont 1955
Rat	38	4.5-6 h	Death 4.5 h into exposure and 24-h post-exposure		
Rat	26	6 h	No mortality		
Rat	260	4 h	Death 1 h into exposure	Ocular discharge, epistaxis, pulmonary edema, circulatory engorgement	Dalhamn 1957
Rat	10	4 h/day x 9 days (over 13 day period)	Death after 10-13 days	Decreased body weight (2nd day), respiratory infection, kidney and liver congestion	
Rat	70	30 min	No mortality	Difficulty breathing	Hecht 1950
Rat	35	6 h	Death	—	
Rat	20	2 h	No mortality	No signs reported	
Rat	10	1 h	No mortality	No signs reported	

(Continued)

TABLE 1-3 Continued

Species	Concentration (ppm)	Exposure Time	Effect	Clinical signs/ Comment	Reference
Mouse	70	30 min	Death	Animals died night following exposure	
Mouse	35	6 h	Death	—	
Mouse	20	2 h	No mortality	No signs reported	
Mouse	10	1 h	No mortality	No signs reported	
Guinea pig	150	44 min	Death	Death occurred during exposure	Haller & Northgraves 1955
Guinea pig	150	5-15 min	Death	Death occurred 5-15 min post- exposure	
Guinea pig	1,000	3 min	Death	—	
Guinea pig	150	45 min	Death	—	Taylor et al. 1940
Guinea pig	45	40 min	No mortality	—	
Guinea pig	14-17	6 h	No mortality	—	
Guinea pig	70	30 min	No mortality	Difficulty breathing	Hecht 1950
Guinea pig	35	6 h	No mortality	Difficulty breathing	
Guinea pig	20	2 h	No mortality	Difficulty breathing	
Guinea pig	10	1 h	No mortality	Difficulty breathing	
Rabbit	70	30 min	Death	Death occurred during exposure	
Rabbit	35	6 h	Death	—	
Rabbit	20	2 h	No mortality	Difficulty breathing	
Rabbit	10	1 h	No mortality	Difficulty breathing	

3.1.1. Rats

DuPont (1955) conducted a series of acute lethality experiments in male Sprague-Dawley rats. Chlorine dioxide was generated by adding a sodium chlorite solution dropwise at a constant rate into a heated flask containing 85% phosphoric acid. Metered air was passed through the flask and then into a bell jar containing 2 or 4 rats. The chlorine dioxide concentration was determined analytically at least 3 times during each exposure period. Groups of two rats were exposed to 54 ppm chlorine dioxide for 1 h or to 38 ppm chlorine dioxide for 4.5 to 6 h. Both rats exposed to 54 ppm died during exposure. One rat exposed to 38 ppm died 4.5 h into the exposure, whereas, the other rat died within 24 h after exposure. Death was attributed to pulmonary congestion and edema observed at necropsy. No lethality was noted in a group of four rats exposed to 26 ppm chlorine dioxide for 6 h (DuPont 1955), and no pathology was observed in the one animal sacrificed 24 h post-exposure or in the remaining three animals sacrificed 10-days post-exposure. Clinical signs were similar in all treatment groups and included cyanosis, dyspnea, salivation, lacrimation, and chromodacryorrhea.

Dalhamn (1957) conducted a series of four experiments to examine both lethal and nonlethal effects of chlorine dioxide inhalation in an unspecified sex and strain of rats. The chlorine dioxide gas was generated by combining hydrochloric acid with solid sodium chlorite. The resulting chlorine and chlorine dioxide gasses were then led into a wash bottle containing sodium chlorite solution. The chlorine gas reacted with this solution to form chlorine dioxide. The chlorine dioxide was then dissolved in distilled water to avoid the presence of chlorine gas in the experiments. Compressed air was then bubbled through the pure chlorine dioxide solution to generate the chlorine dioxide for the rats to inhale. In one experiment, four rats were exposed to approximately 260 ppm chlorine dioxide for 2 h. To maintain a fairly constant concentration, the gas was changed every half-hour; the reported concentrations were 265, 264, 266, and 245 ppm, respectively. Ocular discharge and epistaxis were observed, and one rat died after exposure for 1 h. The other rats were sacrificed immediately after the 2-h exposure. Pulmonary edema and circulatory engorgement were noted in all four rats; however, no control data were presented.

In another experiment, Dalhamn (1957) exposed five rats to 0 or 10 ppm chlorine dioxide 4 h/day for 9 days over a 13 day period. The exposed rats exhibited rhinorrhea and labored respiration and weighed 20-33% less than controls from days 10 to 13. One rat died after 10 expo-

sures, two died on day 11, and the final two died on day 13. Necropsy showed respiratory infection, and acute renal and hepatic congestion in treated rats. No effects were noted in controls.

Hecht (1950) reported that rats exposed to 35 ppm chlorine dioxide for 6 h died. No deaths were reported in rats exposed to 70 ppm for 30 min, 20 ppm for 2 h, or 10 ppm for 1 h. No experimental details were described.

3.1.2. Mice

Hecht (1950) reported that mice exposed to 70 ppm chlorine dioxide for 30 min died during the night following exposure. Mice exposed to 35 ppm for 6 h died, and no deaths were reported in mice exposed to 20 ppm for 2 h, or 10 ppm for 1 h. No experimental details were described.

3.1.3. Guinea Pigs

Hecht (1950) reported no deaths in guinea pigs exposed to 70 ppm chlorine dioxide for 30 min, 35 ppm for 6 h, 20 ppm for 2 h, or 10 ppm for 1 h. No experimental details were described.

Taylor et al. (1940) reported lethality in guinea pigs exposed to 150 ppm chlorine dioxide for 45 min. No deaths were reported in guinea pigs exposed to 14-17 ppm for 6 h or 45 ppm for 45 min. No experimental details were described.

Haller and Northgraves (1955) reported that guinea pigs died during exposure to 150 ppm chlorine dioxide for 44 min. Deaths were also reported in guinea pigs exposed to 150 ppm for 5-15 min and 1,000 ppm for 3 min. No experimental description was provided.

3.1.4. Rabbits

Hecht (1950) reported deaths in rabbits exposed to 70 ppm chlorine dioxide for 30 min and 35 ppm for 6 h. No deaths were reported in rabbits exposed to 20 ppm for 2 h or 10 ppm for 1 h. No experimental details were described.

3.2. Nonlethal Toxicity

3.2.1. Rats

DuPont (1955) conducted a series of repeated-exposure experiments in male Sprague-Dawley rats. Chlorine dioxide was generated by adding a sodium chlorite solution dropwise at a constant rate into a heated flask containing 85% phosphoric acid. Metered air was passed through the flask and then into a bell jar containing 2 or 4 rats. The chlorine dioxide concentration was determined analytically at least three times during each exposure period. A group of four rats was exposed to 12 ppm chlorine dioxide, 6 h/day for 6 or 7 days. Clinical signs observed on the first day of the study included lacrimation, salivation, dyspnea, weakness, and pallor. These signs increased in severity with repeated exposures. All of the rats survived through the sixth exposure. Two of the rats died after the sixth exposure, and two were sacrificed for pathology after the seventh exposure. Necropsy revealed acute bronchitis and emphysema, but no evidence of pulmonary edema, in all four rats.

DuPont (1955) also similarly exposed a group of four rats to 3 ppm chlorine dioxide, 6 h/day for 10 days. Clinical signs observed on the first day of the study included slight salivation, slight lacrimation, and slight chromodacryorrhea. These signs increased in severity with repeated exposures. No animals died, and no gross or microscopic pathology was observed when rats were sacrificed immediately after the tenth exposure.

As mentioned in Section 3.1.1, Dalhamn (1957) conducted a series of four experiments to examine both lethal and nonlethal effects of chlorine dioxide inhalation in an unspecified sex and strain of rats. In one experiment, three rats were exposed once a week for 3 min to decreasing concentrations of chlorine dioxide; the animals were exposed to 3435 ppm chlorine dioxide on day 1, to 1,118 ppm on day 8, and to 760 ppm on day 16. A group of three rats was exposed to compressed air and served as controls. Respiratory distress was observed and mean body weight of the exposed rats was 10% below that of controls on day 16. Necropsy revealed bronchopneumonia and hyperemia of the renal corticomedullary junction in two of the exposed rats; however, the lungs and kidneys of the third exposed rat were normal. The lungs were normal in all three control rats; however, renal hyperemia was noted in two.

In another experiment, Dalhamn (1957) exposed groups of five rats to 0 or 0.1 ppm chlorine dioxide 5 h/day for 10 weeks. No clinical signs were observed during treatment and no treatment-related effects were noted at necropsy.

Paulet and Desbrousses performed a series of repeated-exposure studies in rats. Unfortunately, for the purposes of AEGL derivation, data after single exposures were not reported. Groups of five male and five female rats were exposed to 10 ppm chlorine dioxide, 2 h/day for 30 days. Groups of 10 male and 10 female rats were exposed to 5 ppm, 2 h/day for 30 days, and groups of 10 male and 10 female rats were exposed to 2.5 ppm, 7 h/day for 30 days (Paulet and Desbrousses (1970). The strain of rat was not specified; control groups with equal numbers of rats were used for each exposure scenario. Nasal discharge, red eyes, and bronchopneumonia accompanied by desquamation of alveolar epithelium were observed at 5 and 10 ppm, with effects being more severe at 10 ppm. Increased erythrocyte and leukoctye counts were noted in animals exposed to 10 ppm chlorine dioxide. Rats exposed to 2.5 ppm exhibited lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi. No effects were reported in control animals. In another report, Paulet and Desbrousses (1972) exposed a group of eight Wistar rats (sex not reported) to 1 ppm chlorine dioxide, 5 h/day, 5 days/week for 2 months. Vascular congestion and peribronchiolar edema were observed at necropsy.

In another study, Paulet and Desbrousses (1974) exposed groups of 10-15 rats (sex and strain not reported) to 0, 5, 10, or 15 ppm chlorine dioxide, 15 min, 2 or 4 times/day for 1 month. At 15 ppm, mortality was observed in 1/10 rats exposed 2 times/day and in 1/15 rats exposed 4 times/day. Decreased body weight, nasal and ocular inflammation and discharge, bronchitis, and peribronchiolar lesions were observed at 15 ppm; effects were more severe in animals exposed 4 times/day. Alveolar irritation and decreased body weight were observed at 10 ppm, and no effects were reported at 5 ppm.

3.2.2. Rabbits

A group of four rabbits was exposed to 5 ppm chlorine dioxide, 2 h/day for 30 days, and a group of eight rabbits was exposed to 2.5 ppm, 4 h/day for 45 days (Paulet and Desbrousses 1970). The strain and sex were not specified; control groups with equal numbers of rabbits were used for each exposure scenario. Nasal discharge, red eyes, and bronchopneumonia accompanied by desquamation of alveolar epithelium were observed at 5 ppm. Rabbits exposed to 2.5 ppm exhibited hemorrhagic alveoli and congested capillaries in the lungs at study termination. Pul-

monary effects had resolved in animals sacrificed 15 days after exposure termination (2.5 ppm group).

3.3. Developmental/Reproductive Effects

No information regarding developmental/reproductive effects of chlorine dioxide in animals via the inhalation route was located in the available literature. However, several oral studies were available. No developmental or reproductive effects were noted in Long-Evans rats administered daily gavage doses of 0, 2.5, 5, or 10 mg/kg chlorine dioxide in water (Carlton et al. 1991). Groups of 12 males were treated for 56 days prior to mating and throughout the 10-day mating period, and groups of 24 females were treated 14 days prior to mating, during the mating period and during gestation and lactation.

In another gavage study, Toth et al. (1990) administered daily doses of 0 or 14 mg/kg chlorine dioxide to four male and four female Long-Evans rat pups on postnatal days 1-20. Body weight of treated rats was decreased on days 11, 21, and 35, and forebrain weight was decreased on days 21 and 35. Decreased protein content and DNA content of the brain were also observed on days 21 and 35.

Taylor and Pfohl (1985) administered 0 or 100 ppm chlorine dioxide to female Sprague-Dawley rats in the drinking water 14 days prior to gestation and throughout gestation and lactation. Decreased brain weight, due mainly to a decrease in cerebellar weight, was observed in 21-day-old pups from treated dams. A decrease in total cerebellar DNA content was also noted in these pups. A decrease in exploratory behavior was observed in the 60-day-old pups of treated dams.

Taylor and Pfohl (1985) also administered 0 or 14 mg/kg chlorine dioxide to male Sprague-Dawley rat pups from untreated dams via gavage on postnatal days 5 to 20. Decreased body weight, absolute and relative whole brain and forebrain weights, and forebrain DNA content were observed in 21-day-old treated pups. Decreased home cage activity was observed on days 18-19, and wheel-running activity was decreased on day 10. No other effects were reported.

In another study, groups of six to eight female Sprague-Dawley rats were administered 0, 1, 10, or 100 ppm chlorine dioxide in the drinking water for 2.5 months prior to mating and during gestation days 0-20 (Suh, et al. 1983). There was a trend for decreasing number of implants per litter and number of live fetuses per dam. Total fetal weight and male fetal weight were increased at 100 ppm.

In another drinking water study, groups of 12 female Sprague-Dawley rats were administered 0 or 100 ppm chlorine dioxide for 10 days prior to mating and during the gestation and lactation periods (Mobley et al. 1990). The litter weight of treated animals was lower than controls at birth. Also, chlorine dioxide treated pups exhibited decreased exploratory activity on postconception days 36-38 but not on days 39-40.

3.4. Genotoxicity

No information regarding the genotoxicity of chlorine dioxide in animals via inhalation was located in the available literature. Chlorine dioxide was positive in an in vivo micronucleus assay in mice after an i.p. injection of 3.2-25 mg/kg chlorine dioxide (Hayashi et al. 1988). Meier et al. (1985) administered 0.1 to 0.4 mg chlorine dioxide by gavage to Swiss CD-1 mice for 5 consecutive days; there was no evidence of increased incidences of micronuclei or bone marrow chromosomal aberrations and no effect on sperm head morphology. In an in vitro study, chlorine dioxide was negative for chromosome aberrations in Chinese hamster fibroblast cells (Ishidate et al. 1984). It was negative in the Salmonella typhimurium reverse mutation assay without activation and positive with activation (Ishidate et al. 1984); however, water samples disinfected with chlorine dioxide were negative both with and without activation (Miller et al. 1986).

3.5. Chronic Toxicity/Carcinogenicity

No information regarding the carcinogenicity of chlorine dioxide in animals via the inhalation route was located in the available literature. In a dermal exposure study, the dorsal area of groups of five female SENCAR mice were shaved and the mice were placed in chambers containing 0, 1, 10, 100, 300, or 1000 ppm chlorine dioxide dissolved in water, 10 min/day for 4 days (Robinson et al. 1986). The chambers were designed to prevent inhalation of vapors. An increase in epidermal thickness, suggesting epidermal hyperplasia, was noted at 300 and 1000 ppm.

Miller et al. (1986) tested the carcinogenic potential of concentrates prepared from chlorine dioxide disinfected drinking water in several short-term assays. The concentrates did not increase the incidence of lung adenomas in strain A mice, skin tumor frequency in SENCAR mice, or gammaglutamyl transpeptidase positive foci in rat livers.

3.6. Summary

Lethality data are very limited; no LC_{50} values were available. Reports of lethality were available for rats, mice, guinea pigs and rabbits; however, experimental details were generally poorly reported. Pulmonary congestion and edema were noted at necropsy in some animals after lethal exposure to chlorine dioxide. Sublethal studies were also limited and most used repeat exposure protocols; however, limited data were available describing clinical signs observed after the first exposure. Chlorine dioxide is an irritant as evidenced by lacrimation, salivation, dyspnea, weakness, and pallor, and by difficulty breathing, nasal discharge, ocular irritation and pneumonia observed in rats during or after exposure to sublethal concentrations of chlorine dioxide. Developmental delays were observed in animals following ingestion of chlorine dioxide in water. Genotoxicity studies with chlorine dioxide yielded both positive and negative results and no long-term carcinogenicity studies were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data concerning the metabolism of chlorine dioxide after inhalation were available.

Information regarding the metabolism of chlorine dioxide via ingestion is available. The chloride ion is the ultimate metabolite of chlorine dioxide after oral administration. After a single gavage dose of 100 mg/L $36ClO_2$ in rats, 87% of the radiolabeled chlorine in the urine was in the form of chloride ion and 80% of the label in the plasma was in the form of chloride (Abdel-Rahman et al. 1980a). Chlorite was also a major metabolite accounting for 11% and 21% of label in the urine and plasma, respectively. Approximately 2% of the urinary ^{36}Cl was in the form of chlorate. The radioactive label was primarily excreted in the urine; during the first 24 h after dosing, 18% of the label was in the urine, and 4.5% was detected in the feces. The 72-h sample contained 31% of the label in the urine and 4.5% in the feces. No label was detected in expired air. No parent compound was detected in the urine (Abdel-Rahman et al. 1984a).

The metabolic pathways of inhaled and ingested chlorine dioxide are likely different because chlorine dioxide dissociates in air to form chlorine, oxygen, hydrogen chloride, $HClO_3$, $HClO_4$.ClO, chlorine per-

oxide, and/or chlorine trioxide, dependent on temperature and humidity (Griese et al. 1992; Kaczur and Cawfield 1993) and because chlorite does not persist in the atmosphere either in the ionic form or as the chlorite salt. Given the fact that gaseous chlorine dioxide readily decomposes, it is unlikely that chlorite would be formed from parent chlorine dioxide in the aqueous mucus of the upper respiratory tract; and if the chlorite were to form, it is unlikely that a sufficient amount would be absorbed to induce toxic effects similar to those noted after ingestion of chlorine dioxide in aqueous media. Therefore, use of metabolic information regarding exposure to chlorine dioxide in aqueous media is rather limited for the purposes of derivation of AEGL values for inhalation exposure.

4.2. Mechanism of Toxicity

Inhaled (airborne) chlorine dioxide primarily acts as a respiratory tract and ocular irritant. Lacrimation, salivation, dyspnea, weakness, pallor, and pulmonary congestion and edema were noted in rats after acute exposure to chlorine dioxide (DuPont 1955). Alveolar congestion and hemorrhage, bronchial inflammation, and peribronchiolar edema have also been noted in rats and rabbits after inhalation of chlorine dioxide (Paulet and Desbrousses 1970, 1972, 1974). Limited data from human exposure also indicate respiratory irritation (Elkins 1959; Exner-Friesfeld et al. 1986; Meggs et al. 1996).

After oral exposure to sufficiently high doses, chlorine dioxide may produce hematologic effects such as methemoglobenia and Heinz Body hemolytic anemia. Due to its highly reactive nature, it is unlikely that chlorine dioxide would be absorbed in amounts great enough to produce this toxicity directly. Chlorite is produced and absorbed following oral exposure to chlorine dioxide in animals (Abdel-Rahman et al. 1980a), and is likely responsible for the hematological effects. Chlorite has been shown to be more efficient than chlorine dioxide in the production of methemoglobin, in decreasing blood glutathione, and in alteration of red blood cells (Abdel-Rhaman et al. 1980b; 1984b). Furthermore, in vitro studies have shown that ample amounts of glutathione may prevent chlorine-dioxide (chlorite)- induced osmotic fragility by prevention of the formation of disulfide bonds between hemoglobin and cell membrane components (Abdel-Rhaman et al. 1984b). Thus, it is the chlorine dioxide metabolites and byproducts (especially chlorite) that are responsible for toxicological effects from ingested chlorine dioxide. The chlorite

(CLO_2^-) does not persist in the atmosphere either in ionic form or chlorite salt and, thus is not likely to be inhaled (ATSDR 2002). Therefore, the use of information regarding exposure to chlorine dioxide in aqueous media is limited for the purposes of derivation of AEGL values for inhalation exposure.

4.3. Structure-Activity Relationships

No structure-activity relationships were applicable for establishing AEGLs for chlorine dioxide.

4.4. Other Relevant Information

4.4.1. Species Differences

Data are sparse, inconsistent, and inadequate for comparing differential species sensitivities after chlorine dioxide inhalation.

4.4.2. Susceptible Populations

No data were available concerning susceptible populations following inhalation of chlorine dioxide. However, chlorine dioxide is an ocular and respiratory irritant.

Developmental delays were observed in neonates following ingestion of chlorine dioxide, suggesting that they may be a sensitive subpopulation. However, the reason for this increased sensitivity is not known (EPA, 2000).

Smith and Wilhite (1990) have suggested that individuals undergoing hemodialysis may be at increased risk of erythrocyte damage from water disinfected with chlorine dioxide. Also, persons with an inherited deficiency of red blood cell glucose-6-phosphate dehydrogenase may also be more sensitive to water disinfected with chlorine dioxide than healthy people because chlorite produced in situ can induce Heinz body hemolytic anemia (HBHA) in people deficient in erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) (Calabrese et al. 1979; Moore et al. 1978). Furthermore, subpopulations with abnormal hemoglobins (HbM or HbH) are at increased risk to systemic chlorine dioxide poisoning because these hemoglobins are much more sensitive to oxidant chemicals,

and finally, newborns may be especially susceptible because of the high content of hemoglobin F and their very sluggish methemoglobin reductase. However, it is unlikely that these populations would also have an increased susceptibility to inhaled chlorine dioxide because the chlorite moiety is not present when exposure is via inhalation.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate for derivation of an empirically derived-chemical specific scaling exponent for chlorine dioxide. To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling will be performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

4.4.4. Concurrent Exposure Issues

Occupational accidental exposures to chlorine dioxide have occurred with exposure to chlorine and sulfur dioxide; however, information relevant to derivation of AEGL values was not located.

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data were available for derivation of AEGL-1 values from chlorine dioxide. Occupational exposures were generally to a mixture of chlorine-containing chemicals.

5.2. Animal Data Relevant to AEGL-1

Animal studies describing effects consistent with the definition were limited to one study. Slight lacrimation, slight salivation, and slight chromodacryorrhea were observed in rats exposed to 3 ppm chlorine dioxide for 6 h (DuPont 1955).

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5.3. Derivation of AEGL-1

The AEGL-1 was based on slight salivation, slight lacrimation, and slight chromodacryorrhea in rats exposed to 3 ppm chlorine dioxide for 6 h (DuPont 1955). A modifying factor of 2 will be applied to account for the sparse data base. Interspecies and intraspecies uncertainty factors of 3 each will be applied because chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty/modifying factor is 20. Using the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-1 values that are not supported by the total data set by yielding a value of 0.05 ppm, which is considered excessively low in light of the fact that no irritation was noted in rats exposed to 0.1 ppm chlorine dioxide 5 h/day for 10 weeks (Dalhamn 1957) and no irritation was noted in rats exposed at 5 ppm for 15 min, 2 or 4 times/day for 1 month (Paulet and Desbrousses 1974). The AEGL-1 value was held constant across all time points because minor irritation is not likely to be time dependent. AEGL-1 values are presented in Table 1-4 and Appendix A.

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

Elkins (1959) reported that 5 ppm chlorine dioxide was "definitely" irritating to humans; however no other details were reported. Other studies also reported effects consistent with the definition of AEGL-2; however, neither the exposure duration and/or concentration were clearly measured. Thus, these studies cannot be used for derivation of AEGL-2 values.

TABLE 1-4 AEGL-1 Values for Chlorine Dioxide

10 min	30 min	1 h	4 h	8 h
0.15 ppm ($0.41\ mg/m^3$)	0.15 ppm ($0.41\ mg/m^3$)	0.15 ppm ($0.41\ mg/m^3$)	0.15 ppm ($0.41\ mg/m^3$)	0.15 ppm ($0.41\ mg/m^3$)

6.2. Animal Data Relevant to AEGL-2

Animal studies describing effects at concentrations below those causing incapacitation or unconsciousness from single chlorine dioxide inhalation exposure were limited. Lacrimation, salivation, dyspnea, weakness, and pallor were observed in rats exposed to 12 ppm chlorine dioxide for 6 h (DuPont 1955). Difficulty breathing was noted in guinea pigs and rats exposed to 70 ppm for 30 min, guinea pigs exposed to 35 ppm for 6 h, and guinea pigs and rabbits exposed to 20 ppm for 2 h or 10 ppm for 1 h (Hecht 1950). No effects were noted in rats and mice exposed to 20 ppm chlorine dioxide for 2 h or 10 ppm for 1 h (Hecht 1950).

6.3. Derivation of AEGL-2

The lacrimation, salivation, dyspnea, weakness, and pallor noted in rats exposed to 12 ppm chlorine dioxide for 6 h will be used to derive AEGL-2 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. A modifying factor of 2 will also be applied to account for the sparse data base. Thus, the total uncertainty/modifying factor is 20. Using the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-2 values that are not supported by the total data set by yielding a 4-h AEGL-2 value of 0.23 ppm, yet rats repeatedly exposed to 3 ppm chlorine dioxide (Dupont 1955), 6 h/day for 10 days showed only minor irritation (slight salivation, slight lacrimation, and slight red ocular discharge on the first day of the study). This comparison shows that a combined uncertainty/modifying factor of 60 is excessively large. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points (30 min, 1 h, and 4-h) and n = 1 (8 h) when extrapolating to longer time points using the $C^n \times t = k$ equation. The 30-min AEGL-2 value was also adopted as the 10-min AEGL-2 value due to the added uncertainty of extrapolating from a 6-h time point to 10 min. AEGL-2 values appear in Table 1-5 below and calculations are in Appendix A.

TABLE 1-5 AEGL-2 Values for Chlorine Dioxide

10 min	30 min	1 h	4 h	8 h
1.4 ppm (3.9 mg/m^3)	1.4 ppm (3.9 mg/m^3)	1.1 ppm (3.0 mg/m^3)	0.69 ppm (1.9 mg/m^3)	0.45 ppm (1.2 mg/m^3)

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No human studies of sufficient exposure duration with measured concentrations and producing irreversible or life-threatening effects were located in the available literature.

7.2. Animal Data Relevant to AEGL-3

Non-lethal concentrations of chlorine dioxide were identified in several studies. No deaths were noted in rats exposed to 26 ppm chlorine dioxide for 6 h (DuPont 1955). Taylor et al. (1940) found no deaths in guinea pigs exposed to 14-17 ppm for 6 h or 45 ppm for 45 min. No deaths were noted in guinea pigs and rats exposed to 70 ppm for 30 min (deaths were observed in rabbits and mice exposed to 70 ppm for 30 min (Hecht 1950). No guinea pigs died when exposed to 35 ppm chlorine dioxide for 6 h; however, rabbits, rats, and mice died when similarly exposed (Hecht 1950). Hecht (1950) observed no deaths in guinea pigs, rabbits, rats and mice exposed to 20 ppm chlorine dioxide for 2 h or 10 ppm for 1 h.

7.3. Derivation of AEGL-3

The DuPont (1955) data showing no mortality in rats exposed to 26 ppm for 6 h will be utilized for the derivation of AEGL-3 values; this data set was chosen since DuPont (1955) is more robust than the other studies. Chlorine dioxide is highly reactive and causes serious adverse effects in the lung, including congestion and pulmonary edema. These effects are presumed to be the cause of death and are likely caused by a direct chemical effect on the tissue in the lung. As this effect is not expected to vary greatly among individuals or between species, intraspecies modifying factor of 2 will also be applied to account for the relatively sparse database. Thus, the total uncertainty/modifying factor is 20. Using

the default value of 10 for either intra- or interspecies variability would bring the total adjustment to 60 (total UF × MF) instead of 20. This would generate AEGL-3 values that are not supported by the total data set by yielding a 4-h AEGL-3 value of 0.50 ppm. The value of 0.50 ppm is too low because it is below the 4-h AEGL-2 value of 0.69 ppm which was shown to be a reasonable lower limit of the disabling AEGL-2 value (see rationale above). The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points (30 min, 1 h, and 4-h) and $n = 1$ (8 h) when extrapolating to longer time points using the $C^n \times t = k$ equation. The 30-min AEGL-3 value will also be adopted as the 10-min AEGL-3 value due to the added uncertainty of extrapolating from a 6-h time point to 10 min. AEGL-3 values appear in Table 1-6 below and calculations are in Appendix A.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values are summarized in Table 1-7.

8.2. Comparisons with Other Standards and Guidelines

The values appear in Table 1-8.

8.3. Data Adequacy and Research Needs

The data base for single inhalation-exposure animal studies is very sparse and many of the studies that do exist are dated and poorly reported. There are also no clear data on human exposure concentrations for short inhalation exposure durations. The sparse data base necessitated application of a modifying factor.

TABLE 1-6 AEGL-3 Values for Chlorine Dioxide

10 min	30 min	1 h	4 h	8 h
3.0 ppm (8.3 mg/m^3)	3.0 ppm (8.3 mg/m^3)	2.4 ppm (6.6 mg/m^3)	1.5 ppm (4.1 mg/m^3)	0.98 ppm (2.7 mg/m^3)

TABLE 1-7 Summary of AEGL Values for Chlorine Dioxide (ppm [mg/m^3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)
AEGL-2 (Disabling)	1.4 (3.9)	1.4 (3.9)	1.1 (3.0)	0.69 (1.9)	0.45 (1.2)
AEGL-3 (Lethal)	3.0 (8.3)	3.0 (8.3)	2.4 (6.6)	1.5 (4.1)	0.98 (2.7)

TABLE 1-8 Extant Standards and Guidelines for Chlorine Dioxide (ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.15	0.15	0.15	0.15	0.15
AEGL-2	1.4	1.4	1.1	0.69	0.45
AEGL-3	3.0	3.0	2.4	1.5	0.98
ERPG-1[a]			NA		
ERPG-2[a]			0.5		
ERPG-3[a]			3		
NIOSH REL[b]					0.1
NIOSH IDLH[c]		5			
NIOSH STEL[d]					0.3
OSHA PEL-TWA[e]					0.1
ACGIH-TLV TWA[f]					0.1
ACGIH-TLV STEL[g]			0.3 (20 min, 3 times/day)		
MAK (German)[h]	0.1				
MAC (Dutch)[i]	0.1				

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2002). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for chlorine dioxide is not appropriate. The ERPG-2 is the maximum airborne concen-

(Continued)

tration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for chlorine dioxide is based on human and animal experience and should protect sensitive individuals from irritant effects and accounts for the poor database. It is noted that subchronic animal data may support a higher value. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for chlorine dioxide is based on collective acute and subacute lethality data in animals.

[b]NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH 1997) is defined analogous to the ACGIH TLV-TWA.

[c]Immediately Dangerous to Life and Health (IDLH) is defined by the NIOSH/OSHA Standard Completions Program only for the purpose of respirator selection and represents a maximum concentration from which, in the event of respiratory failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health effects. (Basis: Acute inhalation toxicity in humans, Elkins 1959).

[d]NIOSH (1997) STEL is a 15-min TWA exposure that should not be exceeded at any time during a workday.

[e]OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 1997) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[f]ACGIH (2001) Threshold Limit Value.

[g]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2000) 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.

[h]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) Deutsche Forschungsgemeinschaft (German Research Association) 2000 is defined analogous to the ACGIH-TLV-TWA. Value is a 15-min TWA based on respiratory irritation. No 8 h limit was established because of the corrosive properties of chlorine dioxide.

[i]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA. Value is a 15-min TWA based on respiratory irritation. No 8 h limit was established because of the corrosive properties of chlorine dioxide.

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APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	DuPont 1955
Toxicity end point:	Slight lacrimation, slight salivation, and slight chromodacryorrhea in rats exposed to 3 ppm for 6 h.
Scaling:	None. Value was held constant across time points since minor irritation is unlikely to be time dependent.
Uncertainty factors:	3 for interspecies 3 for intraspecies
Modifying factor:	2 for sparse data base
Total uncertainty/ modifying factor:	20
	10 min, 30 min, 1 h, 4 h, 8 h: 3 ppm ÷ 20 = 0.15 ppm

Derivation of AEGL-2

Key study:	DuPont 1955
Toxicity end point:	Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm for 6 h.
Scaling:	$C^3 \times t = k$ (default for long- to short-time extrapolation) $C^1 \times t = k$ (default for short- to long-time extrapolation)

Uncertainty factors:	3 for interspecies 3 for intraspecies
Modifying factor:	2 for sparse database
Total:	20
Scaling:	$C^3 \times t = k$ (30 min, 1 h, 4 h) $(12 \text{ ppm})^3 \times 6 \text{ h} = 10{,}368 \text{ ppm·h}$ $C^1 \times t = k$ (8 h) $(12 \text{ ppm})^1 \times 6 \text{ h} = 72 \text{ ppm·h}$
10 min AEGL-2	1.38 ppm (The 30-min AEGL-2 is adopted as the 10-min value)
30 min AEGL-2	$C^3 \times 0.5 \text{ h} = 10{,}368 \text{ ppm·h}$ $C^3 = 20{,}736 \text{ ppm}$ $C = 27.5 \text{ ppm}$ 30 min AEGL-2 = $27.5 \div 20 = 1.38$ ppm
1 h AEGL-2	$C^3 \times 1 \text{ h} = 10{,}368 \text{ ppm·h}$ $C^3 = 10{,}368 \text{ ppm}$ $C = 21.8 \text{ ppm}$ 1 h AEGL-2 = $21.8 \div 20 = 1.09$ ppm
4 h AEGL-2	$C^3 \times 4 \text{ h} = 10{,}368 \text{ ppm·h}$ $C^3 = 2592 \text{ ppm}$ $C = 13.7 \text{ ppm}$ 4 h AEGL-2 = $13.7 \div 20 = 0.69$ ppm
8 h AEGL-2	$C^1 \times 8 \text{ h} = 72 \text{ ppm·h}$ $C^1 = 9 \text{ ppm}$ 8 h AEGL-2 = $9 \div 20 = 0.45$ ppm

Derivation of AEGL-3

Key study:	DuPont 1955
Toxicity end point:	No mortality in rats exposed to 26 ppm for 6 h.
Scaling:	$C^3 \times t = k$ (default for long- to short-time

	extrapolation)
	$C^1 \times t = k$ (default for short- to long-time extrapolation)
Uncertainty factors:	3 for interspecies 3 for intraspecies
Modifying factor:	2 for sparse database
Total:	20
Scaling:	$C^3 \times t = k$ (30 min, 1 h, 4 h) $(26 \text{ ppm})^3 \times 6 \text{ h} = 105{,}456 \text{ ppm·h}$
	$C^1 \times t = k$ (8 h) $(26 \text{ ppm})^1 \times 6 \text{ h} = 156 \text{ ppm·h}$
10 min AEGL-3	2.98 ppm (The 30 min AEGL-3 is adopted as the 10-min value)
30 min AEGL-3	$C^3 \times 0.5 \text{ h} = 105{,}456 \text{ ppm·h}$ $C^3 = 210912$ ppm C = 59.5 ppm 30 min AEGL-3 = 59.5 ÷ 20 = 2.98 ppm
1 h AEGL-3	$C^3 \times 1 \text{ h} = 105{,}456 \text{ ppm·h}$ $C^3 = 105{,}456$ ppm C = 47.2 ppm 1 h AEGL-3 = 47.2 ÷ 20 = 2.36 ppm
4 h AEGL-3	$C^3 \times 4 \text{ h} = 105{,}456 \text{ ppm·h}$ $C^3 = 26{,}364$ ppm C = 29.8 ppm 4 h AEGL-3 = 29.8 ÷ 20 = 1.49 ppm
8 h AEGL-3	$C^1 \times 8 \text{ h} = 156 \text{ ppm·h}$ C = 19.5 ppm 8 h AEGL-3 = 19.5 ÷ 20 = 0.975 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLORINE DIOXIDE (CAS No. 10049-04-4)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm

Key Reference: DuPont (1955). Summary of Toxicological Evaluations of Chlorine Dioxide. Haskell Laboratory for Toxicology and Industrial Medicine, Haskell Lab Report No. 80-55 E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

Test Species/Strain/Number: Rat/Sprague-Dawley/male/4.

Exposure Route/Concentrations/Durations: Inhalation/ 3 ppm/ 6 h.

Effects: Slight lacrimation, slight salivation, slight chromodacryorrhea.

End point/Concentration/Rationale: Slight lacrimation, slight salivation, slight chromodacryorrhea in rats exposed to 3 ppm for 6 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues. This type of port-of-entry effect not expected to vary greatly between species or among individuals. Using the default value of 10 for either intra- or interspecies variability would generate AEGL-1 values that are not supported by the total data set by yielding a value of 0.05 ppm, which is considered excessively low in light of the fact that no irritation was noted in rats exposed to 0.1 ppm chlorine dioxide 5 h/day for 10 weeks (Dalhamn 1957) and no irritation was noted in rats exposed at 5 ppm for 15 min, 2 or 4 times/day for 1 month (Paulet and Desbrousses 1974).

Modifying Factor: 2—sparse database.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: AEGL-1 values were held constant across time points since minor irritation is unlikely to vary with time.

Data Adequacy: Data are extremely sparse. The AEGL-1 value is considered protective because no irritation was noted in rats exposed to 0.1 ppm chlorine dioxide 5 h/day for 10 weeks (Dalhamn, 1957) and no irritation was noted in rats exposed at 5 ppm for 15 min, 2 or 4 times/day for 1 month (Paulet and Desbrousses, 1974).

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.4 ppm	1.4 ppm	1.1 ppm	0.69 ppm	0.45 ppm

Key Reference: DuPont (1955). Summary of Toxicological Evaluations of Chlorine Dioxide. Haskell Laboratory for Toxicology and Industrial Medicine, Haskell Lab Report No. 80-55 E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

Test Species/Strain/Sex/Number: rat/Sprague-Dawley/male/4.

Exposure Route/Concentrations/Durations: Inhalation, 12 ppm for 6 h.

Effects: Lacrimation, salivation, dyspnea, weakness, and pallor.

End point/Concentration/Rationale: Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm for 6 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues. This type of port-of-entry effect is not expected to vary greatly between species or among individuals. Using the default value of 10 for either intra- or interspecies variability would generate AEGL-2 values that are not supported by the total data set by yielding a 4-h AEGL-2 value of 0.23 ppm, yet rats repeatedly exposed to 3 ppm chlorine dioxide (Dupont, 1955), 6 h/day for 10 days showed only minor irritation (slight salivation, slight lacrimation, and slight red ocular discharge on the first day of the study).

Modifying Factor: 2—sparse database.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: $C^n \times t = k$, where the exponent, n, is the conservative default of 1 and k is 72 ppm·h (8 h) or 3 and k is 10,368 ppm·h (30 min, 1 h, 4 h). The 30-min AEGL-2 value was adopted as the 10-min value.

Data Adequacy: Both human and animal data are extremely sparse.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.0 ppm	3.0 ppm	2.4 ppm	1.5 ppm	0.98 ppm

Key Reference: DuPont (1955). Summary of Toxicological Evaluations of Chlorine Dioxide. Haskell Laboratory for Toxicology and Industrial Medicine, Haskell Lab Report No. 80-55 E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

Test Species/Strain/Sex/Number: rat/Sprague-Dawley/male/2 or 4

Exposure Route/Concentrations/Durations: Inhalation, 54 ppm for 1 h, 38ppm for 4.5-6 h, 26 ppm for 6 h.

Effects:
54 ppm, 1 h: death of 2/2 rats
38 ppm, 4.5-6 h: death of 2/2 rats
26 ppm, 6 h: No deaths of 4/4 rats

End point/Concentration/Rationale: No mortality/26 ppm for 6 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Chlorine dioxide is highly reactive and causes serious adverse effects in the lung, including congestion and pulmonary edema. These effects are presumed to be the cause of death and are likely caused by a direct chemical effect on the tissue in the lung. This effect is not expected to vary greatly between species or among individuals. Using the default value of 10 for either intra- or interspecies variability would generate AEGL-3 values that are not supported by the total data set by yielding a 4-h AEGL-3 value of 0.50 ppm. The value of 0.50 ppm is too low because it is below the 4-h AEGL-2 value of 0.69 ppm which was shown to be a reasonable lower limit for the disabling AEGL-2 value.

Modifying Factor: 2—sparse database.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: $C^n \times t = k$, where the exponent, n, is the conservative default of 1 and k is 156 ppm·h (8 h) or 3 and k is 105,456 ppm·h (30 min, 1 h, 4 h). The 30 min AEGL-3 value was adopted as the 10-min value.

Data Adequacy: Both human and animal data are extremely sparse.

APPENDIX C

CATEGORY PLOT FOR CHLORINE DIOXIDE

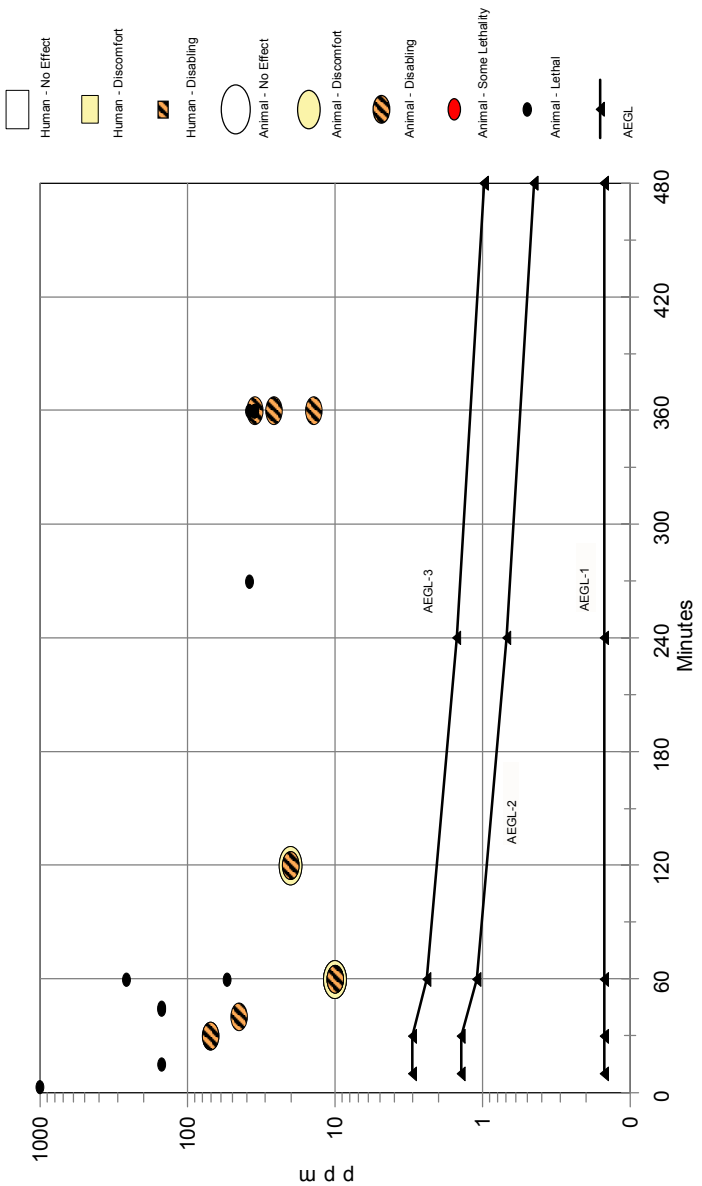

FIGURE C-1 Chemical toxicity—TSD all data, chlorine dioxide.

2

Chlorine Trifluoride[1]

Acute Exposure Guideline Levels

SUMMARY

Chlorine trifluoride (ClF_3) is a greenish-yellow liquid at temperatures <11.7°C and a colorless gas with a sweet, suffocating odor at higher temperatures. While it is not flammable, ClF_3 is an extremely reactive and corrosive oxidizing agent that is used in nuclear reactor fuel processing; as a fluorinating agent; as an incendiary, igniter and propellant for rockets; and as a pyrolysis inhibitor for fluorocarbon polymers. It is unstable in air and rapidly hydrolyzes to hydrogen fluoride (HF) and a number of chlorine-containing compounds including chlorine dioxide

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory) and the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances members Kyle Blackman (Chemical Manager) and Robert Benson, Nancy Kim, and Mark McClanahan (Chemical Reviewers). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

(ClO_2). The toxic effects of ClF_3 are due, at least in part, to the actions of HF and ClO_2.

Chlorine trifluoride is a potent, rapidly-acting mucous membrane irritant. Skin and eye contact with ClF_3 produces burns and inhalation causes acute pulmonary irritation and edema. Inhalation studies with the monkey, dog, rat, and mouse for several end points and exposure durations have been performed. Data on irritant effects were available for the dog and rat; data on sublethal and lethal concentrations were available for the monkey, rat, and mouse. One report of a very brief (1-2 min) human exposure was located, but no data on exposure concentrations were available. The data were considered adequate for derivation of the three AEGL classifications for five exposure periods. Regression analyses of the reported concentration-exposure durations for lethality for the animal species determined that the relationship between concentration and time is $C^{1.3} \times t = k$.

The AEGL-1 was based on slight irritation as evidenced by rhinorrhea (nasal discharge) observed in two of two dogs during the first 3 h of a 6-h exposure to an average concentration of 1.17 ppm (Horn and Weir 1956). Nasal discharge in response to an irritant gas in the sensitive nose of dogs was considered a NOAEL for the AEGL-1. No signs were observed in 20 rats exposed to this concentration for 6 h. Exposure of the dogs for longer than 3 h resulted in obvious lacrimation. Repeated, daily exposures of rats and dogs to 1.17 ppm resulted in severe signs of irritation. The rhinorrhea in dogs exposed for 3 h was considered an appropriate end point for development of the AEGL-1. Exposure to 1.17 ppm for 3 h was extrapolated using a combined interspecies and intraspecies uncertainty factor of 10 (3 for interspecies differences [the dog was more sensitive than the rat] and 3 for intraspecies differences in sensitivity [slight irritation should occur at a similar level among the general population]). Time-scaling was not applied to the AEGL-1 as adaptation to slight sensory irritation occurs. Therefore, the calculated value of 0.12 ppm was adopted for all AEGL-1 time points. The 0.12 ppm value is similar to the ClO_2 AEGL-1 of 0.15 ppm and is one-eighth of the HF AEGL-1 value of 1.0 ppm. Application of an intraspecies factor of 3 is sufficient, since application of a larger factor would result in AEGL-1 values that are not consistent with those of ClO_2 and HF, two of the major decomposition products of ClF_3 (breakdown of one mole of ClF_3 potentially forms three moles of HF and one mole of ClO_2).

The AEGL-2 was based on signs of irritation (salivation, lacrima-

tion, rhinorrhea, and blinking of the eyes) in two of two dogs exposed to a concentration of 5.15 ppm for 6 h (Horn and Weir 1955). These effects were reversible by the end of the first exposure day (i.e. dogs "did not appear markedly affected"), and therefore, were not considered an impairment to the ability to escape. Twenty rats exposed to this concentration for 6 h appeared unaffected. However, repeated daily exposures of rats and dogs to this concentration resulted in increasingly severe signs of irritation. The 6-h concentration of 5.15 ppm was divided by a combined interspecies and intraspecies uncertainty factor of 10 (3 for interspecies differences as the dog was more sensitive than the rat and 3 for intraspecies differences). The resulting value of 0.52 ppm was scaled across time using $C^n \times t = k$, where $n = 1.3$; this concentration-exposure duration relationship was determined from several lethality studies (Appendix A). Because time-scaling data were available over the exposure duration of 13.5 to 222 min, the 10-min AEGL-2 was not set equal to the 30-min value as is usually done when the exposure duration of the key study is greater than 4 h. An intraspecies uncertainty factor of 3 is sufficient as these AEGL-2 values are considerably lower than those of HF (10- and 30-min and 1-, 4-, and 8-h values of 95, 34, 24, 12, and 12 ppm, respectively) and similar to the longer-term AEGL-2 values for ClO_2. The 10- and 30 min AEGL-2 values for ClF_3 (8.1 and 3.5 ppm) are higher than those of ClO_2 (both 1.4 ppm) because information was available for time-scaling ClF_3 values, whereas, in the absence of time-scaling information, the conservative value of $n = 3$ was used for scaling to the shorter time periods for ClO_2.

Lethality data (1 h LC_{50} values) were available for the monkey, rat, and mouse. Based on similar respiratory rates, gross respiratory tract anatomy, amount and distribution of types of respiratory epithelium, and airflow patterns, the monkey was considered the most appropriate model for deposition of ClF_3 and its decomposition products in the human respiratory tract. The AEGL-3 values were based on the highest 1 h concentration that resulted in no deaths in monkeys (MacEwen and Vernot 1970). This concentration, 127 ppm, was divided by interspecies and intraspecies uncertainty factors of 2 and 3, respectively (for a total of 6), and scaled across time using the $C^{1.3} \times t = k$ relationship. This time-scaling relationship was determined from several lethality studies (Appendix A). The interspecies uncertainty factor of 2 was considered appropriate as LC_{50} values were similar in three species and the monkey is an appropriate model for humans. A smaller interspecies uncertainty fac-

tor would result in values that are inconsistent with the HF values. The intraspecies uncertainty factor of 3 was considered appropriate because chlorine trifluoride is a direct-acting irritant and differences among individuals should not differ greatly. In cases where animals died, death was due to massive lung hemorrhaging. Applying the same procedures to the calculated 1 h LC_{01} from the mouse data (135 ppm) results in similar values. The 8-h AEGL-3 value was set equal to the 4-h value because the time-scaled 8 h value of 4.3 ppm is inconsistent with the experimental data. Dogs exposed to 21 ppm for two days did not die during the following month of observation, and dogs and rats tolerated repeated 6 h exposures to 5.15 ppm for several weeks before the first death was recorded (Horn and Weir 1955).

The values appear in Table 2-1.

INTRODUCTION

Chlorine trifluoride (ClF_3) is a colorless, corrosive gas at ambient temperature and pressure. It is one of the most reactive of the halogen

TABLE 2-1 Summary of AEGL Values for Chlorine Trifluoride

Classification	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL–1 (Nondisabling)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	Slight irritation - dog (Horn and Weir 1956)
AEGL–2 (Disabling)	8.1 ppm (31 mg/m^2)	3.5 ppm (13 mg/m^3)	2.0 ppm (7.6 mg/m^3)	0.70 ppm (2.7 mg/m^3)	0.41 ppm (1.6 mg/m^3)	Threshold, impaired ability to escape - dog (Horn and Weir 1955)
AEGL–3 (Lethal)	84 ppm (320 mg/m^3)	36 ppm (140 mg/m^3)	21 ppm (80 mg/m^3)	7.3 ppm (28 mg/m^3)	7.3 ppm (28 mg/m^3)	Threshold for lethality - monkey (MacEwen and Vernot 1970)

fluorides; it is a powerful oxidizing agent that reacts violently with water and may explode on contact with organic materials (Matheson 1980; O'Neil et al. 2001). Chemical and physical properties are listed in Table 2-2. In the vapor phase, ClF_3 is unstable and decomposes by hydrolysis to a variety of substances including ClOF (the initial product), ClF, ClO_2F, ClO_3F, ClO_2, Cl_2, and HF; the proportion of products depends on the availability of water (Bougon et al. 1967; Cooper et al. 1972; Dost et al. 1974). Increased humidity increases the rate of decomposition (MacEwen and Vernot 1970).

Chlorine trifluoride has been used in nuclear reactor fuel processing (to convert uranium to gaseous uranium hexafluoride), as a fluorinating agent, as an incendiary, igniter and propellant for rockets, and as a pyrolysis inhibitor for fluorocarbon polymers (O'Neil et al. 2001). It is

TABLE 2-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Chlorine fluoride chlorotrifluoride	HSDB 2005
Molecular formula	ClF_3	O'Neil et al. 2001
Molecular weight	92.45	O'Neil et al. 2001
CAS Registry Number	7790-91-2	HSDB 2005
Physical description	Colorless (gas) greenish-yellow (liquid) white (solid)	O'Neil et al. 2001
Solubility in water	Violent hydrolysis with water	O'Neil et al. 2001
Vapor pressure	1064 mm Hg at 20°C	Matheson 1980
Vapor density (air = 1)	3.21 at 20°C	Matheson 1980
Liquid density (water = 1)	1.9 kg/L at 0°C	Matheson 1980
Melting point	−76.34°C	O'Neil et al. 2001
Boiling point	11.75°C	O'Neil et al. 2001
Flammability	Not flammable, but may cause fire in contact with some materials	U.S. DOT 1985
Conversion factors	1 ppm = 3.85 mg/m^3 1 mg/m^3 = 0.26 ppm	AIHA 2004

used as a chlorine/fluorine source for plasma etching in the semiconductor industry and for in-situ cleaning of chemical vapor deposition reactors (BOC Group 1997). It is produced commercially by the continuous gas-phase reaction of chlorine and fluorine in a nickel reactor at 290°C. In 1993, U.S. production was estimated at several metric tons per year with most of the product used in nuclear fuel processing. It is shipped as a liquified compressed gas in steel cylinders in quantities of 82 kg/cylinder or less (Bailey and Woytek 1994). The BOC Group (1997) ships cylinders containing either 13 or 26 pounds.

Chlorine trifluoride is a potent, rapidly-acting mucous membrane irritant. Contact with the skin and eyes produces burns and inhalation causes pulmonary irritation and edema (Teitelbaum 2001). No data on human exposures to measured concentrations were found. Inhalation studies for several exposure durations with the monkey, dog, rat, and mouse were located. Because of the reactive nature of ClF_3, difficulty in generating and monitoring the compound was encountered in some of the studies (Horn and Weir 1955; Dost et al. 1974).

2. HUMAN DATA

2.1. Acute Lethality

Deichmann and Gerarde (1969) concluded that exposure to 50 ppm may be fatal within 30 min to 2 h. No further details were given, and neither the source nor the basis of that conclusion was cited.

2.2. Nonlethal Toxicity

Although an odor threshold was not located, Teitelbaum (2001) states that the pungent odor and irritation associated with ClF_3 are detectable at such a low concentration that exposed individuals would escape before experiencing severe effects. The odor has been described as sweet and suffocating (O'Neil et al. 2001). Signs experienced by a worker exposed to an unknown concentration for 1-2 min included headache, abdominal pain, and dyspnea that lasted about 2 h (Longley et al. 1965). No systemic or local effects were found. Except for fatigue (duration not given), there were no apparent sequelae.

2.3. Developmental/Reproductive Effects

No data concerning potential developmental or reproductive toxicity of ClF_3 in humans were identified.

2.4. Genotoxicity

No data concerning the genotoxicity of ClF_3 in humans were identified.

2.5. Carcinogenicity

No data concerning the potential carcinogenicity of ClF_3 in humans were identified.

2.6. Summary

No studies of developmental or reproductive toxicity, genotoxicity, or carcinogenicity of ClF_3 in humans were located. Exposure to sufficiently high ClF_3 concentrations may cause skin and mucous membrane irritation (Teitelbaum 2001) as well as headache, abdominal pain, and dyspnea (Longley et al. 1965). Deichmann and Gerarde (1969) report that 50 ppm may be fatal within 30 min to 2 h, but neither the source nor basis of that conclusion was cited.

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

Acute toxicity data, available for the monkey, dog, rat, and mouse, are summarized in Table 2-3 and discussed below. Longer-term studies using dogs and rats described irritant effects during the first day of exposure. It should be noted that in the 2-day and longer-term studies reported by Horn and Weir (1955, 1956), groups of 2 dogs and 20 rats were exposed at the same time, presumably in the same 500-liter exposure chamber.

TABLE 2-3 Acute Inhalation Toxicity in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Monkey	230	1 h	LC_{50}	MacEwen and Vernot 1970
	127	1 h	No deaths; signs of sneezing, coughing, and gagging	
Dog	21	6 h[b]	Extreme eye and mucous membrane irritation, singed hair; recovery by next morning except inflamed eyes	Horn and Weir 1955; 1956
	5.15	6 h[b]		
	1.17	6 h[b]	irritation, salivation, sneezing, lacrimation, coughing nasal discharge within 45 min, lacrimation after 3 h	
Rat	800	13-14 min	Approximate LC_{50}	Dost et al. 1974
		10 min	No deaths; severe inflammation of mucosal surfaces, preening, skin burns, lacrimation, brittle hair, corneal ulceration, shallow respiration	
	400	28 min	Approximately LC_{50}	
	400	25 min	Same signs as 10-min exposure to 800 ppm	
Rat	480	70 min	100% mortality	Horn and Weir 1955
		40 min	ET_{50}[c]	
Rat	299	1 h	LC_{50}	MacEwen and Vernot 1970; Vernot et al. 1977
	200	1 h	No deaths; signs of lacrimation, salivation, labored breathing, and rhinorrhea; bloody discharge from eyes and nares	
Rat	96	4.5 h	80 %mortality	Horn and Weir 1955
		3.7 h	ET_{50}[c]	
Rat	21	6 h[b]	Rhinorrhea, lacrimation, singed hair; recovery by morning	Horn and Weir 1955
	5.15	6 h[b]	Little observed effect	
	1.17	6 h[b]	No effects	

Mouse	178	1 h	LC_{50}	MacEwen and Vernot 1970; Vernot et al. 1977
	125	1 h	No deaths; signs of lacrimation, salivation, labored breathing, and rhinorrhea; bloody discharge from eyes and nares	

[a]LC_{50} values were obtained 14 days post-exposure (MacEwen and Vernot 1970).
[b]Exposures were repeated; the listed signs were observed during the first day.
[c]ET_{50} is defined as effective time to 50% mortality.

3.1.1. Nonhuman Primates

Groups of four Rhesus monkeys of both sexes inhaled 0, 127, 150, 200, 300, or 400 ppm for 1 h (MacEwen and Vernot 1970). Concentrations were measured based on the reaction of ClF_3 or its decomposition products with dimethylamine. Measurements showed that concentrations of ClF_3 were stable in the test chamber. Observations were made during exposure and continued 14 days post-exposure. Signs observed in exposed animals included sneezing, coughing, and gagging. Animals exposed to lethal concentrations (150 ppm) demonstrated general paresis, labored breathing, and cyanosis prior to coma and death. Massive alveolar and interstitial hemorrhages involving the entire lungs were present in all animals that died. Most of the deaths occurred 2 to 3 h after the cessation of exposure. Animals were cyanotic, but no methemoglobin was formed during these exposures. Mortality ratios were 0/4, 2/4, 1/4, 2/4, and 4/4 animals at the 127, 150, 200, 300, and 400 ppm concentrations, respectively. The 1-h LC_{50} was 230 ppm. Pulmonary congestion, edema, hemorrhage, and emphysema were observed in surviving monkeys at 14 days post-exposure. No differences in clinical chemistry parameters were found between exposed and control animals.

3.1.2. Dogs

Two dogs were exposed to 21 ppm for 6 h/day for two days (Horn and Weir 1955). Shortly after exposure was initiated, lacrimation, cough, rhinorrhea, rapid respiration and salivation were observed. Rhinorrhea and lacrimation were observed approximately 10 min after the exposure was initiated. The dogs became nauseated, coughed up a small quantity of mucoid material, and had rapid respiration and salivation. The eyes were extremely irritated by the end of the exposure and the hair had a "singed feel." The morning after the first exposure the animals appeared essentially normal with the exception of inflamed eyes. During the second day of exposure, the study was terminated due to equipment failure which resulted in a concentration considerably higher than 21 ppm. Corneal ulcers and a burn in the vicinity of the nose developed following the exposures. No deaths were reported during the following month of observation

Two male dogs were exposed to 5.15 ppm for 6 h/day, 5 days/week

for 6 weeks (Horn and Weir 1955). Signs of exposure occurred during the first day and included salivation, lacrimation, and rhinorrhea; coughing and sneezing were also noted. However, by the end of the first day of exposure, the dogs "did not appear markedly affected." Respiratory distress was evident at the midpoint of the study, and the dogs died on days 17 and 26. The authors experienced difficulty in maintaining constant concentrations in the exposure chambers, and during the exposures, concentrations of one-half to two times the average value were recorded.

Two dogs were exposed to an average concentration of 1.17 ppm for 6 h/day, 5 days/week for 6 months (Horn and Weir 1956). During the early part of the study, signs of irritation included rhinorrhea, usually within 45 min of exposure, and obvious lacrimation after 3 hs of exposure. All animals developed a "singed feel" of the hair following the first exposure. The animals appeared normal by the following morning. By the 28th day, the dogs were coughing up bloody mucoid material and showed signs of blinking of the eyes and a change in respiratory pattern at the beginning of each exposure. After more than 60 days (42 exposures) the dogs began showing signs of pneumonia. Penicillin was administered, but one dog died on the 115th day of the study (during the 82nd exposure). The other dog was sacrificed at the termination of the experiment. Examination of the lungs revealed purulent bronchitis and pulmonary abscesses in the dog that died and alveolar hemorrhage, interstitial edema, and irritation in the surviving dog.

3.1.3. Rats

Groups of 4-10 male Sprague-Dawley rats inhaled 400 ppm for 20, 25, 30, 35, or 40 min or 800 ppm for 10, 13, 15, 20, 25, or 30 min (Dost et al. 1974). Gas flow rates were measured with mass flow meters; exposure chamber ClF_3 concentrations were verified by infrared spectral analysis. Rats began preening at initiation of ClF_3 exposure, and exposures produced severe inflammation of all exposed mucosal surfaces. Time-respective mortalities for the 400 ppm exposure were: 0/8, 0/4, 4/6, 7/8, and 8/8. Time-respective mortalities for the 800 ppm concentration were: 0/10, 1/8, 10/10, 8/8, 6/6, and 4/4. LC_{50} values were not calculated by the authors.

The authors found that prolonged exposures or high ClF_3 concentrations caused burning of the exposed skin, and the hair became brittle

and yellowed. Corneal ulceration was a frequent occurrence. Respiration became shallow without an appreciable increase in rate. Exposures to 400 ppm for 30 min or 800 ppm for 15 min were lethal. Deaths occurred within 3 h of exposure. Although the post-exposure observation period was not given in terms of days, the authors stated that "rats that survived 4 h after exposure to ClF_3 in air were able to survive the primary inhalation injury indefinitely, with minimal after care."

Groups of 20 rats (sex and strain not stated) were exposed to 96 or 480 ppm under conditions of continuous exposure until all animals were dead (Horn and Weir 1955). Chlorine trifluoride was measured by drawing a known quantity of the chamber atmosphere through sodium hydroxide solution and then analyzing for chloride. Deaths were concentration-related as mortalities were 50 and 80% after 3.7 and 4.5 h, respectively, at a concentration of 96 ppm. Exposure to 480 ppm killed 50 and 100% after 40 and 70 min, respectively (Table 2-3). Excessive preening, deep gasping respiration, rhinorrhea, salivation, and lacrimation occurred soon after the exposures began. Marked eye irritation, corneal damage, and singed hair were observed. The authors noted the corrosive effect of the gas on the equipment; deviations from the measured concentrations of one-half to two times the average value occurred.

Groups of 8 male Wistar rats inhaled 200 or 400 ppm for 1 h (MacEwen and Vernot 1970; Vernot et al. 1977). Although both publications described the same study, MacEwen and Vernot (1970) report the strain of rats as Wistar, whereas Vernot et al. (1977) report the strain as Sprague-Dawley. Observations were made during the exposures and for 14 days post-exposure. Signs observed in all exposed animals included lacrimation, salivation, labored breathing, and rhinorrhea. No deaths occurred at 200 ppm, but 6 of 8 rats died at 400 ppm. The LC_{50} was 299 ppm. Massive alveolar and interstitial hemorrhage involving the entire lung was present in all animals that died. Deaths occurred within 2 to 3 h after the exposure. Survivors developed bloody discharge from the eyes and nares that lasted for several days. Near lethal concentrations induced congestion, edema, hemorrhage, and emphysema in localized or discrete areas of the lungs.

Twenty rats (sex and strain not stated) were exposed to 21 ppm for 6 h/day for two days (Horn and Weir 1955). Shortly after exposure was initiated, the rats began preening and showed signs of rhinorrhea and lacrimation. At the end of the first day, rhinorrhea and lacrimation were observed and the fur had a “singed feel.” The animals appeared normal the

following morning. During the second day of exposure, the study was terminated due to equipment failure resulting in a considerably higher concentration. No deaths were reported.

Horn and Weir (1955) exposed 20 rats (sex and strain not stated) to an average concentration of 5.15 ppm, 6 h/day, 5 days/week for 6 weeks (31 exposures). At the end of the first day of exposure the authors noted that "the rats did not appear to be affected." On the second day the rats appeared restless, and there was a moderate amount of preening, salivation, and rhinorrhea. Signs and symptoms of irritation increased with increasing exposure time; one death occurred at the end of the 36th day of the experiment. No further deaths occurred before termination of the experiment on the 43rd day. Animals sacrificed at the termination of the experiment had severe lung pathology, including varying degrees of hyperemia, hemorrhage, and edema. During the exposures, concentrations of one-half to two times the average value were recorded.

Twenty rats (sex and strain not stated) were exposed to an average concentration of 1.17 ppm for 6 h/day, 5 days/week for 6 months (Horn and Weir 1956). During the early part of the study, the rats appeared unaffected by the exposures. By the 9th day the rats began preening immediately after exposure began. After 10 min, preening was followed by reduced physical activity that lasted throughout the exposure period. After several weeks, blood tinged exudate around the nares and eyes occurred on occasion. Five deaths (days 56-178) occurred in the treated group versus two in the concurrent control. Examination of the lungs revealed pulmonary edema and bronchopneumonia in the rats that died and pulmonary irritation in the survivors.

3.1.4. Mice

Groups of 15 mice were exposed to concentrations of 125, 150, 175, 200, or 400 ppm for 1 h (MacEwen and Vernot 1970). Signs observed during exposure included lacrimation, salivation, labored breathing, and rhinorrhea. Most fatalities occurred 2 to 3 h after exposure; all deaths occurred within 36 h post-exposure. Deaths occurred at concentrations $\geq$ 150 ppm; the LC_{50} was 178 ppm (95% confidence limits, 169-187 ppm). Mortality ratios were 0/15, 2/15, 4/15, 14/15, and 15/15 at concentrations of 125, 150, 175, 200, and 400 ppm, respectively. Examination of surviving mice at 14 days post-exposure revealed localized areas of congestion, edema, hemorrhage, and emphysema in the lungs.

3.2. Developmental/Reproductive Toxicity

No information on potential developmental or reproductive toxicity associated with ClF_3 exposure was located in the available literature.

3.3. Genotoxicity

No information on genotoxicity was located in the available literature.

3.4. Chronic Toxicity/Carcinogenicity

No information on the chronic toxicity or carcinogenic potential of ClF_3 in animals was located in the available literature.

3.5. Summary

Data were available on lethality in three species (monkey, rat, and mouse) and the consequences of ClF_3-induced irritation in two species (dog and rat). The 1-h LC_{50} values for the monkey, rat, and mouse were 230, 299, and 178 ppm, and the 1-h exposures resulting in no deaths for the respective species were 127, 200, and 125 ppm. Concentration-dependent ocular, mucous membrane, and pulmonary tract irritation was noted in dogs at 1.17, 5.15, and 21 ppm for an exposure duration of 6 h. The dog was more sensitive than the rat to the irritant effects of airborne ClF_3 as no signs of irritation were observed in a group of 20 rats during the first day of exposure to 1.17 or 5.15 ppm; rhinorrhea, lacrimation, and singed hair were observed in both species during the first day of exposure to 21 ppm. No information on potential developmental/reproductive toxicity, genotoxicity, or carcinogenicity was located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Tissue distribution of fluoride ion was analyzed at 0, 2, 6, and 24-h

after male Sprague-Dawley rats inhaled 400 ppm ClF_3 for 15 min (Dost et al. 1970). Distribution was uniform among soft tissues. There was no evidence of increased fluoride burden in the lung at any time after exposure. Nonsignificant, transient increases in fluoride were observed in the spleen immediately after exposure and at 2 h post-exposure. Bone fluoride increased from 118 µg F/g tissue at 0 h to 172 µg F/g tissue at 24 h post-exposure.

4.2. Mechanism of Toxicity

ClF_3 is corrosive to all tissues. In rats that inhaled 400 ppm and had previously been injected with 14C-labeled $NaHCO_3$, $14CO_2$ production was reduced sharply during the first 30 min and remained so for up to 6 h (Dost et al. 1974). A decrease in CO_2 expiration indicates damage to the lungs.

Analysis of ClF_3 in ambient air (at 65% relative humidity) by an infrared technique found approximately 85% of the ClF_3 had degraded within 6 sec (MacEwen and Vernot 1970). Dilutions of ClF_3 with air and 50% humidity at nominal concentrations of 1000, 2000, and 5000 ppm showed ClF_3 when analyzed within 30 sec. Reaction products had little or no infrared absorption (hydrogen fluoride [HF] and chlorine [Cl_2] have little or no infrared absorption).

In the moist respiratory tract, ClF_3 is predicted to hydrolyze to ClOF which further degrades to ClO_2F and ClF (Dost et al. 1974). ClO_2F rapidly hydrolyzes to ClO_2, HF, and ClO_x anions; the first two products predominate and are thought to be responsible for ClF_3 toxicity as the ClO_x anions are relatively nontoxic.

4.3. Structure-Activity Relationships

The chemical reactivity of the halogenated fluorine compounds in order of decreasing reactivity is: chlorine pentafluoride (ClF_5) > ClF_3 bromine pentafluoride (BrF_5) > iodine heptafluoride (IF7) > chlorine monofluoride (ClF) > bromine trifluoride (BrF_3) > bromine monofluoride (BrF) (Bailey and Woytek 1994).

Signs produced by ClF_3 exposure are similar to those of other respiratory irritants including ClF_5 and HF. MacEwen and Vernot (1971) and

Darmer et al. (1972) compared the toxicity of ClF_3 with that of oxygen difluoride (OF_2, a potent oxidizer), HF, and ClF_5. Table 2-4 lists 1 h LC_{50} values for these chemicals in order of decreasing toxicity. In the monkey, ClF_3 is slightly less potent than ClF_5 but 7 times more toxic than HF (in all three species for which data are available, ClF_5 is almost exactly ten times more toxic than HF). In the rat and mouse, ClF_3 is approximately 4 times more toxic than HF.

MacEwen and Vernot (1970) found ClF_3 exposure induced toxicity similar to that of its principal hydrolysis product, HF; thus, the relative toxicities of HF and ClF_3 on an equivalent molar basis (3 moles of HF formed per mole of ClF_3) would be 690, 897, and 534 ppm (3 times the ClF_3 1-h LC_{50} values of 230, 299, and 178 ppm), respectively. The response to ClF_3 in monkeys was not due entirely to HF, but HF was a major factor in the response of rats and mice. Additional effects were thought due to one or more chlorine-containing degradation products. The hydrolysis of ClF_5 is very exothermic which may contribute to its enhanced toxicity compared with HF (Syage 1994).

Inhalation studies with rats also indicated that the toxicity of ClF_3 was comparable to that of ClO_2 based on the number of chlorine equivalents (Dost et al. 1974). Two of five rats that inhaled 500 ppm ClO_2 for 15 min died, and all 8 rats exposed to 1,000 ppm ClO_2 for 30 min died. Exposure to 2,000 ppm ClO_3F for 25 min or to 1,000 ppm ClO_3F for 60 min was not lethal. The authors stated that the toxicity of ClF_3 was comparable to that of ClO_2 on a chlorine equivalent basis and that the toxicity of inhaled ClF_3 was comparable to that of HF on a fluorine equivalent basis.

4.4. Other Relevant Information

4.4.1. Species Differences

There is little variation in species sensitivity to lethal concentrations

TABLE 2-4 Comparative 1 h LC_{50} Values for ClF_3 and Related Compounds

Species	OF_2	ClF_5	ClF_3	HF
Monkey	16.0	173	230	1774
Dog	26.0	122	—	—
Rat	2.6	122	299	1276
Mouse	1.5	57	178	501

Source: Darmer et al. 1972.

of ClF_3. The 1-h LC_{50} values for the monkey, rat, and mouse were 230, 299, and 178 ppm, respectively (MacEwen and Vernot 1970). No monkeys died at 127, and no mice died at 125 ppm. Data from the MacEwen and Vernot (1970) study allowed calculation of LC_{01} values for the mouse and rat (Table 2-5); however, only two data points were available for the rat. The data set for the monkey did not allow calculation of a reliable LC_{01}.

Although 1 h LC_{50} values were not reported in studies of Horn and Weir (1955) and Dost et al. (1974), these values can be calculated (see section 4.4.3 for time scaling). In the study by Horn and Weir (1955), the 1-h ET_{50} values would be 262 and 351 ppm based on the 96 and 480 ppm exposures, respectively. It should be noted that these values underestimate the LC_{50} as the protocol did not allow for post-exposure observation. In the Dost et al. (1974) study, the 1-h LC_{50} concentration would be 222 ppm. If these values are considered, then all 1 h LC_{50} values across species are within a factor of two (range, 178-351 ppm).

The nasal passages vary considerably in size and shape among species. The nasal passages of rodents and primates differ in gross anatomy, the amount and distribution of types of respiratory epithelium, and airflow patterns. The noses of primates (humans and monkeys) show great similarity in these three factors (Schreider 1986), and the monkey is a more appropriate model for extrapolation of inhalation toxicity data for irritants to humans than is the rodent.

The respiratory rate of primates is lower than that of rodents. Therefore, the delivered dose to the respiratory tract in primates is lower than that of rodents exposed to the same concentration. Furthermore, based on relative body size, the respiratory rate of humans is lower that of monkeys, with a resulting lesser dose to the target tissues in the respiratory tract.

TABLE 2-5 Comparative ClF_3 1-H Lethal Values for Three Species

Species	LC_{50} (95% confidence limits)	No deaths (ppm)	LC_{01} (ppm)
Monkey	230	127	—
Rat	299	200	156
Mouse	178 (169-187)	125	135

Source: MacEwen and Vernot 1970.

4.4.2. Susceptible Populations

Asthmatics may respond to exposure to primary irritants with increased bronchial responsiveness. No information on the relative susceptibility of asthmatic and otherwise healthy people to inhaled ClF_3 was located. The elderly and those with compromised lung function could potentially experience increased susceptibility to airborne ClF_3, but there are neither animal data nor clinical experience to suggest that such is the case.

People engaged in emergency situations and those engaged in physical activity will experience greater ClF_3 deposition and pulmonary irritation than sedentary individuals. Furthermore, individuals who breathe through their mouth would receive a larger pulmonary delivered dose since scrubbing and deposition in the nasal passages would be bypassed.

4.4.3. Concentration-Exposure Duration Relationship

Lethality data were available for three species and for exposure durations of 13.5 to 222 min. These data are graphed in Appendix A. The inverse of the slope of the line (n) is 1.3. This value of n was used in the time-scaling relationship, $C^n \times t = k$, for both the AEGL-2 and AEGL-3 because tissue damage from a direct-contact irritant is a matter of degree between the AEGL-2 and AEGL-3. Comparing the LC_{01} value for the mouse, 135 ppm, with the lower confidence limit on the LC_{50} value, 169 ppm, shows that the concentration-response curve is very steep. In the Dost et al. (1974) study, a 3-min time difference separated highest nonlethal and LC_{50} values for exposures to both 400 and 800 ppm.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to the calculation of an AEGL-1 were located.

5.2. Animal Data Relevant to AEGL-1

The only animal study using a concentration relevant to AEGL-1 was the subchronic study in dogs and rats exposed to 1.17 ppm, 6 h/day, 5 days/week, for 6 months (Horn and Weir 1956). While the rats remained unaffected during the early exposures, dogs displayed rhinorrhea within 45 min of the first exposure; lacrimation developed after 3 h. Signs of irritation became increasingly severe with continued exposures.

5.3. Derivation of AEGL-1

Although the Horn and Weir (1956) account did not clearly state on which day the signs of irritation to ClF_3 began in dogs, nasal discharge indicates slight sensory irritation as the end point (NOAEL) for the AEGL-1. Obvious lacrimation was not observed until after 3 h of exposure. The AEGL-1 was based on nasal discharge observed in dogs during the first 3 h of exposure to 1.17 ppm. The 1.17 ppm concentration for an exposure duration of 3 h was divided by a combined interspecies and intraspecies uncertainty factor of 10 (3 for interspecies differences [the dog was more sensitive than the rat] and 3 for intraspecies differences in sensitivity [slight irritation should occur at a similar level among the general population]). Time-scaling was not applied because adaptation to slight irritation occurs. Therefore, the calculated value of 0.12 ppm was adopted for all AEGL-1 timepoints. The 0.12 ppm AEGL-1 value is similar to the ClO_2 AEGL-1 of 0.15 ppm (also based on slight sensory irritation; EPA 2005), and the AEGL-1 is one-eighth of the HF AEGL-1 value of 1.0 ppm (NRC 2004). Application of an intraspecies factor of 3 is sufficient, since application of a larger factor would result in AEGL-1 values that are not consistent with those of ClO_2 and HF, two of the major decomposition products of ClF_3 (breakdown of one mole of ClF_3 potentially forms three moles of HF and one mole of ClO_2). The AEGL-1 values are listed in Table 2-6. Figure 2-1 category plot contains ClF_3 data including the AEGL-1 end point and the AEGL-1 value.

TABLE 2-6 AEGL-1 Value for Chlorine Trifluoride

10 min	30 min	1 h	4 h	8 h
0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^2)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of an AEGL-2 were located.

6.2. Animal Data Relevant to AEGL-2

There were no single exposure studies designed to evaluate nonlethal effects. Two dogs exposed to 5.15 ppm, 6 h/day, 5 days/week, for 6 weeks showed salivation, lacrimation, rhinorrhea, blinking of the eyes, severe coughing, and sneezing. The duration of ClF_3 exposure required to induce these signs was not clearly stated, but "signs of mucous membrane irritation" observed in dogs during the first day appeared to be reversible by the end of the first day as the dogs at that time "did not appear markedly affected." A group of twenty rats exposed to the same concentration did not appear to be affected either during the exposure or at the end of the first day (Horn and Weir 1955).

6.3. Derivation of AEGL-2

The signs in dogs exposed to 5.15 ppm for 6 h - irritation, salivation, lacrimation, rhinorrhea, coughing, and sneezing - may be extremely uncomfortable but are reversible. Thus, these signs are considered consistent with a NOAEL for disabling effects or an impaired ability to escape. Twenty rats exposed to this concentration for 6 h appeared unaffected. However, repeated daily exposures of rats and dogs to this concentration resulted in increasingly severe signs of irritation. The AEGL-2 was calculated based on the 6-h exposure of dogs to 5.15 ppm. A combined uncertainty factor of 10 was applied: 3 for interspecies differences in sensitivity (the value is based on the dog which was considerably more sensitive than the rat) and 3 for intraspecies differences in sensitivity (irritation should occur at a similar concentration among the general population). Scaling across time was based on the time-scaling relationship derived in Section 4.4.3. Although the end point for time scaling was lethality in several species, the same relationship can be utilized for the AEGL-2 because the difference between severe irritation (AEGL-2) and lethality from tissue destruction (AEGL-3) is one of degree. The 10-min value was time-scaled from the 6-h point of departure because time-scaling data were available for 13.5 to 222 min. An intraspecies uncer-

tainty factor of 3 is sufficient as these AEGL-2 values are considerably lower than those of HF (10- and 30-min and 1-, 4-, and 8 h values of 95, 34, 24, 12, and 12 ppm, respectively) and similar to the longer-term AEGL-2 values for ClO_2. The 10- and 30 min AEGL-2 values for ClF_3 (8.1 and 3.5 ppm) are higher than those of ClO_2 (both 1.4 ppm) because information was available for time-scaling ClF_3 values, whereas, in the absence of time-scaling information, the conservative value of $n = 3$ was used for scaling to the shorter time periods for ClO_2. Calculations appear in Appendix B and values are listed in Table 2-7. The AEGL-2 end point and AEGL-2 values are plotted in Figure 2-1.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Deichmann and Gerarde (1969) state that 50 ppm may be fatal in 30 min to 2 h. No further details were given. The source of that conclusion was not cited and cannot be treated as reliable.

7.2. Animal Data Relevant to AEGL-3

Exposure of 20 rats or 2 dogs for 6 h to 21 ppm resulted in lacrimation, rhinorrhea, cough, rapid respiration, and salivation shortly after initiation of exposure, but no deaths were reported, even when the animals were exposed a second day (Horn and Weir 1955). Thus, this concentration-exposure duration may be below the threshold for lethality as defined by the AEGL-3.

The 1-h LC_{50} values for the monkey, rat, and mouse were 230, 299, and 178 ppm, respectively, and the 1-h values resulting in no deaths for the same species were 127, 200, and 125 ppm, respectively (MacEwen and Vernot 1970). Data were sufficient to derive LC_{01} values for mouse and rat. The data set for the monkey did not allow calculation of a reliable LC_{01}.

TABLE 2-7 AEGL-2 Values for Chlorine Trifluoride

10 min	30 min	1 h	4 h	8 h
8.1 ppm (31 mg/m^3)	3.5 ppm (13 mg/m^3)	2.0 ppm (7.6 mg/m^3)	0.70 ppm (2.7 mg/m^3)	0.41 ppm (1.6 mg/m^3)

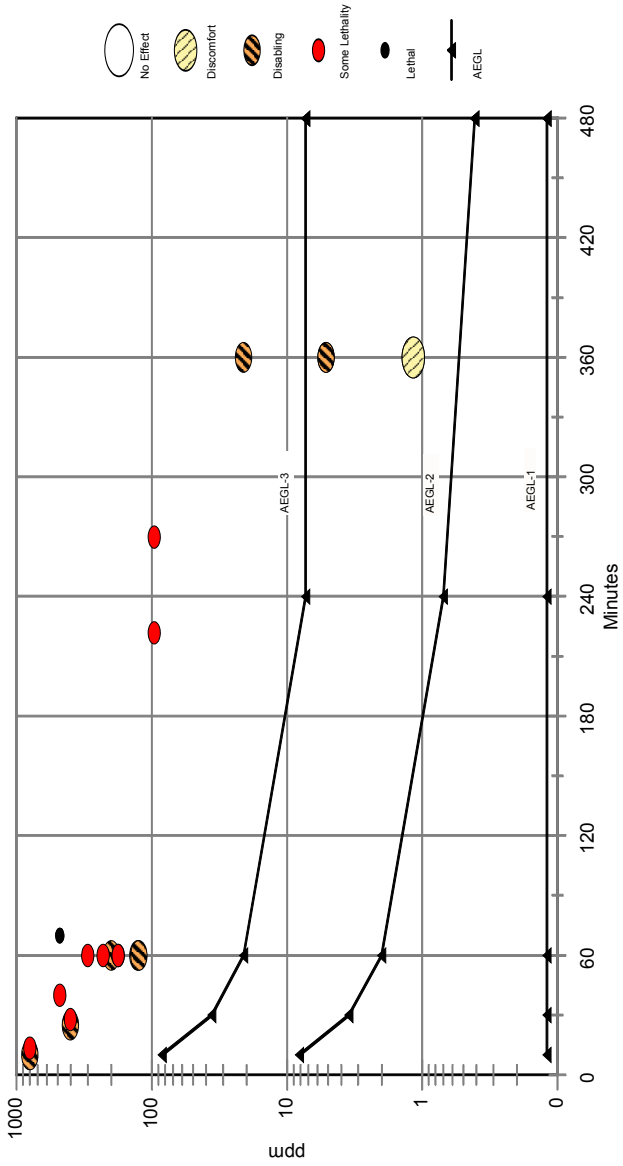

FIGURE 2-1 Animal toxicity data and AEGL values for chlorine trifluoride.

7.3. Derivation of AEGL-3

Of the three species tested, the mouse is the most sensitive species as determined by the 1-h LC_{50} of 178 ppm. However, based on similar respiratory rates, gross respiratory tract anatomy, amount and distribution of types of respiratory epithelium, and nasal airflow patterns, the monkey is a more appropriate model for chemical deposition in the human respiratory tract. The AEGL-3 values were based on the highest 1 h concentration that resulted in no deaths in monkeys (MacEwen and Vernot 1970). This concentration, 127 ppm, was divided by interspecies and intraspecies uncertainty factors of 2 and 3, respectively (for a total of 6), and scaled across time using the $C^{1.3} \times t = k$ relationship. The interspecies uncertainty factor of 2 was considered adequate as the monkey is an appropriate model for extrapolation to humans. An intraspecies uncertainty factor of 3 was considered appropriate as differences among individuals in sensitivity to contact irritants (the concentration at which lung tissue damage occurs) should not differ greatly. The 8-h AEGL-3 value was set equal to the 4-h value because the time-scaled 8 h value of 4.3 ppm is inconsistent with the experimental data. Dogs exposed to 21 ppm for two days did not die during the following month of observation, and dogs and rats tolerated repeated 6 h exposures to 5.15 ppm for several weeks before the first death was recorded (Horn and Weir 1955). The AEGL-3 end point and AEGL-3 values are plotted in Figure 2-1. The AEGL-3 values are listed in Table 2-8.

Probit analyses of the mouse data resulted in an LC_{01} value of 135 ppm. Using the same uncertainty factors and time scaling relationship as for the monkey, the AEGL-3 values based on the mouse data are very similar, 89, 38, 23, 7.7, and 7.7 ppm for the 10- and 30 min and 1-, 4-, and 8 h time periods, respectively.

Chlorine trifluoride decomposes within seconds to HF among other products (MacEwen and Vernot 1970). Compared with the 1-h LC_{50} value for HF in monkeys (1774 ppm), the response to inhaled ClF_3 in monkeys cannot be attributed entirely to HF (3 moles of HF formed), but HF may be a major factor (MacEwen and Vernot 1970). The difference in expected lethality may be due to the high water solubility and consequent scrubbing in the upper respiratory tract of HF compared with ClF_3.

TABLE 2-8 AEGL-3 Values for Chlorine Trifluoride

10 min	30 min	1 h	4 h	8 h
84 ppm (320 mg/m^3)	36 ppm (140 mg/m^3)	21 ppm (80 mg/m^3)	7.3 ppm (28 mg/m^3)	7.3 ppm (28 mg/m^3)

Nevertheless, the AEGL-3 values for ClF_3 are appropriate to those of HF.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL-1 was based on slight irritation (rhinorrhea in the sensitive nose of the dog) during the first 3 h of a 6-h exposure to ClF_3 at 1.17 ppm; notable discomfort (lacrimation) was observed after 3 h. A combined uncertainty factor of 10: 3 for interspecies differences in sensitivity (the dog was considerably more sensitive to ClF_3 than the rat) and 3 for intraspecies differences in sensitivity was applied. No time scaling was applied as tolerance develops to the slight irritation that defines the AEGL-1.

The AEGL-2 was based on obvious irritation observed in dogs exposed to an average concentration of 5.15 ppm for 6 h. Although these signs resolved by the end of the day, they were considered a threshold for impaired ability to escape. Rats exposed to 5.15 ppm for 6 h appeared unaffected. The 6-h concentration of 5.15 ppm was divided by a combined interspecies and intraspecies uncertainty factor of 10 and scaled across time using the $C^{1.3} \times t = k$ relationship.

The AEGL-3 was based on the highest non-lethal 1 h value for the Rhesus monkey (127 ppm). The 127 ppm concentration was divided by a combined interspecies and intraspecies uncertainty factor of 6 and scaled across time using the same reasons and relationships as for the AEGL-1 above. Were the AEGL-3 values to be based on the LC_{01} for the mouse (135 ppm), essentially the same values would be derived.

The AEGL values for three levels and five exposure periods are summarized in Table 2-9.

8.2. Comparisons with Other Standards

Standards and guidance levels for community and occupational exposures are listed in Table 2-10. The 1-h AEGL-1 value is similar to the 1-h ERPG-1 value, and the 1-h AEGL-2 and -3 values are higher than the respective ERPG values. The AEGL-1 and -2 values were based on studies with ClF_3, whereas the ERPG-1 and -2 values for ClF_3 are based on

analogies with chlorine and HF. The AEGL-3 and ERPG-3 values were based on the same lethality study (MacEwen and Vernot 1970), but used different species. The ERPG-3 was calculated by dividing the 1-h LC_{50}

TABLE 2-9 Summary of AEGL Values

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)
AEGL-2 (Disabling)	8.1 ppm (31 mg/m^3)	3.5 ppm (13 mg/m^3)	2.0 ppm (7.6 mg/m^3)	0.70 ppm (2.7 mg/m^3)	0.41 ppm (1.6 mg/m^3)
AEGL-3 (Lethal)	84 ppm (320 mg/m^3)	36 ppm (140 mg/m^3)	21 ppm (80 mg/m^3)	7.3 ppm (28 mg/m^3)	7.3 ppm (28 mg/m^3)

TABLE 2-10 Extant Standards and Guidelines for Chlorine Trifluoride (ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.12	0.12	0.12	0.12	0.12
AEGL-2	8.1	3.5	2.0	0.70	0.41
AEGL-3	84	36	21	7.3	7.3
ERPG-1 (AIHA)[a]			0.1 (0.3 as HF)		
ERPG-2 (AIHA)			1 (3 as HF)		
ERPG-3 (AIHA)			10 (30 as HF)		
EEGL (NRC)[b]	7	3	1		
IDLH (NIOSH)[c]		20			
Ceiling (OSHA)[d]					0.1
Ceiling (NIOSH)[e]					0.1
TLV-Ceiling (ACGIH)[f]					0.1

(Continued)

MAC-Ceiling (Netherlands)[g]	0.1

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2004).
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.
[b]EEGL (Emergency Exposure Guidance Levels, National Research Council (NRC 1984)
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.
[c]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (Ludwig et al. 1994; NIOSH 2004) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.
[d]OSHA PEL-Ceiling (Permissible Exposure Limits - Ceiling Term Exposure Limit) (NIOSH 2004) must not be exceeded during any part of the workday.
[e]NIOSH Ceiling (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Ceiling) (NIOSH 2004) must not be exceeded during any part of a 10-hour workday.
[f]ACGIH TLV-Ceiling (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Ceiling) (ACGIH 2004) is the concentration that should not be exceeded during any part of the workshift.
[g]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

for the mouse (178 ppm) by approximately 20, whereas the AEGL-3 was derived by adjusting the highest non-lethal value in the monkey by a total uncertainty factor of 6.

The AEGL-1 value for ClF_3 is less than the corresponding value for HF (1 ppm for all time periods; NRC 2004). The HF data base is exten-

sive and the AEGL-1 value for HF is based on markers of exposure in human subjects exposed to 0.2 to 6.3 ppm for 1 h. A total uncertainty factor of 3 was applied in development of the HF values.

The 10-min EEGL of 7 ppm is 58 times the 10-min AEGL-1, but it is similar to the 10-min AEGL-2. Exposure at the EEGL may involve discomfort, and the EEGL is considered by AIHA as an acceptable level for healthy adults, whereas the AEGL values are designed to account for the entire population. The 30-min and 1 h EEGL values are approximately 25 and eight times higher than the corresponding AEGL-1 values, but are similar to the corresponding AEGL-2 values. The basis for the 1984 EEGL values was not explained.

The 30-min NIOSH IDLH of 20 ppm (Ludwig et al. 1994) lies between the 30-min AEGL-2 and AEGL-3. The IDLH is based on 6 h exposures of dogs and rats to 21 ppm (Horn and Weir 1955). The 20 ppm IDLH was considered conservative by the NIOSH authors in light of the estimates of human fatal exposure concentrations by Deichmann and Gerarde (1969).

Workplace exposure limits, as 8 h ceiling values, are all 0.1 ppm and are intended to control and prevent the noxious ocular, mucous membrane and pulmonary irritation associated with exposure to ClF_3. The workplace 0.1 ppm concentration limits are similar to the AEGL-1 value of 0.12 ppm. A German maximum workplace concentration (MAK) has not been established for this material.

8.3. Data Adequacy and Research Needs

Human data were lacking. Lethal and sublethal data were available for four animal species and several exposure durations. For each species, relatively consistent values for lethality were observed among studies. However, monitoring data and analytical techniques demonstrated problems in maintaining consistent exposure concentrations. The most recently published study was in 1974; techniques for the analysis of ClF_3 in air have improved since that time.

Values similar to the derived AEGL-3 values can be derived from the rat data. There were no deaths following 1 h exposures of rats to 200 ppm (MacEwen and Vernot 1970) or during 25- or 10-min exposures to 400 or 800 ppm, respectively (Dost et al. 1974). Application of a total uncertainty factor of 10 (an interspecies uncertainty factor of 3 would be

applied to the non-primate data) to each of these concentrations and time scaling with an *n* value of 1.3 results in 10 min time-scaled values of 79-81 ppm. Application of a total uncertainty factor of 10 to the 1-h mouse non-lethal (125 ppm) or LC_{01} (135 ppm) values results in lower 10 min values, 50 and 54 ppm, respectively. The rat data support selection of the monkey data and use of an interspecies uncertainty factor less than 3.

Few data are available to support the AEGL-1 and AEGL-2 values. However, both key studies were 6 h in duration (eliminating the uncertainty of extrapolating from short-term to long exposure durations) and used two species. The values were based on the dog, the more sensitive species as indicated by signs of irritation.

MacEwen and Vernot (1970) suggested that the toxicity of ClF_3 may be associated with the formation of HF. Three moles of HF would be formed from the spontaneous decomposition of one mole of ClF_3 in moist air. The AEGL-2 values for HF (12-95 ppm; NRC 2004) are approximately a factor of 10 times the respective AEGL-2 values for ClF_3 (0.41-8.1 ppm), showing that the AEGL-2 values for ClF_3 may be conservative (the data base for HF is extensive). The AEGL-3 values for HF and ClF_3 more closely follow the molar relationship.

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APPENDIX A

TIME: CONCENTRATION RELATIONSHIP FOR LETHALITY

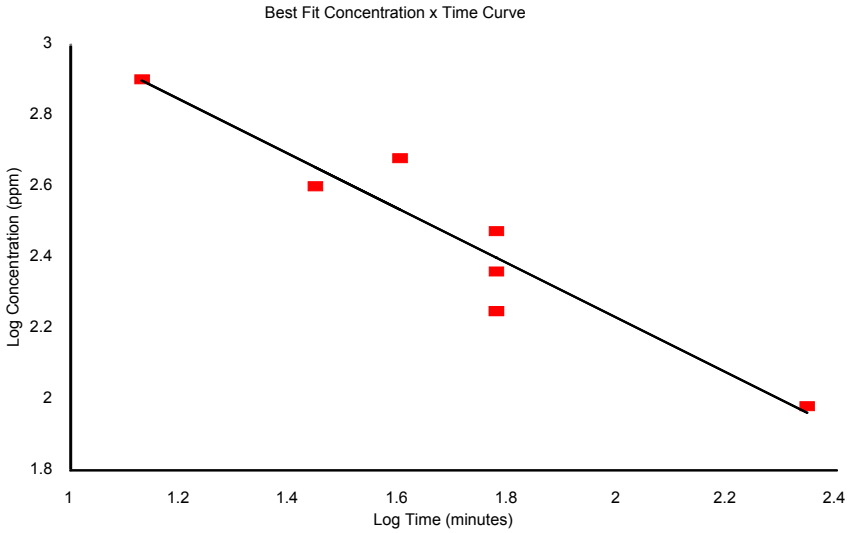

FIGURE A-1 Chlorine trifluoride: LC_{50} values for three species—monkey, rat, and mouse (Horn and Weir 1955; MacEwen and Vernot 1970; Dost et al. 1974).

Time	Conc.	Log Time	Log Conc.
13.5	800	1.1303	2.9031
28	400	1.4472	2.6021
40	480	1.6021	2.6812
60	178	1.7782	2.2504
60	230	1.7782	2.3617
60	299	1.7782	2.4757
222	96	2.3464	1.9823
n =	1.3		
k =	79325.99		

Regression Output:	
Intercept	3.7684
Slope	−0.7692
R Squared	0.9014
Correlation	−0.9494
Degrees of Freedom	5
Observations	7

APPENDIX B

DERIVATION OF AEGL VALUES

DERIVATION OF AEGL-1 FOR CHLORINE TRIFLUORIDE

Key study: Horn and Weir 1956

Toxicity end point: Mucous membrane irritation as evidenced by nasal discharge, the only sign of irritation during the first 3 h of a 6-h exposure of dogs to 1.17 ppm.

Uncertainty factors: 3 for interspecies
3 for intraspecies
combined uncertainty factor of 10[a]

Scaling: No time scaling was utilized. Adaptation occurs to the slight irritation that defines the AEGL-1.

Calculation: (Concentration/uncertainty factors) = AEGL-1
(1.17 ppm/10) = 0.12 ppm

Because tolerance develops to the slight irritation that defines the AEGL-1, the 0.12 ppm value was used for all AEGL-1 exposure durations.

[a]Each uncertainty factor of 3 is actually the geometric mean of 10 which is 3.16; $3.16 \times 3.16 = 10$.

Derivation of AEGL-2 for Chlorine Trifluoride

Key study: Horn and Weir 1955

Toxicity end point: Strong irritation in dogs exposed to a concentration of 5.15 ppm for 6 h.

Uncertainty Factors: 3 for interspecies
3 for intraspecies
combined uncertainty of 10

Scaling: $C^{1.3} \times t = k$ (this document; based on LC_{50} concentration and exposure duration relationships in Horn and Weir [1955], MacEwen and Vernot [1970], and Dost et al. [1974]).

Calculations:

$(C^{1.3}/\text{uncertainty factors}) \times t = k$
$([5.15\ \text{ppm}^{1.3}]\ /10) \times 360\ \text{min} = 151.93\ \text{ppm}^{1.3} \cdot \text{min}$

10 min AEGL-2: $151.93\ \text{ppm}^{1.3} \cdot \text{min}/10\ \text{min} = 8.1\ \text{ppm}$

30 min AEGL-2: $151.93\ \text{ppm}^{1.3} \cdot \text{min}/30\ \text{min} = 3.5\ \text{ppm}$

1 h AEGL-2: $151.93\ \text{ppm}^{1.3} \cdot \text{min}/60\ \text{min} = 2.0\ \text{ppm}$

4 h AEGL-2: $151.93\ \text{ppm}^{1.3} \cdot \text{min}/240\ \text{min} = 0.70\ \text{ppm}$

8 h AEGL-2: $151.93\ \text{ppm}^{1.3} \cdot \text{min}/480\ \text{min} = 0.41\ \text{ppm}$

Derivation of AEGL-3 for Chlorine Trifluoride

Key study: MacEwen and Vernot 1970

Toxicity end point: Highest 1 h non-lethal value in monkeys (127 ppm)

Uncertainty Factors: 2 for interspecies
3 for intraspecies
combined uncertainty factor of 6

Scaling: $C^{1.3} \times t = k$ (this document; based on LC_{50} concentration and exposure duration relationships in Horn and Weir [1955], MacEwen and Vernot [1970], and Dost et al. [1974]).

Calculations: $(C^{1.3}/\text{uncertainty factors}) \times t = k$
$(127\ \text{ppm}^{1.3}/6) \times 60\ \text{min} = 3173.2\ \text{ppm}^{1.3} \cdot \text{min}$

$k = 3173.2\ \text{ppm}^{1.3} \cdot \text{min}$

10 min
AEGL-3: $3173.2\ \text{ppm}^{1.3} \cdot \text{min}/10\ \text{min} = 84\ \text{ppm}$

30 min
AEGL-3: $3173.2\ \text{ppm}^{1.3} \cdot \text{min}/30\ \text{min} = 36\ \text{ppm}$

1 h
AEGL-3: $3173.2\ \text{ppm}^{1.3} \cdot \text{min}/60\ \text{min} = 21\ \text{ppm}$

4 h
AEGL-3: $3173.2\ \text{ppm}^{1.3} \cdot \text{min}/240\ \text{min} = 7.3\ \text{ppm}$

8 h
AEGL-3: $3173.2\ \text{ppm}^{1.3} \cdot \text{min}/480\ \text{min} = 4.3\ \text{ppm}$[b]

[b]Because the time-scaled 8 h AEGL-3 value of 4.3 ppm is inconsistent with the experimental data, the 8-h value was set equal to the 4-h value of 7.3 ppm.

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLORINE TRIFLUORIDE (CAS REG. NO. 7790-91-2)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm

Key Reference: Horn, H.J. and R.J. Weir. 1956. Inhalation toxicology of chlorine trifluoride. II. Chronic toxicity. A.M.A. Arch. Indust. Health 13:340-345.

Test Species/Strain/Number: Two dogs and 20 rats, breed and strain not stated.

Exposure Route/Concentration/Duration: Inhalation: 1.17 ppm, 6 h/day, 5 days/week for 6 months.

Effects during first day:
Dogs: 1.17 ppm for 6 h - nasal discharge (began within 0 to 45 min) obvious lacrimation (after 3 h).
Rats: 1.17 ppm for 6 h - no observed effects.

End point/Concentration/Rationale: A concentration of 1.17 ppm for 3 h resulted in no signs of irritation in dogs other than nasal discharge. Nasal discharge is considered to be within the definition of the AEGL-1 (mild sensory irritation). Lacrimation after 3 h of exposure was considered the threshold for notable discomfort.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3—The dog is a sensitive species for nasal irritation and provides a good model for humans. Dogs exposed to 1.17 ppm showed obvious lacrimation after 3 h yet rats showed no effects at the same concentration for 6 h.
Intraspecies: 3—The concentration at which slight irritation is induced in the general population should not differ greatly.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: Not applied; adaptation occurs to the slight sensory irritation that defines the AEGL-1.

Data Adequacy:
Although only two dogs were tested in the key study, the concomitant exposure of 20 rats contributes to confidence in the data. The value was based on the dog, which appeared to be more sensitive to respiratory irritants than the rat. Although no histopathological examinations were performed until the termination of the experiment or death, exposure continued for 56 days (39 exposures) before a death occurred in the treated rats.

The hydrolysis of ClF_3 potentially produces three moles of hydrogen fluoride (HF). Confidence in the AEGL-1 values is boosted by the fact that the values for ClF_3 are one-eighth of the AEGL-1 values for HF. The database for HF is extensive.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
8.1 ppm	3.5 ppm	2.0 ppm	0.70 ppm	0.41 ppm

Key Reference: Horn, H.J. and R.J. Weir. 1955. Inhalation toxicology of chlorine trifluoride. I. Acute and subchronic toxicity. A.M.A. Arch. Indust. Health 12:515-521.

Test Species/Strain/Sex/Number: Two dogs and 20 rats, breed and strain not stated.

Exposure Route/Concentration/Duration: Inhalation: 5.15 ppm for 6 h/day, 5 days/week for 6 months.

Effects (observed during the first day) for exposures to 5.15 ppm for 6 h:
Dogs: strong irritation (salivation, lacrimation, rhinorrhea, coughing, sneezing) apparent recovery at end of day.
Rats: no observed effects.

End point/Concentration/Rationale 5.15 ppm for 6 h resulted in strong signs of irritation (salivation, lacrimation, rhinorrhea, coughing, sneezing) in the dog. These signs and symptoms are consistent with the definition of the AEGL-2 (threshold for irreversible or other serious, long-lasting effects or impaired ability to escape). Following 2 days of exposure to 21 ppm, corneal ulcers were observed.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3—The dog is a sensitive species for nasal irritation and provides a good model for the human. Dogs exposed to 5.15 ppm

(Continued)

AEGL-2 VALUES Continued

showed signs of strong irritation (salivation, lacrimation, rhinorrhea, coughing, sneezing) during a 6-h exposure period yet rats showed no effects at the same concentration for 6 h.
Intraspecies: 3—The concentration that induces irritation among the general population should not vary greatly.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: $C^n \times t = k$ where $n = 1.3$; based on the time-concentration relationship for LC_{50} values in monkeys, rats, and mice for exposure durations of 13.5-222 min (Horn and Weir 1955; MacEwen and Vernot 1970; Dost et al. 1974).

Data Adequacy: Although only two dogs were tested in the key study, the concomitant exposure of 20 rats contributes to confidence in the data. The value was based on the dog which appeared to be more sensitive to respiratory irritants than the rat.

No histopathological examinations were performed until termination of the experiment or death; exposures continued for 26 days before a death occurred in the treated dogs.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
84 ppm	36 ppm	21 ppm	7.3 ppm	7.3 ppm

Key Reference: MacEwen, J.D. and E.H. Vernot. 1970. Toxic Hazards Research Unit Annual Technical Report: 1970, AMRL-TR-70-77, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Test Species/Strain/Sex/Number: Male and female rhesus monkeys, 4/exposure group.

Exposure Route/Concentration/Duration: Inhalation: 127, 150, 200, 300, or 400 ppm for 1 h.

Effects from 1 h exposure:

Concentration	Mortality
127 ppm:	0/4
150 ppm:	2/4
200 ppm:	1/4
300 ppm:	2/4

400 ppm: 4/4
1 h LC_{50} is 230 ppm (provided in reference)
1 h LC_{01} could not be calculated

End point/Concentration/Rationale: 127 ppm for 1 h, the highest non-lethal value in the monkey, was considered the threshold for lethality, the defined end point for the AEGL-3.

Uncertainty Factors/Rationale:
Total uncertainty factor: 6
Interspecies: 2—Based on the similarity in respiratory parameters among primates. In addition, effects were similar among species and LC_{50} values varied by less than a factor of two for the monkey, rat, and mouse (indicating similar species sensitivity).
Intraspecies: 3—The concentration at which extreme irritation and pulmonary damage may lead to lethality should not differ by more than a factor of 3 among the general population.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: $C^n \times t = k$ where $n = 1.3$; based on the time-concentration relationship for LC_{50} values in monkeys, rats, and mice for exposure durations of 13.5-222 min (Horn and Weir 1955; MacEwen and Vernot 1970; Dost et al. 1974).

Data Adequacy: The key study was well conducted and documented. LC_{50} values from several additional studies were within a factor of two for all tested species. Similar values can be derived using the rat data (MacEwen and Vernot 1970; Dost et al. 1974) and a total uncertainty factor of 10.

3

Cyclohexylamine[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 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory) and Mark McClanahan (National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member (Chemical Manager)). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

for each of five exposure periods (10 and 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:

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, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

EXECUTIVE SUMMARY

Cyclohexylamine is a respiratory, eye, and skin irritant, as well as a strong base (pK_a = 10.7) with a fishy, amine odor. It is used primarily for boiler water treatment (corrosion inhibition) as well as organic synthesis of rubber and agricultural chemicals. Occupational exposure to cyclohexylamine has been reported to cause headache, nausea, dizziness, vomiting, eye, nose and throat irritation, and rapid and irregular heart-

beat. Acute exposure of animals resulted in extreme mucous membrane irritation, gasping, tremors, clonic muscular spasms, lung hemorrhage, opaque corneas, vascular lesions, and hemolysis.

The level of distinct odor awareness (LOA) for cyclohexylamine is 2.0 ppm (see Appendix B for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

AEGL-1, AEGL-2, and AEGL-3 values were derived from a study in which Sprague-Dawley rats (5/sex/dose) were exposed for 4 h to 54.2 ppm (Group III) or 567 ppm (Group II) cyclohexylamine vapor, or to a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol (Group I) (Bio/dynamics, Inc. 1990). This well-conducted study was the most comprehensive of the available acute exposure studies. At 54.2 ppm, rats developed labored breathing, partially closed eyes, and red nasal discharge. Rats exposed to the two higher concentrations also exhibited rales, gasping, dried red facial material, tremors, body weight loss, and ocular lesions (corneal opacity, ulceration). Corneal opacity and ulceration were irreversible in Groups I and II (i.e., still present 3 weeks after exposure), but most other effects were reversible in both Groups I and II or only in Group II. Two Group I rats died and developed alopecia and lesions in the nasal turbinates, lungs, and/or urinary bladder.

AEGL-1 values were obtained by dividing 54.2 ppm by a modifying factor of 3, because the effects seen in rats at 54.2 ppm were more severe than prescribed by the AEGL-1 definition. Because mild sensory irritation is not expected to vary greatly over time, the same AEGL value was adopted for exposures of 10 min to 8 h. Uncertainty factors of 3 were applied for interspecies and intraspecies variability, respectively. Mild sensory irritation is not likely to vary greatly among humans or animals, and both human and additional animal data indicate that a greater UF was not warranted. The AEGL-1 is consistent with a study in which chemical workers exposed to 4-10 ppm for an undefined duration (<8 h) reported “no symptoms of any kind” (Watrous and Schulz 1950), but which was inappropriate for AEGL-1 derivation because effects were below AEGL-1 severity criteria. The AEGL-1 values are also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989), from which it is predicted that 2.7 or 5.1 ppm

should result in some sensory irritation in humans, whereas 0.27 or 0.51 ppm should cause no sensory irritation (Alarie 1981).

AEGL-2 values were based on the Bio/dynamics, Inc. (1990) inhalation exposure of rats to cyclohexylamine for 4 h to 54.2 ppm. The rats had moderate respiratory effects and ocular irritation but no irreversible ocular lesions, consistent with an earlier study in which rats, a rabbit, and guinea pigs exposed to 150 ppm 7 h/day for up to 2 weeks had no eye lesions, but those exposed to 800 ppm had corneal opacity (Watrous and Schulz 1950). Data were not available to determine the concentration-time relationship for cyclohexylamine toxicity. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using $n = 3$ to extrapolate to exposure times <4 h (exposure duration in the key study), except for the 10-min values, and $n = 1$ to extrapolate to exposure times >4 h. The 30-min values were adopted as 10-min values due to unacceptably large uncertainty in extrapolating from ≥4 h to 10 min and to be protective of human health (NRC 2001). A total uncertainty factor of 10 was applied (3 for interspecies variability and 3 for intraspecies variability) because effects seen at 54.2 ppm were clearly reversible, and a larger uncertainty factor yields values at or below the AEGL-1.

The AEGL-3 values were based on irreversible ocular lesions and an estimated lethality threshold in rats, from exposure for 4 h to 567 ppm. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al. (1986) equation $C^n \times t = k$ and $n = 1$ or $n = 3$, as for the AEGL-2 (NRC 2001). A total uncertainty factor of 30 was used: 10 for interspecies variability because, although tissue destruction caused by a severely corrosive agent is not expected to vary greatly among animals, the dose spacing in the key study failed to delineate the LOAEL for ocular lesions or the threshold for lethality in rats, and the set of animal studies was limited. An intraspecies uncertainty factor of 3 was applied because tissue destruction caused by a severely corrosive agent is not expected to vary greatly among humans; a greater uncertainty factor is not warranted because it yields concentrations comparable to AEGL-2 values in Table 3-1.

TABLE 3-1 Summary of AEGL Values for Cyclohexylamine

Classification	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL-1[a] (Non-disabling)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	Mild sensory and/or ocular irritation in rats (Bio/dynamics, Inc. 1990).
AEGL-2 (Disabling)	11 ppm (45 mg/m^3)	11 ppm (45 mg/m^3)	8.6 ppm (35 mg/m^3)	5.4 ppm (22 mg/m^3)	2.7 ppm (11 mg/m^3)	Moderate respiratory effects and ocular irritation; NOAEL for irreversible ocular lesions (Bio/dynamics, Inc. 1990).
AEGL-3 (Lethal)	38 ppm (150 mg/m^3)	38 ppm (150 mg/m^3)	30 ppm (120 mg/m^3)	19 ppm (77 mg/m^3)	9.5 ppm (39 mg/m^3)	Lethality threshold and irreversible ocular lesions (Bio/dynamics, Inc. 1990).

[a]Reported odor thresholds vary from 2.6 to 110 ppm.

1. INTRODUCTION

Cyclohexylamine is a strong base (pK_a = 10.6; HSDB 2002) and a flammable liquid. Cyclohexylamine occurs naturally, in the wood of the plant *Toddalia asiatica* (Tsai et al. 1998). Cyclohexylamine is produced by the catalytic hydrogenation of aniline at elevated temperatures and pressures, by the ammonolysis of cyclohexanol, or by the reduction of nitrocyclohexane (Sandridge and Staley 1978). Its uses include boiler water treatment (corrosion inhibition), synthesis of rubber chemicals, agricultural chemicals, plasticizers, and emulsifying agents (HSDB 2002). In the 1960s, a major use of cyclohexylamine was the production of cyclamate sweeteners for beverages and food products; this practice was banned by the U.S. Food and Drug Administration in 1970 (IARC 1980). U.S. demand for cyclohexylamine was estimated as 25 million lbs for 2002, which included exports up to 5 million pounds per year (HSDB 2002). As of 1994, the U.S. International Trade Commission listed only two U.S. producers, but the amounts produced or sold were not disclosed (USITC 1995).

Cyclohexylamine is a respiratory, eye, and skin irritant. The marked corrosive, irritant properties and foul odor generally limit human exposure to airborne cyclohexylamine. Watrous and Schulz (1950) pointed out that "the strong, disagreeable smell of cyclohexylamine, and its intensely bitter taste provide good warning properties." Reported odor thresholds vary widely, ranging from 2.6 ppm (Amoore and Hautala 1983) to 26-110 ppm (Ruth 1986). Occupational exposure to cyclohexylamine has caused symptoms including headache, nausea, dizziness, vomiting, eye, nose, and throat irritation, and rapid and irregular heartbeat. Acute exposure of animals resulted in extreme mucous membrane irritation, gasping, lung hemorrhage, opaque corneas, tremors, restlessness and clonic spasm of the trunk and paw muscles, hemolysis, and vascular lesions.

The primary fate of cyclohexylamine in the atmosphere is reaction with hydroxyl radicals, with a half-life of approximately 1.82 days (EPA 1987). Chemical and physical properties of cyclohexylamine are listed in Table 3-2.

TABLE 3-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Cyclohexanamine, aminocyclohexane, aminohexahydrobenzene, cyclohexylamine, hexahydroaniline, hexahydrobenzenamine	IARC 1980
Chemical formula	$C_6H_{13}N$	Budavari et al. 1996
Molecular weight	99.18	Budavari et al. 1996
CAS Registry Number	108-91-8	IARC 1980
Physical state	Liquid	IARC 1980
Color	Colorless or yellow	HSDB 2002
Solubility in water	Completely miscible	Budavari et al. 1996
Acid ionization constant, pK_a	10.6	HSDB 2002
Vapor pressure	8.4 mm Hg at 20°C	Eastman Kodak 1984
Vapor density (air = 1)	3.42	Verschueren 1996
Liquid density (water = 1)	0.8647 at 25/25°C	Budavari et al. 1996
Melting point	−17.7°C	Budavari et al. 1996
Boiling point	134.5°C at 760 mm	Budavari et al. 1996
Flammability/explosive limits	1.5-9.4%	NIOSH 2005
Conversion factors	1 mg/m^3 = 0.247ppm; 1 ppm = 4.06 mg/m^3	Verschueren 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human lethality resulting from acute cyclohexylamine exposure were located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

The odor detection threshold for cyclohexylamine was reported to be 2.6 ppm by Amoore and Hautala (1983). The value of 2.6 ppm was stated to be the geometric mean of all available literature data (not given), omitting extreme points and duplicate values, although the methods used to obtaining the individual odor thresholds were not described. Another secondary source listed the low and high reported odor detection thresholds for cyclohexylamine of 26 and 110 ppm, respectively (Ruth, 1986). It is possible that the low threshold in the latter source was a typographic error and should have been 2.6 ppm.

2.2.2. Occupational Exposure

Watrous and Schulz (1950) described three cases of industrial cyclohexylamine exposure. A 42-year-old chemical operator, exposed for about an hour, noticed a strong, fishy smell, felt lightheaded and became very anxious. Later the same day, he reported loss of appetite, anxiety that prevented his falling asleep, burning in his throat, and a rapid heartbeat. Medical examination the following day revealed no abnormalities although the man still complained of anxiety. Air cyclohexylamine concentrations were not obtained at the time but were measured at a later time (not specified) and found to be 4-10 ppm. The location and number of operators involved were not given, though "this exposure caused no symptoms of any kind in the operators."

In the second case, a 27-year-old operator was splattered on the face with liquid cyclohexylamine dissolved in a caustic solution (not identified). The skin on his face became red and developed many small white spots characteristic of coagulative necrosis. The man became nau-

seated and vomited an hour after the accident and twice more later. He had a normal pulse and blood pressure but became drowsy, had slurred speech and widely dilated pupils that responded poorly to light. The next day he apparently recovered except for some facial crusting.

The third clinical case described by Watrous and Schulz (1950) was of a supervisor of the process that used cyclohexylamine. He was exposed to cyclohexylamine vapor on several occasions and said that he became nauseated, although he did not vomit (no further details were provided).

NIOSH conducted a Health Hazard Evaluation of the Cincinnati Electronics Corp. (Hills and Lushniak 1989; Hills et al. 1990). Employees reported symptoms including headache, rapid and irregular heartbeat, nausea, dizziness, vomiting, and eye, nose and throat irritation that persisted for several hours to several days. They worked in an area humidified by a water boiler to which was added four times the normal amount of a corrosion inhibitor containing cyclohexylamine (and diethylaminoethanol). The odor was described as musty-acrid, ammonia-like, musty radiator, or pungent. Air samples were not collected during the incident. Samples collected by NIOSH several days later (2 h, 0.2 liters/min [LPM]) had cyclohexylamine concentrations below detectable limits (~0.08 ppm), likely due to the six boiler steam purgings and daily addition of clean replacement water to the boiler after the incident prior to the NIOSH investigation.

2.3. Neurotoxicity

No descriptions of neurologic involvement other than the case descriptions by Watrous and Schulz (1950) were located.

2.4. Developmental/Reproductive Toxicity

There are no confirmed reports of cyclohexylamine-induced reproductive or developmental toxicity in humans. Microgastria, a rare congenital anomaly arising from a defect in embryological development and resulting in effects including asplenia, upper limb hypoplasia, and intestinal malrotation, was reported in a 2.75-year old boy conceived as the result of insemination by donor following Clomid stimulation (Hanson et al. 1990). While this individual was in utero, his mother was ex-

posed to cyclohexylamine on pregnancy day 34 or 35. The boy was born a normal size (7.5 lbs) and had a normal karyotype. No details of the cyclohexylamine exposure were given. No causal relationship between the microgastria and cyclohexylamine exposure was asserted by the study authors.

2.5. Genotoxicity

Cyclohexylamine did not induce cytogenetic changes (rings, dicentrics, chromatid breaks or aberrations) in human lymphocytes in vitro (Brewen et al. 1971). Cells were exposed at the G_0, G_1, S, or G_2 stages of the cell cycle with up to 500 μg/mL cyclohexylamine.

2.6. Carcinogenicity

No epidemiologic studies or case reports of carcinogenicity occurring from cyclohexylamine exposure by any route were located. IARC (1987) and the ACGIH (2004) concluded that there is inadequate evidence in humans and in experimental animals to establish the carcinogenicity of cyclohexylamine. IARC placed cyclohexylamine (with cyclamates) in carcinogenicity Group 3 and the ACGIH placed it in Group A4. The Environmental Protection Agency (EPA) has not provided a carcinogenicity weight-of-evidence classification for cyclohexylamine (EPA 2005).

2.7. Summary

Several occupational studies described effects from acute inhalation exposure to unknown air concentrations of cyclohexylamine. Workers reported headache, rapid and irregular heartbeat, nausea, dizziness, vomiting, and eye, nose and throat irritation. Watrous and Schulz (1950) found that exposure during an unspecified fraction of a workday to 4-10 ppm cyclohexylamine "caused no symptoms of any kind," but there was no indication whether the workers were able to detect the characteristic odor. Widely varying odor detection thresholds were reported for cyclohexylamine in two secondary sources (2.6 ppm and 26-110 ppm). There

was no evidence in humans of cyclohexylamine inhalation causing carcinogenicity, reproductive or developmental effects, or genotoxicity.

3. ANIMAL TOXICITY DATA

Only a small number of animal studies were located; these used rats, mice, guinea pigs, and rabbits. Unfortunately, most had incomplete reporting of the methods and/or results. The cyclohexylamine inhalation studies are summarized in Table 3-3.

3.1. Acute Lethality

3.1.1. Rats

In a 4-h acute inhalation toxicity study conducted by Bio/dynamics, Inc. (1990), Sprague-Dawley rats (5/sex/dose) were administered nominal concentrations of 8.8 (Group I), 6.4 (Group II), or 0.57 mg/L (Group III) cyclohexylamine (determined using the test substance weight and delivered air volume). Exposure was in a 100-L Plexiglas chamber. The analytical concentrations of cyclohexylamine vapor were measured hourly, and for Groups I, II, and III were, respectively, 2.2, 2.3, and 0.22 mg/L (542 ppm, 567 ppm, and 54.2 ppm). The Group I atmosphere also contained cyclohexylamine aerosol (mean of 612 mg/m^3 range of 5.5-1,500 mg/m^3; mean mass median diameter [MMMD] of 11 μM, measured hourly). The aerosol appeared to have formed by reaction of the vapor with moisture from the animals, since aerosol was not seen during empty chamber trials at the same target concentration. Additional desiccation of the chamber air during exposure of Group II and III animals eliminated all but small amounts of aerosol (Group II: 0.00011-0.59 mg/m^3, 12 μM MMMD; Group III: 0.88-54 mg/m^3, 2.2 μM MMMD). Rats were observed for 2 weeks (Group III) or 3 weeks (Groups I, II) post exposure and were weighed on days 1 (preceding exposure), 2, 3, 5, 8, 15, and for Groups I and II, also on day 22. Necropsies were performed on all animals (no histopathology was performed).

Two Group I rats died on day 2. They had alopecia and nasal, lung, and urinary bladder lesions. Groups I and II rats had dyspnea, gasping, tremors, partly or completely shut eyes, profuse lacrimation, corneal opacity and ulceration, red nasal discharge, dried red or brown stains on

TABLE 3-3 Cyclohexylamine Inhalation Exposure Animal Studies

Single-Exposure Studies

Species	Exposure Time	Conc. (ppm)	Time of Death	Mortality	Effects, Comments (Reference)
Rat	6 h 6 h	1,000 12,000	(none) 48 h	0/3 2/3	No death or reported effects Death; no other details (Eastman Kodak,1984)
Rat	4 h 4 h ≤2 h	4,000 8,000 ~15,000	(none) ? (none)	0/6 6/6 0/6	No death or reported effects Death; no other reported effects No death, reported effects (Smyth, et al. 1969)
Rat	4 h 4 h 4 h	54.2 567 >542[a]	(none) (none) Day 2	0/10 0/10 2/10	Lacrimation, red nasal discharge (see Table 3) Corneal lesions, severe respiratory effects As above; 2/10 died (Bio/dynamics, Inc. 1990)
Rat	Not given (<8 h ?)	443 1,059 1,847 2,833	(none) Mainly on days 7-14	LC_0 LC_{Lo} LC_{50} LC_{100}	Effects reported but not ascribed to a specific dose or species include irritation of mucous membranes, restlessness, muscle spasm, hemolysis, vascular lesions, organ weight changes. Mice given 2.5 ppm had changes in subthreshold impulse summation. (Lomonova 1965)
Mouse	not given (<8 h ?)	2.5, 12.3 24.6 264 1,059	(none) Mainly on days 1-5	LC_0 LC_{Lo} LC_{50} LC_{100}	
Mouse	15 min 120 min	26-84 79-220	(none) (none)	0/6 0/6	RD_{50} = 51 ppm (Gagnaire et al. 1989; 1993) Tracheally cannulated RD_{50} = 51 ppm

Mouse	30 min	4-355	(none)	0/4	RD_{50} = 27 ppm; 75% lower respiration rate at 355 ppm (Nielsen and Yamagiwa 1989)
		32-345	(none)	0/4	Tracheally cannulated RD_{50} = 78 ppm
Multiple-Exposure Studies					
Rat	2 h/d x 2 mo	172	2 mo	3/6	↓ BW gain, vascular changes, organ lesions
	4 h/d x 5 mo	24.6	4 mo	1/20	Leukocytosis at 3-5 mo. (Lomonova 1965)
Rat	7 h/d x 10 d	150	≤10 day	1/5	1 death; no other reported effects
		800	24 h	0/5[b]	Corneal opacity; death possibly (unclear)
		1,200	7 h	4/5[b]	Extreme irritation, lung hemorrhage, opaque corneas, death (Watrous and Schulz 1950)
Guinea pig	7 h/d x 10 d	150	≤10 day	0/2?[b]	No reported effects
		800	14 h	2/?[b]	Corneal opacity; 2 deaths
		1,200	7 h	All	Extreme irritation, lung hemorrhage, opaque corneas, death (Watrous and Schulz 1950)
Rabbit	7 h/d x 10 d	150	7 h	1/?[b]	1 death; no other reported effects
		800	14 h	1/?[b]	Corneal opacity; 1 death
		1,200	7 h	All	Extreme irritation, lung hemorrhage, opaque corneas, death (Watrous and Schulz 1950)

?, Unknown; not reported.
[a]Highest conc. was 542 ppm vapor + ~612 mg/m^3 aerosol.
[b]Total number of animals tested and the results for the entire 70-h exposure period were not reported.

face, moist and dry rales, yellow ano-genital stains, alopecia, and marked body weight loss. Many of these effects persisted during the 3-week post-exposure observation period in Group I. Necropsy revealed numerous eye lesions (ulcerations, opacity, corneal scars, tissue damage, and discoloration) in Groups I and II but no other significant findings. Group III rats had a much milder response, consisting of reversible respiratory effects and sensory irritation. The Bio/dynamics, Inc. (1990) study is summarized in Table 3-4.

White rats were exposed to 150, 800, or 1,200 ppm cyclohexylamine for up to 70 h (7 h/day, 5 days/week) by Watrous and Schulz (1950). A titration method was used to measure air cyclohexylamine concentrations. It was not explicitly stated how many rats were treated at each concentration (although it appeared to be 5) or how many days the animals were exposed to each concentration (appeared to be 2 weeks). All but one rat died after the first 7 h exposure to 1,200 ppm; the rats showed signs of extreme mucous membrane irritation and had lung hemorrhage. Of the rats exposed to 800 ppm, "five survived 24 h of exposure;" it was not stated how many animals died after 24 h of exposure. Of the rats exposed to 150 ppm cyclohexylamine, 4/5 survived 70 h of exposure. The higher concentrations (presumably 800 and 1,200 ppm) caused the corneas of all the animals to become opaque. No convulsant effects were seen.

Several published rat inhalation studies were poorly reported but help provide an overall picture of cyclohexylamine acute toxicity. Smyth et al. (1969) showed that the maximum period for which albino rats survived exposure to air saturated with cyclohexylamine vapor was 2 h (cyclohexylamine air saturation occurs at ~15,000 ppm; Amoore and Hautala 1983). Exposure of rats to 4,000 ppm cyclohexylamine for 4 h resulted in 0/6 deaths, whereas exposure to 8,000 ppm for 4 h resulted in 6/6 deaths after 14 days (Smyth et al., 1969). Exposure of rats to 1000 ppm cyclohexylamine for 6 h resulted in 0/3 deaths, whereas 2/3 rats died after exposure for 6 h to 12,000 ppm (Eastman Kodak 1984). Lomonova (1965) exposed rats to 443-2833 ppm for an single unspecified duration and obtained a 14-day LC_{50} of 1847 ppm; rats had visible mucous membrane irritation, as well as clonic muscle spasms, decreased body weight, body temperature, respiration rate, and urine output, 8-16% methemoglobinemia, evidence of hemolysis, organ weight changes, and vascular lesions (not clearly defined). Lomonova (1965) exposed other groups of rats to172 ppm cyclohexylamine 2 h/day for 2 months or to 24.6 ppm 4 h/day for 5 months. Both treatment groups had premature

TABLE 3-4 Observations in Rats Inhaling Cyclohexylamine Vapor for 4 h

Observation	Number of Affected Animals (n = 10) during Exposure[a]						Number of Affected Animals (n = 8-10) Post-Exposure[b]			
	¼	½	¾	1	2	4	2 h	7 d	14 d	22 d
GROUP I (2.2 mg/L + 612 mg/m^3 aerosol)				Observations could not			n=10	n=8	n=8	n=8
Excessive lacrimation	Few	All	All	be made due to clouding			2	1	0	1
Mucoid nasal discharge	—	Few	Most	or residual build-up			0	0	0	0
Red nasal discharge (wet or dried)	—	—	—	inside the chamber			3	1	0	0
Dried brown material on face	—	—	—				1	4	0	0
Labored breathing	Few	Most	Most				10	2	1	1
Gasping	—	—	—				7	0	0	1
Rales: moist or dry	—	—	—				6	4	5	5
Eyes closed	All	All	All				0	0	0	0
Coarse tremors	—	—	—				6	0	0	0
Corneal opacity	—	—	—				2	7	8	7
Corneal irregularity or ulceration	—	—	—				9	1	0	8
Yellow ano-genital stains	—	—	—				2	2	2	0
Alopecia	—	—	—				0	0	1	2
Decreased activity	—	—	—				10	0	0	0
GROUP II (567 ppm)					Observations		n=10	n=10	n=10	n=10
Excessive lacrimation	—	Few	Few	Few	could not be		5	0	0	0
Chromodacryorrhea	—	—	—	—	made due to		0	0	0	0
Mucoid nasal discharge	—	Few	Few	Few	residual build-up inside the chamber		0	0	0	0

(Continued)

TABLE 3-4 Continued

Observation	Number of Affected Animals (n = 10) during Exposure[a]						Number of Affected Animals (n = 8-10) Post-Exposure[b]			
	¼	½	¾	1	2	4	2 h	7 d	14 d	22 d
GROUP II (567 ppm) *(continued)*					Observations		n=10	n=10	n=10	n=10
Red nasal discharge (wet or dried)	—	—	—	—	could not be		6	2	0	0
Dried brown material on face	—	—	—	—	made due to		8	8	1	0
Labored breathing	Few	Some	Some	Some	residual build-		10	0	5	0
Gasping	—	Few	Few	Few	up inside the		0	0	0	0
Rales: moist or dry	—	—	—	—	chamber		10	10	10	7
Eyes partially closed	All	All	All	All			0	0	0	0
Coarse tremors	—	—	—	—			2	0	0	0
Corneal opacity	—	—	—	—			0	9	10	7
Corneal irregularity or ulceration	—	—	—	—			10	1	10	10
Yellow ano-genital stains	—	—	—	—			8	6	0	0
Alopecia	—	—	—	—			0	0	5	2
GROUP III (54.2 ppm)							n=10	n=10	n=10	All sacri-
Excessive lacrimation	—	—	—	—	—	—	1	0	0	ficed on
Chromodacryorrhea	—	—	—	—	—	—	0	0	0	day 15
Mucoid nasal discharge	—	—	—	—	—	—	0	0	0	
Red nasal discharge (wet or dried)	—	—	—	Few	Few	Few	0	1	0	
Dried brown/red material on face	—	—	—	—	—	—	9	1	0	
Labored breathing	Few	Some	Most	Most	All	All	0	0	0	
Eyes partially closed	—	—	—	Most	All	All	0	0	0	

[a]The animals (5/sex) were observed as a group, and the number of affected animals was presented as few = 10-30%, some = 40-60%, most = 70-90%, all = 100%.

[b]Observations were made 30 min, 1 h and 2 h, after exposure and thereafter daily until sacrifice. The daily incidence at the stated time is presented. One male and one female Group I rat died on post-treatment day 2.

Source: Bio/dynamics, Inc. 1990.

decedents, decreased body temperature and respiratory rate, and the 172-ppm rats had decreased body weight gain, evidence of hemolysis, vascular changes in most internal organs, and lesions in the heart, kidneys, trachea, lungs, and adrenal cortex.

3.1.2. Mice

Mice received a single exposure of 12.3-1,059 ppm cyclohexylamine for an unspecified duration; most died within 1-5 days of exposure (Lomonova 1965; summarized in Table 3-3). Mice appeared more sensitive than rats to acute cyclohexylamine exposure. However, the dose-lethality pattern for mice was different than for rats. The "absolute lethal," "median lethal," and "minimum lethal" concentrations were about 2.7-fold, 7-fold, and 43-fold lower, respectively, for mice than for rats.

3.1.3. Rabbits

Rabbits were exposed to 150, 800, or 1,200 ppm cyclohexylamine for 7 h/day, 5 days/week by Watrous and Schulz (1950). Air cyclohexylamine concentrations were measured by a titration method. It was not specified how many animals were treated at each concentration, but only one rabbit was mentioned at any given concentration. The total number of exposures which the animals survived was not stated; 10 days was the maximum exposure duration. At 1,200 ppm, all animals showed signs of extreme mucous membrane irritation, developed pulmonary hemorrhages, and died after the first exposure. Animals exposed to the "higher concentrations" (presumably 800 and 1,200 ppm) developed opaque corneas. The mortality patterns of the rabbits were difficult to distinguish due to the limited number of rabbits studied. At 800 ppm, one rabbit died after the second 7 h exposure; at 150 ppm one rabbit died after 7 h.

3.1.4. Guinea Pigs

Guinea pigs were exposed to 150, 800, or 1,200 ppm cyclohexylamine for 7 h/day, 5 days/week (Watrous and Schulz 1950). Air cyclohexylamine concentrations were measured by a titration method. It was not specified how many animals were included at each concentration, but

only two guinea pigs were mentioned at any given concentration. The total number of exposures which the animals survived was not stated; 10 days was the maximum exposure duration. At 1,200 ppm, all animals showed extreme mucous membrane irritation, had lung hemorrhage, and died after the first 7 h exposure. At 800 ppm, two guinea pigs died after the second 7 h exposure and at 150 ppm two guinea pigs survived 70 h exposure." Animals exposed to "higher concentrations" (presumably 800 and 1,200 ppm) developed opaque corneas.

3.2. Nonlethal Toxicity

3.2.1. Rats

In a GLP study conducted by Bio/dynamics, Inc. (1990), Sprague-Dawley rats were exposed for 4 h to 542 ppm cyclohexylamine vapor + 612 mg/m^3 aerosol (Group I), 567 ppm vapor (Group II), or 54.2 ppm vapor (Group III). As shown in Table 3-4 and described in Section 3.1.1, 2/10 Group I rats died and Group I and II rats had severe respiratory, neurological, and ocular effects. These alterations persisted to the end of the 3-week observation period in Group I and in some cases (corneal lesions and rales) in Group II. Rats inhaling 54.2 ppm displayed milder effects, which during exposure consisted of labored breathing, partially closed eyes and red nasal discharge. Over the 2-h following exposure, rats had lacrimation, chromodacryorrhea, mucoid or red nasal discharge, and dried red or brown nasal discharge or facial material. Red nasal discharge was seen in several animals during the 2-week observation but was no longer present by day 14. The rats did not gain weight until post-exposure day 4.

Several other studies described in Section 3.1.1 and summarized in Table 3-4 included non-lethal exposures. Lomonova (1965) found mucous membrane irritation, CNS excitability, decreased body weight, increased blood methemoglobin, hemolysis (not at 24.6 ppm), vascular lesions, and/or organ weight changes, but no mortality in groups of albino rats exposed once to 443 ppm (duration unknown), for <2 months (2 h/day) to 172 ppm, or <4 months (4 h/day) to 24.6 ppm. No mortality occurred among 3 rats exposed for 6 h to 1,000 ppm (Eastman Kodak 1984) or among 6 rats exposed for 4 h to 4,000 ppm (Smyth et al. 1969).

3.2.2. Mice

The concentration of cyclohexylamine causing a 50% decrease in the breathing rate of male OF_1 Swiss mice (RD_{50}) was determined to be 51 ppm in an oronasal exposure study conducted by Gagnaire et al. (1989). Mice were exposed for 15 min to 26-84 ppm cyclohexylamine vapor (6/concentration) by enclosing the head in a 200-liter stainless steel exposure chamber into which cyclohexylamine vapor was delivered by bubbling air through the liquid amine. Respiratory rates were measured using plethysmographic techniques (American Standard Method E981-84). The effect on breathing rate was maximal 10-15 min into the exposure, and recovery after the 15-min exposure occurred within 1 min. The decreased breathing rate is due to stimulation of the trigeminal nerves in the nasal mucosa, and was monitored with a pressure transducer. (Gagnaire et al. [1993] reports the same RD_{50} results; however, the stated exposure was 60 min; it is unclear whether the 1993 reference was for a new experiment.)

Pulmonary irritation was similarly assessed in anesthetized, tracheally cannulated (TC) mice by determining the $RD_{50}TC$ (i.e., concentration causing 50% respiratory inhibition). $RD_{50}TC$ values for upper airway irritants are typically higher than RD_{50} values (for nasally exposed mice) due to the bypass of the trigeminal nerves in the nasal mucosa of the TC animals. The TC mice were exposed to 79-220 ppm cyclohexylamine for 120 min (Gagnaire et al. 1989; results also reported in Gagnaire et al. 1993), and an $RD_{50}TC$ of 184 ppm was determined. The maximal decrease in the breathing rate was seen after 120 min of exposure; recovery of breathing rate to pre-exposure levels was incomplete (animals were observed 20-30 min after exposure based on Gagnaire et al. 1993). The lower value of the RD_{50} compared to the $RD_{50}TC$ indicates that the respiratory toxicity of cyclohexylamine is primarily related to its upper airway irritant effects. The decrease in breathing rate is due to a reflex reaction induced by stimulation of the irritant and mechanosensitive alveolar receptors.

Nielsen and Yamagiwa (1989) also determined RD_{50} values for cyclohexylamine. Respiratory rates and tidal volumes were measured using plethysmographic techniques (American Standard Method E981-84). Male Ssc:CF-1 mice (4/concentration) were exposed for 30 min. Exposure was head-only in a 3.3-L chamber into which evaporated cyclohexylamine was delivered in the air (52-97 L/min). Chamber concentrations were monitored continuously by infrared spectroscopy. The

RD_{50} for cyclohexylamine was determined to be 27 ppm by exposure of the mice to 4-355 ppm cyclohexylamine. A slight (~20%) decrease in the respiratory rate occurred at 4 ppm and the maximal inhibition (about 75%) was seen at 355 ppm, but no animals died. For tracheally cannulated mice exposed to 32-345 ppm cyclohexylamine, the 50% respiratory inhibition ("tRD_{50}", analogous to $RD_{50}TC$), was 78 ppm. Maximal pulmonary irritation occurred at ~100 ppm, but no animals died at that concentration or at a 3.5-fold higher concentration (345 ppm), indicating that the decrease in respiratory rate is not directly correlated to the mortality rate. The concentration-response curve for cyclohexylamine was linear for non-cannulated mice, suggesting that the decreased respiratory rate at all tested concentrations were due to sensory irritation. Tidal volume was slightly altered (~20% increase) at only the highest dose tested in non-cannulated mice, and sensory and pulmonary irritation reached a plateau within 10 min of exposure.

Lomonova (1965) reported that the lowest single exposure concentration that altered the CNS capacity for summation of subthreshold impulses in mice was 2.5 ppm and that 12.3 ppm was the "maximum tolerated" dose (see Section 3.1.1. and Table 3-3).

3.3. Neurotoxicity

No studies were located assessing the neurotoxicity of cyclohexylamine in animals.

3.4. Developmental/Reproductive Toxicity

No animal studies were located that addressed the developmental or reproductive effects of cyclohexylamine following inhalation exposure.

Oral studies have generally associated cyclohexylamine with developmental and/or reproductive toxicity but not teratogenicity in mammals (reviewed in IARC 1980; Beard and Noe 1981). Subchronic oral treatment (63-90 days) of rats and dogs with 200-400 mg/kg-day cyclohexylamine or lifetime administration of 50-300 mg/kg-day cyclohexylamine caused effects including testicular tubular atrophy and calcium deposition, decreased testicular weights, impaired spermatogenesis, and/or lowered sperm count and motility (Gaunt et al. 1974; Oser et al.

1976; Mason and Thompson 1977; James et al. 1981; Roberts et al. 1989). Conversely, mice fed 3000 ppm (~390 mg/kg) cyclohexylamine hydrochloride for up to 80 weeks failed to develop testicular atrophy or degeneration (Hardy et al. 1976). Reproductive performance was not significantly affected in the Gaunt et al. (1976) chronic rat study or in the Gaunt et al. (1974) 13-week study, but was impaired slightly in the Oser et al. (1976) multigeneration study (reduction in litter size and weaning weight). Embryotoxicity was observed in a six-generation mouse study by Kroes et al. (1977), in which mice given 0.5% dietary cyclohexylamine sulfate had a significant reductions in implantations, live-born fetuses, and the offspring showed evidence of growth retardation. Parental toxicity was not evaluated, although it was noted that treated mice had significantly lower body weight but a better survival rate than controls. Oser et al. (1976) and Gaunt et al. (1974; 13-week study) found no treatment-related malformations in offspring of treated parents. No evidence of teratogenesis was seen in ICR mice or Rhesus monkeys treated orally with 75 or 100 mg/kg-day or in Wistar rats given 1.8-36 mg/kg-day during organogenesis (Takano and Suzuki 1971; Wilson 1972; Tanaka et al. 1973).

3.5. Genotoxicity

Cyclohexylamine (33-10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, or TA1537 when tested using a modified preincubation assay, with or without rat or hamster liver S9 mix (Mortelmans et al. 1986). In vitro, cyclohexylamine enhanced the virus-mediated transformation of Syrian hamster embryo cells and induced chromosome aberrations in kangaroo rat cells (IARC 1987). It did not, however, induce somatic or sex-linked recessive lethal mutations, aneuploidy, or heritable translocations in *Drosophila* (Knaap et al. 1973). Negative results were obtained in most of the reported dominant-lethal rodent assays; questionable or positive findings in two assays were difficult to interpret because either postimplantation loss or the experimental design were not adequately reported (EPA 1987). Weakly positive results were obtained in the mouse spot test (IARC 1987). Cyclohexylamine induced chromosomal aberrations in vivo in hamster lymphocytes and in rat spermatogonia but not in rat leukocytes, hamster, lamb, or rat bone marrow, or hamster and mouse spermatogonia (IARC 1987).

Cultured (48-68 h) peripheral blood lymphocytes from living sheep fetuses that had been infused in utero with 50-250 mg/kg cyclohexylamine for 5 or 18 h had increased levels of chromosome aberrations. The number of aberrations at 18 h as 4-5 times greater than at 5 h (Turner and Hutchinson 1974).

Cyclohexylamine was negative in the mammalian CHO/HGPRT forward mutation assay (172-1720 μg/mL tested) and in the unscheduled DNA synthesis assay in rat hepatocytes (4.3-860 μg/mL) (Brusick et al. 1989). The upper concentrations tested in each of the assay systems were cytotoxic.

3.6. Carcinogenicity

No inhalation carcinogenicity bioassays were located in the literature. Several oral exposure studies were conducted that showed no definitive evidence of cyclohexylamine carcinogenicity. ASH-CS1 mice (48-50/sex) that received up to 3,000 ppm (~390 mg/kg BW) dietary cyclohexylamine hydrochloride for 80 weeks had tumor incidences and types within historical control ranges (Hardy et al. 1976). Sprague-Dawley rats (52/sex) fed cyclohexylamine at 200 mg/kg BW for 30 months, FDRL rats (30/sex) fed at 15-150 mg/kg BW for 2 years, and Wistar rats (48/sex) fed at 24-440 mg/kg BW for 2 years had tumor incidences similar to controls (Schmahl 1973; Oser et al. 1976; Gaunt et al. 1976). A rare invasive bladder carcinoma was reported in 1/25 male Sprague-Dawley rats (0/25 females) given 15 mg/kg BW dietary cyclohexylamine sulfate for 2 years (0.15 and 1.5 mg/kg-day were also tested) (Price et al. 1970). This appeared to be a spontaneous tumor unrelated to treatment, since bioassays conducted by other investigators who used greater numbers of animals did not find treatment-related increases in tumor incidence or any bladder tumors (EPA 1987).

Both IARC (1987) and the ACGIH (2004) concluded that there was inadequate evidence in humans and in experimental animals to establish the carcinogenicity of cyclohexylamine. EPA has not provided a carcinogenicity weight-of-evidence classification for cyclohexylamine (EPA 2005).

3.7. Summary

Cyclohexylamine acute lethality inhalation studies were located for rats, mice, guinea pigs, and rabbits. The most comprehensive study

was that conducted by Bio/dynamics, Inc. (1990), in which Sprague-Dawley rats were exposed for 4 h to ≥54.2 ppm cyclohexylamine vapor. Many of the other available studies had incomplete reporting of the methods and/or results. Several multiple-exposure inhalation studies were also conducted using rats and mice. Rats appeared less sensitive to cyclohexylamine than mice, guinea pigs, or rabbits with respect to lethality in two studies. The data, however, were inadequate to define the most sensitive species. No studies were suitable for determination of cyclohexylamine concentration-time relationships.

RD_{50} values of 51 ppm (Gagnaire et al. 1989) and 27 pm (Nielsen and Yamagiwa 1989) were obtained for cyclohexylamine in male OF_1 Swiss mice. RD_{50} values for tracheally cannulated mice were higher in both experiments (184 ppm and 78 ppm, respectively), indicating that the response was primarily related to upper airway irritation.

No animal inhalation studies were located that addressed the developmental or reproductive effects of cyclohexylamine. Several subchronic and chronic oral studies with rats and dogs indicated that cyclohexylamine had developmental and reproductive but not teratogenic potential. However, these effects were not seen by other investigators using mice and monkeys. Genotoxicity assays yielded mixed results. Carcinogenicity studies did not show conclusive evidence of cyclohexylamine-induced neoplasms. Both IARC (1987) and ACGIH (2004) concluded that there was inadequate evidence in humans or in experimental animals to determine the carcinogenic potential of cyclohexylamine (IARC Group 3; ACGIH Group A4).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No human or animal studies were located that described the metabolism or disposition of cyclohexylamine following inhalation exposure. However, oral studies showed that cyclohexylamine was absorbed rapidly and nearly completely from the gastrointestinal tract by humans, rats, rabbits, and guinea pigs (Renwick and Williams 1972). Excretion was primarily by urine, with 61-90% of radiolabel from ^{14}C-cyclohexylamine-HCl recovered within 24 h of administration. All tested animals as well as man excreted primarily the parent compound, with 4-5% of the administered dose metabolized in 24 h in the rat and guinea

pig, 1-2% in man and 30% in rabbits. In rats, metabolism of cyclohexylamine was mainly through hydroxylation of the cyclohexane ring, in guinea pigs and rabbits by ring hydroxylation and deamination, and in humans by deamination. The extent of hydroxylation was not related to the development of testicular toxicity in rats (Roberts et al. 1989). Mice absorbed and eliminated orally administered cyclohexylamine more rapidly than rats; the steady-state plasma clearance rates of 33 and 66 mL/min/kg were estimated for rats and mice, respectively (Roberts and Renwick 1986; Roberts et al. 1989).

4.2. Mechanism of Toxicity

Cyclohexylamine is a strong base (pK_a = 10.7) and a severe eye, skin and respiratory irritant. Its alkalinity is likely responsible for the corneal lesions (opacity, irregularities, ulceration) found in rats, guinea pigs, and rabbits exposed to ≥542 ppm cyclohexylamine (Watrous and Schulz 1950; Bio/dynamics, Inc. 1990). The marked irritancy of cyclohexylamine has been held responsible for pulmonary edema and hemorrhage, along with extreme mucous membrane irritation and gasping seen in rodents. Occupationally exposed workers reported similar effects, including eye, nose and throat irritation, headache, rapid and irregular heartbeat, nausea, dizziness, and vomiting. Other effects have also been observed in animals treated by inhalation, such as tremors, clonic muscular spasms, vascular lesions, and hemolysis. The mechanism by which these systemic effects occur is less clear.

Lee and Dixon (1972) have reported that cyclohexylamine (150-1250 mg/kg) injected into Swiss Webster mice caused sniffling, vicious fighting, panting, hyperexcitability, hyperpyrexia, and excessive salivation. High ambient temperatures and crowding increased the cyclohexylamine-induced mortality. Death by systemic cyclohexylamine intoxication was prevented by the administration of the anti-adrenergic drugs reserpine, chlorpromazine, tolazoline, and phenoxybenzamine (Lee and Dixon 1972). These signs and the response to high ambient temperatures, crowding, and sympatholytic drugs are characteristic of other sympathomimetic amines such as amphetamine. However, it is unclear whether a direct parallel can be drawn between exposure to inhaled, very basic cyclohexylamine (100% pure) and the injection of cyclohexylamine hydrochloride that is dissolved in water and neutralized to pH 7.4 with sodium hydroxide (purity not stated). For example, in the

Bio/dynamics, Inc. (1990) study, 10/10 rats in the high-dose group (542 ppm aerosol + 612 mg/m^3 vapor) exhibited "decreased activity" up to 2 h after the 4-h exposure, and 1/10 rats felt "cold to the touch" two days after exposure, whereas hyperthermia and hyperactivity were two hallmark features of rats injected with cyclohexylamine hydrochloride. Additionally, Lee and Dixon (1972) showed that pre-treatment with monoamine oxidase (MAO) inhibitors (pargyline or JB-516) had no effect on cyclohexylamine lethality, whereas Brittain et al. (1964) found that pretreatment with MAO inhibitors (phenelzine and tranylcypromine) increased amphetamine toxicity 15- to 20-fold.

4.3. Structure-Activity Relationships

In addition to investigations with cyclohexylamine, Lomonova (1965) also examined the inhalation toxicity of dicyclohexylamine (DCHA). Compared to cyclohexylamine, the LC_{100} of DCHA for mice was 17-fold lower, although the minimum lethal concentrations (LC_{Lo}) were comparable; the animals died within 1-2 h. The mice were initially restless; increased motor activity was followed by tonic-clonic spasms. Repeated exposure to a sublethal concentration of DCHA (2 h/day for 30 days) did not cause lesions in mice but caused liver and kidney degeneration in rats.

N,N-dimethylcyclohexylamine, a compound structurally similar to cyclohexylamine, was somewhat less irritating than cyclohexylamine. It produced CNS effects such as weakness, tremor, salivation, gasping, and convulsions (Beard and Noe 1981).

Gagnaire et al. (1993) obtained RD_{50} values for *n*-hexylamine of 42 ppm for nasally exposed mice and 93 ppm for tracheally cannulated mice. These RD_{50} values are comparable to the RD_{50} values obtained for cyclohexylamine in the same study (51 and 184 ppm for nasally exposed and cannulated mice, respectively) and by Nielsen and Yamagiwa (1989; RD_{50} of 27 and 78 ppm for nasally exposed and cannulated mice, respectively).

4.4. Other Relevant Information

4.4.1 Species Variability

Because cyclohexylamine is a surface-contact alkaline irritant that

is water and lipid soluble, it is reasonable to expect that at low concentrations, i.e. those that result primarily in sensory irritation, there is little variability in the degree of irritation among animal species. At higher concentrations, where deep lung damage and/or systemic toxicity may result, the sensitivity of various species to cyclohexylamine vapor could not be established from the available studies.

The Lomonova (1965) experiments with rats and mice could be taken to indicate that mice were more sensitive than rats, since the mouse LC_{50} was 7-fold lower than the rat LC_{50}. This study protocol appeared flawed because exposure durations were not given and outcomes were not given at specific concentrations nor separately for each species. Watrous and Schulz (1950) suggested that rats were less sensitive to inhaled cyclohexylamine than guinea pigs or rabbits, but some of the results were inconsistent and the study lacked sufficient methodological details to draw a definitive conclusion regarding species sensitivities.

4.4.2. Susceptible Populations

No studies were located identifying specific populations susceptible to cyclohexylamine exposure.

4.4.3. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for cyclohexylamine inhalation toxicity. Ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5, and n ranged from 1 to 3 for 90% of the chemicals examined. To obtain protective AEGL-2 and AEGL-3 values for 30, 60, and 480 min, scaling across time was performed using $n = 3$ to extrapolate to shorter exposure times and $n = 1$ to extrapolate to longer exposure times, to provide AEGL values that would be protective of human health (NRC 2001) (the AEGL-1 was not scaled). The 10-min value was not extrapolated from 4 h (exposure duration in key study) because extrapolating from ≥4 h to 10 min is associated with unacceptably large inherent uncertainty. Therefore, the 30-min value was adopted for 10 min to be protective of human health.

5. RATIONALE FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Watrous and Schulz (1950) reported that exposure of chemical operators for an undetermined time period to 4-10 ppm cyclohexylamine "caused no symptoms of any kind," although it was not noted whether the operators could detect an odor. In the same chemical plant, workers previously exposed to higher (unknown) concentrations of cyclohexylamine for a short period (≤1½ h) reported headache, rapid and irregular heartbeat, nausea, dizziness, vomiting, and eye, nose and throat irritation. This study is not appropriate for derivation of AEGL-1 values because in one case, effects were below AEGL-1 severity criteria, and in the other case, the exposure concentration was unknown.

5.2. Summary of Animal Data Relevant to AEGL-1

The 4-h inhalation rat study by Bio/dynamics, Inc. (1990) can be used for AEGL-1 derivation. "At the two higher test concentrations (567 ppm and the 542 ppm vapor/aerosol mixture), rats also had rales, gasping, dried red facial material, tremors, weight loss, and irreversible ocular lesions. Two of 10 rats exposed to the aerosol/vapor mixture died, and necropsy revealed nasal, lung, and urogenital lesions."

5.3. Derivation of AEGL-1

AEGL-1 values were derived from the Bio/dynamics, Inc. (1990) rat study, in which 54.2 ppm caused notable respiratory and ocular effects (labored breathing, red nasal discharge, partially closed eyes). Because the effects seen at 54.2 ppm are more severe than prescribed by the AEGL-1 definition, 54.2 ppm was divided by a modifying factor of 3 (per Section 2.6.2., NRC 2001). Mild sensory irritation is not expected to vary greatly over time, so the same AEGL value was adopted for 10 min to 8 h. An uncertainty factor of 3 was applied for interspecies variability, and 3 was applied for sensitive humans (yielding 1.8 ppm for 10 min to 8 h), because mild sensory irritation from an alkaline irritant gas is not likely to vary greatly among humans or animals, and both human and additional animal data indicate that a greater UF is not needed. The

AEGL-1 is consistent with a study in which chemical workers exposed to 4-10 ppm for an undefined duration (<8 h) reported "no symptoms of any kind" (Watrous and Schulz 1950), but which was inappropriate for AEGL-1 derivation because effects were below AEGL-1 severity criteria. The AEGL-1 values are also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989), from which it is predicted that 2.7 or 5.1 ppm should result in some sensory irritation in humans, whereas 0.27 or 0.51 ppm should cause no sensory irritation (Alarie 1981). The latter assertion is based on two mouse RD_{50} studies, in which exposure to 4 ppm for 30 min caused a 20% decrease in respiratory rate in mice, and RD_{50} values of 27 and 51 ppm were obtained (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989). According to Alarie (1981), exposure to 0.1 of the RD_{50} (i.e., 2.7 or 5.1 ppm) for several hours-days should result in some sensory irritation in humans, whereas $0.01 \times RD_{50}$ (0.27 or 0.51 ppm) should cause no sensory irritation. The AEGL-1 values are shown in Table 3-5 and calculations are detailed in Appendix A.

6. RATIONALE FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data was located that was appropriate for derivation of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

The Bio/dynamics, Inc. (1990) study was considered appropriate for AEGL-2 derivation. In this study, rats were exposed for 4 h to 54.2 or 567 ppm cyclohexylamine vapor, or to a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol. At 54.2 ppm, rats displayed dyspnea and had partially closed eyes and red nasal discharge.

TABLE 3-5 AEGL-1 Values for Cyclohexylamine

10 min	30 min	1 h	4 h	8 h
1.8 (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)

At ≥542 ppm, rats also had rales, gasping, dried red facial material, tremors, weight loss, irreversible ocular lesions (corneal opacity, ulceration), and two rats exposed to the aerosol-containing atmosphere died.

Another study that potentially has end points within the scope of AEGL-2 is that of Watrous and Schulz (1950), in which rats, rabbits and guinea pigs were exposed to 150, 800, or 1,200 ppm cyclohexylamine 7 h/day, 5 days/week for up to 10 days. Animals exposed to 800 or 1200 ppm developed opaque corneas and died before 10 days; at 150 ppm, no animals had opaque corneas, four of five rats and two guinea pigs (not stated out of how many) survived 70 h of exposure, and one rabbit died after one 7-h exposure (no dose-response). Although this study was not considered useful for AEGL-2 derivation because of the inconsistency in response and incomplete reporting of results, the study provides a higher NOAEL for corneal opacity (i.e., 150 ppm), and supports the Bio/dynamics (1990) study for this end point.

6.3. Derivation of AEGL-2

AEGL-2 values were derived from the Bio/dynamics, Inc. (1990) study, based on exposure for 4 h to 54.2 ppm, at which concentration the rats had moderate respiratory effects and ocular irritation, and which was a NOAEL for irreversible ocular lesions. This NOAEL is consistent with an earlier study in which rats, a rabbit, and guinea pigs exposed to 150 ppm 7 h/day for up to 2 weeks had no eye effects but those exposed to 800 ppm had corneal opacity (Watrous and Schulz 1950). Data were not available to determine the concentration-time relationship for cyclohexylamine toxicity. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using $n = 3$ to extrapolate to exposure times <4 h (exposure duration in the key study), except for the 10-min values, and $n = 1$ to extrapolate to exposure times >4 h. The 30-min values were adopted as 10 min values due to unacceptably large uncertainty in extrapolating from ≥4 h to 10 min (NRC 2001). An uncertainty factor of 10 was applied (3 for interspecies variability and 3 for intraspecies variability) because the effects seen at 54.2 ppm were clearly reversible, and a larger uncertainty factor yields values at or below the AEGL-1. The resulting AEGL-2 values are shown in Table 3-6 and calculations are detailed in Appendix A.

TABLE 3-6 AEGL-2 Values for Cyclohexylamine

10 min	30 min	1 h	4 h	8 h
11 ppm (45 mg/m^3)	11 ppm (45 mg/m^3)	8.6 ppm (35 mg/m^3)	5.4 ppm (22 mg/m^3)	2.7 ppm (11 mg/m^3)

7. RATIONALE FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No quantitative information on lethal cyclohexylamine exposure in humans was located.

7.2. Summary of Animal Data Relevant to AEGL-3

Studies considered appropriate for AEGL-3 derivation, for which sufficient details of the experimental methods and study results were given include: (1) the Bio/dynamics, Inc. (1990) study, in which rats were exposed for 4 h to 54.2 ppm had labored breathing, partially closed eyes, and red nasal discharge, and rats exposed to 567 ppm or to a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol additionally had rales, gasping, dried red facial material, tremors, weight loss, irreversible ocular lesions, and two rats exposed to the aerosol-containing atmosphere died; (2) the sensory irritation study by Nielsen and Yamagiwa (1989) in which mice exposed for 30 min to 355 ppm cyclohexylamine did not die but had a 75% decrease in breathing rate; and (3) the multiple-exposure study by Watrous and Schulz (1950) in which rats exposed to 150 ppm cyclohexylamine 7 h/day for up to 10 days had fractional mortality (use one 7 h exposure for derivation).

7.3. Derivation of AEGL-3

The study chosen for AEGL-3 derivation was the GLP study in which Sprague-Dawley rats (5/sex/dose) exposed to 567 ppm cyclohexylamine vapor for 4 h had reversible dyspnea, tremors, weight loss, and irreversible ocular lesions, although none died within the 3-week observation period (Bio/dynamics, Inc. 1990). The AEGL-3 end points were irreversible ocular lesions and an estimated lethality threshold in rats (at the next higher exposure concentration, i.e., 542 ppm + 612

mg/m^3 aerosol), lethality occurred in 1/5 males and 1/5 females, and animals that died had nasal, lung, and urogenital tissue damage. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al. (1986) equation $C^n \times t = k$ where $n = 1$ or $n = 3$, as was done for the AEGL-2. A total uncertainty factor of 30 was used: 10 for interspecies variability because, although tissue destruction caused by a severely corrosive agent is not expected to vary greatly among animals, the dose spacing in the key study did not precisely delineate the LOAEL for ocular lesions or the threshold for lethality in rats, and the set of animal studies was limited. An intraspecies uncertainty factor of 3 was applied because tissue destruction caused by a severely corrosive agent is not expected to vary greatly among humans; a greater uncertainty factor is not warranted because it yields concentrations comparable to AEGL-2 values. The resulting AEGL-3 values are shown in Table 3-7; calculations are detailed in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for cyclohexylamine and their relationship to one another are shown in Table 3-8. AEGL-1, AEGL-2, and AEGL-3 values were derived from a study in which Sprague-Dawley rats (5/sex/dose) were exposed for 4 h to 54.2 or 567 ppm cyclohexylamine vapor, or to a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol (Bio/dynamics, Inc. 1990). At 54.2 ppm, rats had labored breathing, partially closed eyes, and red nasal discharge; rats exposed to 567 ppm or to the vapor/aerosol combination also had rales, gasping, dried red facial material, tremors, weight loss, and irreversible ocular lesions. Two of the rats exposed to the aerosol-containing atmosphere died, and had alopecia, red areas in the lining of the nasal turbinates, GI tract (male), and bladder (male), and the female had lung hemorrhage and edema and thin red fluid in the urinary bladder.

AEGL-1 values were derived from the Bio/dynamics, Inc. (1990) rat study, in which 54.2 ppm caused notable respiratory and ocular effects (labored breathing, red nasal discharge, partially closed eyes). Because the effects seen at 54.2 ppm are more severe than prescribed by the AEGL-1 definition, 54.2 ppm was divided by a modifying factor of 3.

TABLE 3-7 AEGL-3 Values for Cyclohexylamine

10 min	30 min	1 h	4 h	8 h
38 ppm (150 mg/m^3)	38 ppm (150 mg/m^3)	30 ppm (120 mg/m^3)	19 ppm (77 mg/m^3)	9.5 ppm (39 mg/m^3)

TABLE 3-8 Summary of AEGL Values for Cyclohexylamine

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)
AEGL-2 (Disabling)	11 ppm (45 mg/m^3)	11 ppm (45 mg/m^3)	8.6 ppm (35 mg/m^3)	5.4 ppm (22 mg/m^3)	2.7 ppm (11 mg/m^3)
AEGL-3 (Lethal)	38 ppm (150 mg/m^3)	38 ppm (150 mg/m^3)	30 ppm (120 mg/m^3)	19 ppm (77 mg/m^3)	9.5 ppm (39 mg/m^3)

Mild sensory irritation is not expected to vary greatly over time, so the same AEGL value was adopted for 10 min to 8 h. An uncertainty factor of 3 was applied for interspecies variability and 3 for sensitive humans, yielding AEGL values of 1.8 ppm for 10 min to 8 h. Both human and additional animal data indicate that a greater UF was not needed. The AEGL-1 is consistent with a study in which chemical workers exposed to 4-10 ppm for an undefined duration (<8 h) reported "no symptoms of any kind" (Watrous and Schulz 1950), but which was inappropriate for AEGL-1 derivation because effects were below AEGL-1 severity criteria. The AEGL-1 values are also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989), from which it is predicted that 2.7 or 5.1 ppm should result in some sensory irritation in humans, whereas 0.27 or 0.51 ppm should cause no sensory irritation (Alarie 1981).

AEGL-2 values were based on exposure for 4 h to 54.2 ppm, at which concentration the rats had moderate respiratory effects and ocular irritation, and which was a NOAEL for irreversible ocular lesions. This NOAEL is consistent with an earlier study in which rats, a rabbit, and guinea pigs exposed to 150 ppm 7 h/day for up to 2 weeks had no eye effects, but those exposed to 800 ppm had corneal opacity (Watrous and Schulz 1950). Data were not available to determine the concentration-time relationship for cyclohexylamine toxicity and scaling across time was performed using the equation $C^n \times t = k$, using the exponent $n = 3$ to extrapolate to exposure times <4 h (exposure duration in the key study),

except for the 10-min values, and $n = 1$ to extrapolate to exposure times >4 h, as described in Section 4.4.3. The 30-min values were adopted as 10 min values due to unacceptably large uncertainty in extrapolating from ≥4 h to 10 min and to be protective of human health. A total uncertainty factor of 10 was applied (3 for interspecies variability and 3 for intraspecies variability) because the effects seen at 54.2 ppm were clearly reversible, and a larger uncertainty factor yields values at or below the AEGL-1.

The AEGL-3 values were based on irreversible ocular lesions and an estimated lethality threshold in rats, which resulted from exposure for 4 h to 567 ppm. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the equation $C^n \times t = k$ with $n = 3$ or $n = 1$, as was done for the AEGL-2. A total uncertainty factor of 30 was used: 10 for interspecies variability because, although tissue destruction caused by a severely corrosive agent is not expected to vary greatly among animals, the dose spacing in the key study failed to delineate the LOAEL for ocular lesions or the threshold for lethality in rats, and the set of animal studies was limited. An intraspecies uncertainty factor of 3 was applied because tissue destruction caused by a severely corrosive agent is not expected to vary greatly among humans; a greater uncertainty factor is not warranted because it yields concentrations comparable to AEGL-2 values in Table 3-8.

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for cyclohexylamine are shown in Table 3-9.

The 8-h TWA of 10 ppm was adopted by ACGIH in 1974, and the OSHA PEL of 10 ppm was established to be consistent with the ACGIH value. OSHA encourages employers to follow the 10 ppm limit, although

TABLE 3-9 Extant Standards and Guidelines for Cyclohexylamine (ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.8	1.8	1.8	1.8	1.8
AEGL-2	11	11	8.6	5.4	2.7

(Continued)

TABLE 3-9 Continued

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-3	38	38	30	19	9.5
REL-TWA (NIOSH)[a]					10
TLV-TWA (ACGIH)[b]					10
MAK (Germany)[d]					(10)[c]
MAK Peak Limitation (Germany)[e]	10 (15 min)				
MAC (Netherlands)[g]					(5)[f]
LLV (Sweden)[h]					5
STV (Sweden)[i]	10 (15 min)				

[a]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[b]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (adopted 1974; ACGIH 1996) 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]This 8 h value is superceded by the assignment of 10 ppm as also the "peak limit."

[d]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (DFG [Deutsche Forschungs-gemeinschaft or German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

[e]MAK Peak Limitation (Category I, excursion factor = 1) (DFG 2002) is the maximum "momentary value" concentration which should not be exceeded at any time. The peak values are determined using a sampling period of 15 min. The peak limitation value is intended to avoid short exposure peaks that could lead to significant irritating effects, which could occur because the MAK value is close to the irritation threshold determined in the RD_{50} study of Gagnaire et al. (1993) (Greim, 2002).

[f]A value of 1.2 ppm was proposed upon a recent reassessment of the Health Council of the Netherlands (HCN 2000) and is likely the current Dutch exposure limit, although post-2000 Dutch values were not available to verify this.

[g]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the

ACGIH-TLV-TWA. A skin notation was present, indicating a danger of percutaneous absorption.)
[h]LLV (Level Limit Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July, 2000. Defined analogous to the ACGIH-TLV-TWA.
[i]STV (Short-Term Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July, 2000. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 min.

its PEL of 10 ppm was deleted in 1992 by the 11th Circuit Court of Appeals. The ACGIH (1996) documentation of TLV and BEI indicates that the TWA was based on the Watrous and Schulz (1950) study, in which "4-10 ppm caused no symptoms of any kind in workmen exposed, apparently, under acute conditions." No accounting is made for inurement of the workers to the smell, and no intraspecific uncertainty factors were applied in generating this TLV-TWA. The German MAK of 10 ppm was based on the RD_{50} of 51 ppm obtained by Gagnaire et al. (1989; 1993), although the German documentation for the value, as well as a footnote for cyclohexylamine in the 2002 "List of MAK and BAT Values," states that the 10 ppm should be regarded as a momentary value that should not be exceeded (Greim 2002). Therefore the 8-h TLV/MAK of 10 ppm loses its meaning as an average value because no excursions above the "moment value" are permitted. The lower RD_{50} of 27 ppm obtained by Nielsen and Yamagiwa (1989) was not cited in the rationale for the German TLV/MAK.

A recent health-based reassessment of administrative occupational exposure limits for the Netherlands (HCN 2000) recommends a health-based occupational exposure limit (HBROEL) of 1.2 ppm as an 8-h time-weighed average for systemic effects. This value was derived by route-to-route extrapolation from a chronic, multigenerational study in rats with a NOAEL was 15 mg/kg BW (at higher doses found decreased weight gain and food intake, decreased kidney weight, and microscopic changes in the testes, kidneys, and bladder). The Dutch rationale also states that because cyclohexylamine is an irritant, and adequate data on irritation from inhalation exposure are lacking, it is unclear whether the limit of 1.2 ppm will protect workers from irritation.

Nielsen and Yamagiwa (1989) estimated a theoretical occupational TLV for cyclohexylamine using mouse RD_{50} study data. They multiplied the RD_{50} (27 ppm) by 0.03 (Alarie 1981) or the RD_0 (2 ppm) by 0.2

(Nielsen et al. 1985), obtaining TLVs of 0.8 and 0.4 ppm, respectively. They also obtained a TLV of 0.8 ppm by multiplying the tRD_{50} (78 ppm) by 0.01, using the approach of Ferguson et al. (1986). The latter approach is less well-established because the relationship between pulmonary irritation and the TLVs is not as well defined as the relationship between sensory irritation and the TLV. Nielsen and Yamagiwa (1989) concluded that the current 10 ppm NIOSH and ACGIH occupational TLVs for cyclohexylamine may "need reconsideration."

8.3. Data Quality and Research Needs

The data set used to derive cyclohexylamine AEGL values was limited and would be improved by the availability of (1) additional studies with end points within the scope of AEGL-2, since in the key study there was a 10-fold difference in the lowest test concentration, which was used for AEGL-2 derivation, and the next higher test concentration, which was used for AEGL-3 derivation, (2) lethality studies with species other than rats to determine the species variability, (3) a study that could be used to determine the concentration-time relationship (n in $C^n t = k$), and (4) human data to define the odor and irritation thresholds and intraspecies variability.

Despite these limitations, there is a reasonable degree of confidence in the derived AEGL-1, AEGL-2, and AEGL-3 values because they are based on a reliable and robust GLP rat study (Bio/dynamics, Inc. 1990) that was consistent with the other available data, and uncertainty factors (total of 10 for AEGL-2 and 30 for AEGL-3) were applied to account for the limited data set.

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APPENDIX A

Derivation of AEGL Values

Derivation of AEGL-1

Key study:	Bio/dynamics, Inc. 1990. Rats exposed for 4 h to 54.2 ppm cyclohexylamine had labored breathing, partially closed eyes, and red nasal discharge; 54.2 ppm was divided by a modifying factor of 3 because the effects seen at 54.2 ppm are more severe than prescribed by the AEGL-1 definition, yielding a concentration (18 ppm) expected to cause mild sensory irritation. At the two higher doses, rats also displayed rales, gasping, dried red material on the facial area, tremors, weight loss, ocular irritation, and irreversible ocular lesions; 2/10 rats exposed to the aerosol/vapor mix died (had nasal, lung, and urogenital lesions).
Toxicity end point:	Mild respiratory and/or ocular irritation from exposure to 18 ppm for 4 h
Scaling:	None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time
Uncertainty factors:	Total Uncertainty Factor: 10
Interspecies:	3—Mild sensory irritation from an alkaline irritant gas is not likely to vary greatly among animals; supported by two mouse respiratory irritation studies (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989).
Intraspecies:	3—Mild sensory irritation from an alkaline irritant gas is not likely to vary greatly among humans; supported by occupational exposure data (Watrous and Schulz 1950).

Modifying Factor: 3—Effects seen at 54.2 ppm are more severe than prescribed by the AEGL-1 definition.

Calculations:

10 min AEGL-1 = 54.2 ppm/30 = 1.8 ppm [7.3 mg/m^3]

30 min AEGL-1 = 54.2 ppm/30 = 1.8 ppm [7.3 mg/m^3]

1 h AEGL-1 = 54.2 ppm/30 = 1.8 ppm [7.3 mg/m^3]

4 h AEGL-1 = 54.2 ppm/30 = 1.8 ppm [7.3 mg/m^3]

8 h AEGL-1 = 54.2 ppm/30 = 1.8 ppm [7.3 mg/m^3]

Derivation of AEGL-2

Key study: Bio/dynamics, Inc. 1990. Rats were exposed for 4 h to 54.2 ppm, 567 ppm or a vapor/aerosol combination (542 ppm vapor + ~612 mg/m^3 aerosol). At 54.2 ppm, rats had labored breathing, red nasal discharge, ocular irritation. At the two higher doses, rats also displayed rales, gasping, dried red material on the facial area, tremors, weight loss, ocular irritation, and irreversible ocular lesions; 2/10 rats exposed to the aerosol/vapor mix died (had nasal, lung, and urogenital lesions).

Toxicity end point: Moderate respiratory effects and ocular irritation, NOAEL for irreversible ocular lesions (54.2 ppm)

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n, so used $n = 3$ to extrapolate to <4 h and $n = 1$ to extrapolate to >4 h, except the 30-min values were adopted as 10 min values to be protective of human health (NRC 2001; see Section 4.4.3.).

Uncertainty factors: Total Uncertainty Factor: 10

Interspecies: 3—Effects seen at 54.2 ppm were clearly reversible and a larger uncertainty factor yields values at or below the AEGL-1.

Intraspecies: 3—Effects seen at 54.2 ppm were clearly reversible and a larger uncertainty factor yields values at or below the AEGL-1.

Calculations for 10 and 30 min, and 1 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{54.2 \text{ ppm}}{10}^{.3} \times \text{time (4 h)} = k = 637 \text{ ppm}^{.3}\text{-h}$$

10 min and 30 min AEGL-2 $C^3 \times 0.5 \text{ h} = 637 \text{ ppm}^{.3}\text{-h}$
30 min AEGL-2 = 11 ppm [45 mg/m^3]

1 h AEGL-2 $C^3 \times 1 \text{ h} = 637 \text{ ppm}^{.3}\text{-h}$
1 h AEGL-2 = 8.6 ppm [35 mg/m^3]

Calculations for 4 h:

4 h AEGL-2 C = 54.2 ppm
4 h AEGL-2 = 54.2/10 = 5.4 ppm [22 mg/m^3]

Calculations for 8 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{54.2 \text{ ppm}}{10}^{.1} \times \text{time (4 h)} = k = 21.7 \text{ ppm-h}$$

8 h AEGL-2 $C^1 \times 8 \text{ h} = 21.7 \text{ ppm-h}$
8 h AEGL-2 = 2.7 ppm [11 mg/m^3]

Derivation of AEGL-3

Key study: Bio/dynamics, Inc. 1990. Rats were exposed for 4 h to 54.2 ppm, 567 ppm or a vapor/aerosol combination (542 ppm vapor + ~612 mg/m^3

aerosol). At 54.2 ppm, rats had labored breathing, red nasal discharge, ocular irritation. At the two higher doses, rats also displayed rales, gasping, dried red material on the facial area, tremors, weight loss, ocular irritation, and irreversible ocular lesions; 2/10 rats exposed to the aerosol/vapor mix died (had nasal, lung, and urogenital lesions).

Toxicity end point: 567 ppm was considered the threshold for lethality and caused irreversible ocular lesions

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n, so used $n = 3$ to extrapolate to <4 h and $n = 1$ to extrapolate to >4 h, except the 30-min values were adopted as 10 min values to be protective of human health (NRC 2001; see Section 4.4.3.).

Uncertainty factors: Total Uncertainty Factors: 30

Interspecies: 10—Although tissue destruction caused by a severely corrosive agent is not expected to vary greatly among animals, the dose spacing in the key study did not precisely delineate the LOAEL for ocular lesions or the threshold for lethality in rats, and the set of animal studies was limited.

Intraspecies: 3—Tissue destruction caused by a severely corrosive agent is not expected to vary greatly among humans; a greater uncertainty factor is not warranted because it yields concentrations comparable to AEGL-2 values.

Calculations for 10 and 30 min, and 1 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{567 \text{ ppm}}{30}^{.3} \times \text{time (4 h)} = k = 27005 \text{ ppm}^{.3}\text{-h}$$

$$\underline{\text{10 min and 30 min AEGL-3}} \quad C^3 \times 0.5 \text{ h} = 27005 \text{ ppm}^3\text{-h}$$

30 min AEGL-3 = 38 ppm [150 mg/m^3]

$\underline{\text{1 h AEGL-3}}$ $C^3 \times 1\text{ h} = 27005\text{ ppm}^3\text{-h}$
1 h AEGL-3 = 30 ppm [120 mg/m^3]

Calculations for 4 h:

$\underline{\text{4 h AEGL-3}}$ = 567/30 = 19 ppm [77 mg/m^3]

Calculations for 8 h:

$\underline{\text{Concentration}}{}_{\text{UF}}$ $\left(\underline{\frac{567\text{ ppm}}{30}}\right)^{.1} \times \text{time (4 h)} = k = 75.6\text{ ppm-h}$

$\underline{\text{8 h AEGL-3}}$ $C^1 \times 8\text{ h} = 75.6\text{ ppm-h}$
8 h AEGL-3 = 9.5 ppm [39 mg/m^3]

APPENDIX B

Derivation of the Level of Distinct Odor Awareness

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT; stated to be the geometric mean of all available literature data, omitting extreme points and duplicate values; method of obtaining values not stated) of 2.6 ppm was obtained for cyclohexylamine from Amoore and Hautala (1983). The same citation listed an odor detection threshold of 0.83 for *n*-butanol, as compared to the reference value of 0.04 ppm as the odor threshold provided by van Doorn et al (2002). Based on the differences in *n*-butanol values from the two sources, an "inter-laboratory" correction factor is applied to 0.83 ppm as follows:

0.04 ppm *n*-butanol × 2.6 ppm OT Cyclohexylamine = 0.13 ppm "corrected" OT_{50} Cyclohexylamine 0.83 ppm *n*-butanol

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

$$I = k_w \times \log C / OT_{50}) + 0.5$$

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

$3 = 2.33 \times \log C / 0.13) + 0.5$, which can be rearranged to
$\log C / 0.13) = (3 - 0.5) / 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 0.13 = 1.53$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life, factors such as sex, age, sleep, smoking, upper airway infections and allergies, as well as distraction, increase the odor detection threshold by a factor of 4. In addi-

tion, it takes into account that odor perception is very fast (about 5 sec) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

$$LOA = C \times 1.33 = 1.53 \text{ ppm} \times 1.33 = 2.0 \text{ ppm}$$

The LOA for Cyclohexylamine is 2.0 ppm.

APPENDIX C

ACUTE EXPOSURE GUIDELINES FOR CYCLOHEXYLAMINE (108-91-8)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm

Key Reference: Bio/dynamics, Inc. 1990. An acute inhalation toxicity study of C-1388 in the rat. Final Report. Project no. 89-8214. December 4, 1990.

Test Species/Strain/Sex/Number: Sprague-Dawley rats; 5/sex/dose.

Exposure Route/Concentrations/Durations: Inhalation for 4 h of 54.2 ppm, 567 ppm, or a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol.

Effects: At 54.2 ppm, rats had labored breathing, red nasal discharge, and partly closed eyes primarily during the 4-h exposure. Rats exposed to 567 ppm or the vapor/aerosol combination had severe respiratory effects and irreversible ocular lesions; 2/10 rats exposed to the aerosol-containing atmosphere died.

End point/Concentration/Rationale: Mild respiratory and/or ocular irritation is expected to result from exposure to 18.1 ppm (obtained by dividing 54.2 ppm by the modifying factor of 3).

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3—Mild sensory irritation from an alkaline irritant gas is not likely to vary greatly among animals. Supported by other animal (RD_{50}) data.
Intraspecies: 3—Mild sensory irritation from an alkaline irritant gas is not likely to vary greatly among humans. Supported by human (occupational) data.

Modifying Factor: 3—Effects seen at 54.2 ppm are more severe than prescribed by the AEGL-1 definition.

Animal to Human Dosimetric Adjustment: Not performed.

(Continued)

AEGL-1 VALUES Continued

Time Scaling: None; using the same value for 10 min to 8 h was considered appropriate because mild irritant effects do not vary greatly over time.

Data Adequacy: The data set was small, but the key study was well-conducted (GLP). The derived AEGL-1 level (and appropriateness of the total UF) is supported by a human study (chemical workers exposed to 4-10 ppm for <8 h reported "no symptoms of any kind"; Watrous and Schulz 1950) and by two mouse respiratory depression (RD_{50}) studies (Gagnaire et al. 1989; Nielsen and Yamagiwa 1989), from which it is predicted that 2.7 or 5.1 ppm should result in some sensory irritation in humans, whereas 0.27 or 0.51 ppm should cause no sensory irritation (Alarie 1981).

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
11 ppm	11 ppm	8.6 ppm	5.4 ppm	2.7 ppm

Key Reference: Bio/dynamics, Inc. 1990. An acute inhalation toxicity study of C-1388 in the rat. Final Report. Project no. 89-8214. December 4, 1990.

Test Species/Strain/Sex/Number: Sprague-Dawley rats; 5/sex/dose.

Exposure Route/Concentrations/Durations: Inhalation for 4 h of 54.2 ppm, 567 ppm, or a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol.

Effects: At 54.2 ppm, rats had labored breathing, red nasal discharge, and partly closed eyes primarily during the 4-h exposure. Rats exposed to 567 ppm or the vapor/aerosol combination had severe respiratory effects and irreversible ocular lesions; 2/10 rats exposed to the aerosol-containing atmosphere died.

End point/Concentration/Rationale: Exposure to 54.2 ppm for 4 h caused moderate respiratory effects and ocular irritation; is NOAEL for irreversible ocular lesions.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3—Effects seen at 54.2 ppm were clearly reversible and a larger uncertainty factor yields values at or below the AEGL-1.

Intraspecies: 3—Effects seen at 54.2 ppm were clearly reversible and a larger uncertainty factor yields values at or below the AEGL-1.

Modifying Factor: none.

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n, so used $n = 3$ to extrapolate to <4 h and $n = 1$ to extrapolate to >4 h, except the 30-min values were adopted as 10-min values to be protective of human health (NRC 2001; see Section 4.4.3.).

Data Adequacy: The data set was small but the key study was well-conducted (GLP guidelines used). There were no data to determine the value of n for time scaling. The NOAEL for corneal opacity was supported by another study with several species.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
38 ppm	38 ppm	30 ppm	19 ppm	9.5 ppm

Key Reference: Bio/dynamics, Inc. 1990. An acute inhalation toxicity study of C-1388 in the rat. Final Report. Project no. 89-8214. December 4, 1990.

Test Species/Strain/Sex/Number: Sprague-Dawley rats; 5/sex/dose

Exposure Route/Concentrations/Durations: Inhalation; 4 h; 54.2 ppm, 567 ppm, or a vapor/aerosol combination containing 542 ppm vapor and ~612 mg/m^3 aerosol.

Effects: At 54.2 ppm, rats had labored breathing, red nasal discharge, and partly closed eyes primarily during the 4-h exposure. Rats exposed to 567 ppm or the vapor/aerosol combination had labored breathing, rales, gasping, dried red material on the facial area, tremors, weight loss, irreversible ocular lesions, and 1/5 males and 1/5 females exposed to the aerosol-containing atmosphere died and had nasal, lung, and urogenital tissue damage.

End point/Concentration/Rationale: Exposure to 567 ppm for 4 h caused irreversible ocular lesions and was the lethality threshold.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10—Although tissue destruction caused by a severely corrosive agent is not expected to vary greatly among animals, the dose spacing in the key study did not precisely delineate the LOAEL for ocular lesions or the threshold for lethality in rats, and the set of animal studies was limited.

(Continued)

AEGL-3 VALUES Continued

Intraspecies: 3—Tissue destruction caused by a severely corrosive agent is not expected to vary greatly among humans; a greater uncertainty factor is not warranted because it yields concentrations comparable to AEGL-2 values.
Modifying Factor: None.
Animal to Human Dosimetric Adjustment: No data.
Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n, so used $n = 3$ to extrapolate to <4 h and $n = 1$ to extrapolate to >4 h, except the 30-min values were adopted as 10-min values to be protective of human health (NRC 2001; see Section 4.4.3.).
Data Adequacy: The data set was small but the key study was well-conducted (GLP guidelines used). There were no data to determine the value of n for time scaling. Supporting studies with lethality as an end point were limited.

APPENDIX D

Category Plot for Cyclohexylamine

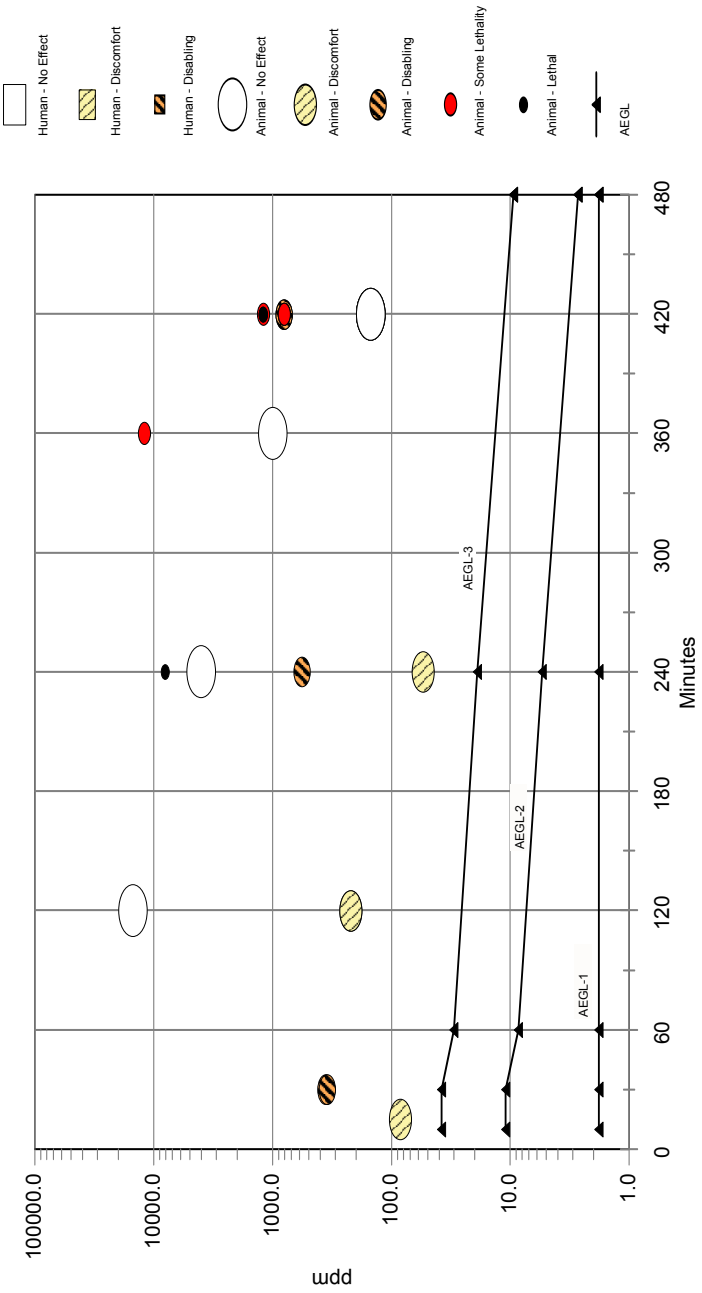

FIGURE D-1 Chemical toxicity—TSD all data, cyclohexylamine. Note that multiple-exposure studies were input as single exposures.

4

Ethylenediamine[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 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory) and Mark McClanahan (National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member (Chemical Manager)). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

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, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

EXECUTIVE SUMMARY

Ethylenediamine (EDA) is a hygroscopic, flammable liquid and a strong base (pK_{a1} = 10.7; pK_{a2} = 7.6). EDA is a high production volume chemical, and is used to stabilize rubber latex, as an inhibitor in antifreeze solutions, and in the preparation of dyes, insecticides, and fungicides. EDA is an eye, mucous membrane, and respiratory irritant and a known respiratory and skin sensitizer. Occupational inhalation exposure

has resulted in an asthmatic response (rhinitis, coughing, wheezing, shortness of breath, and bronchospasm).

EDA-sensitized individuals may experience more severe and/or different effects at a given exposure concentration or duration than non-sensitized people. The qualitative and quantitative differences in the response of the two groups to EDA are undefined. The derived AEGL values are for a once-in-a lifetime exposure and do not consider previous sensitization.

The level of distinct odor awareness (LOA) for EDA is 2.1 ppm (see Appendix B for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

AEGL-1 values were not recommended due to insufficient data. Absence of AEGL-1 values does not imply that exposure to concentrations below the AEGL-2 is without adverse effects.

AEGL-2 values were based on a study in which rats and guinea pigs (6/group) were exposed to approximately 484 ppm EDA (1,000 ppm nominal) for 30 min to 8 h. Both species exposed for 8 h had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney" (Carpenter et al., 1948). [The same laboratory showed in another study that the analytical concentration was approximately 50% of the nominal concentration, 1,000 ppm nominal corresponding to 484 ppm analytical (Pozzani and Carpenter 1954).] This was the only single-exposure study adequate for AEGL-2 derivation. No data were available to determine the concentration-time relationship for EDA toxic effects. The concentration-time relationship for many irritant and systemically acting vapors and gases was described by ten Berge et al. (1986) with the equation $C^n \times t = k$, where the exponent n ranged from 1 to 3 for 90% of the chemicals examined. To obtain AEGL-2 values, scaling from 8 h to 30, 60, and 240 min was performed using $n = 3$. The 30-min value was adopted as the 10-min value because scaling from 8 h to 10 min was associated with unacceptably large uncertainty. An uncertainty factor of 3 was used for interspecies variability because a similar response was seen in two species, and a modifying factor of 3 was used because the key study did not specify the severity of the bronchiolar edema. An intraspecies uncertainty factor of 10 was applied because the data were insufficient to determine the mode of lung and kidney lesions (or which was the more

sensitive end point) in the key study and consequently the potential variability of the human response to EDA. The AEGL-2 values are supported by a study in which 1/26 rats had unspecified lesions but no mortality after 30 exposures to 132 ppm EDA for 7 h/day (Pozzani and Carpenter, 1954).

AEGL-3 values were derived from a range-finding test (Smyth et al. 1951) in which 0/6 rats died from exposure for 8 h to ~1,000 ppm but 6/6 died from 8-h exposure to ~2,000 ppm (stated as 2000 ppm and 4,000 ppm nominal, respectively; analytical estimates based on Pozzani and Carpenter 1954). Toxic effects (other than death) were not described, and 1,000 ppm was considered to be the lethality threshold. This was the only single-exposure study adequate for AEGL-3 derivation. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the equation $C^n \times t = k$ and $n = 3$, as was done for AEGL-2. A total uncertainty factor of 100 was applied: 10 for interspecies variability (cause of death was undefined and there were no studies using other species) and 10 for intraspecies variability (lack of toxicity data in key study precludes definition of the mode or variability of the toxic response in humans). Target organs (liver and kidneys) were identified in a study where rats received 225 ppm EDA 7 h/day for up to 30 days (first deaths on exposure day 4), although the mode of toxicity was unclear (Pozzani and Carpenter 1954).

The values appear in Table 4-1.

TABLE 4-1 Summary of AEGL Values for Ethylenediamine

Classification	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL-1[a] (Nondisabling)	Not recommended due to insufficient data.					
AEGL-2 (Disabling)	12 ppm (30 mg/m^3)	12 ppm (30 mg/m^3)	9.7 ppm (24 mg/m^3)	6.1 ppm (15 mg/m^3)	4.8 ppm (12 mg/m^3)	Bronchiolar edema, kidney swelling (Carpenter et al. 1948)
AEGL-3 (Lethal)	25 ppm (62 mg/m^3)	25 ppm (62 mg/m^3)	20 ppm (49 mg/m^3)	13 ppm (32 mg/m^3)	10 ppm (25 mg/m^3)	Lethality threshold (Smyth et al. 1951)

1. INTRODUCTION

Ethylenediamine (EDA) is a very basic, hygroscopic and fuming liquid (25% solution has a pH of 11.9 at 25°C; pK_{a1} = 10.7; pK_{a2} = 7.6). It has a low flash point (93°F; open cup) and is very flammable (Benya and Harbison 1994). EDA vapor is an eye, mucous membrane, and respiratory irritant and a well-known respiratory and skin sensitizer (Beard and Noe 1981). EDA liquid is corrosive and produces chemical burns in the skin and eyes (Carpenter and Smyth 1946; Smyth et al. 1951). The EDA odor threshold has been reported as 1.0 ppm (Verschueren 1996; Amoore and Hautala 1983) and 1-11 ppm (Ruth 1986). Occupational inhalation exposure has resulted in both immediate and delayed asthmatic symptoms including rhinitis, coughing, wheezing, shortness of breath, and bronchospasm. In animal studies, EDA vapor caused hair loss and lung, kidney, and liver damage.

EDA is used to stabilize rubber latex, as an inhibitor in antifreeze solutions, as a pharmaceutic aid (aminophylline stabilizer), in the preparation of dyes, synthetic resins, insecticides, carbamate fungicides, and asphalt wetting agents (HSDB 2005). EDA vapor readily absorbs CO_2 from the air to form a non-volatile carbonate (Budavari et al. 1996). EDA is manufactured mainly by reacting ethylene chloride with aqueous or liquid ammonia at about 100°C (HSDB 2005). EDA use in chemical synthesis is in closed systems (Cary et al. 1999). EDA is a high production volume chemical: U.S. production was >58 million pounds in 1993 (HSDB 2005). Some of the chemical and physical properties of EDA are listed in Table 4-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

A 36-year-old worker in France was accidentally splashed on the chest with EDA liquid and also breathed in EDA vapors for a "few minutes" (Niveau and Painchaux 1973). The exposure concentration was not determined. The man quickly removed his clothes and washed up but, nevertheless, 4 h after exposure had red-brown generalized erythema, anuria, tachycardia (up to 100/min), and symptoms of hemolysis: increased blood potassium (275 mg/L), and lowered RBC count ($5.16 \times 10^6/mm^3$). Twelve hours after exposure, the man had elevated body tem-

TABLE 4-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	1,2-ethanediamine; 1,2-diaminoethane	Budavari et al. 1996
Chemical formula	$C_2H_8N_2$	Budavari et al. 1996
Molecular weight	60.10	Budavari et al. 1996
CAS Registry Number	107-15-3	Benya and Harbison 1994
Physical state	Thick liquid	Budavari et al. 1996
Color	Colorless, clear	Budavari et al. 1996
Solubility in water	Freely soluble, forming a hydrate	Budavari et al. 1996
Acid ionization constant, pK_a	pK_{a1} = 10.7; pK_{a2} = 7.6	HSDB 2005
Vapor pressure	10.7 mm Hg at 20°C 10 mm Hg at 21.5°C 12.1 mm Hg at 25°C	Parmeggiani 1983 Benya and Harbison 1994 HSDB 2005
Vapor density (air = 1)	2.07	Benya and Harbison 1994
Liquid density (water = 1)	0.898 at 25°C	Budavari et al. 1996
Melting point	8.5°C	Benya and Harbison 1994
Boiling point	116-117°C at 760 mm	Budavari et al. 1996
Flammability/explosive limits	2.5-12% (at 212°F)	NIOSH 2005a
Conversion factors	1 mg/m^3 = 0.407 ppm; 1 ppm = 2.46 mg/m^3	Benya and Harbison 1994

perature (39°C) and pulse (120/min), coughing with expectoration, abdominal cramps, diarrhea, blackish vomiting, and anuria resulting in an increased blood urea (0.8 g/L). His condition continued to worsen and he died from cardiac collapse 55 h after exposure.

2.2. Nonlethal Toxicity

Studies were conducted with EDA-sensitized and non-sensitized individuals. In many cases there was incomplete information about the actual EDA exposure concentration or time that elicited the human responses. Studies in which quantitative data were provided for air EDA concentration and/or exposure duration are summarized in Table 4-3.

Several secondary sources (Cary et al. 1999; IPCS 2005) list effects potentially caused in humans by EDA inhalation as irritation of the respiratory tract (a burning sensation, cough, dyspnea, a sore throat), lung edema, and an asthmatic response. It is noted that symptoms of lung edema often do not become manifest until a few hours after exposure,

TABLE 4-3 Summary of Quantitative Human Ethylenediamine (EDA) Inhalation Studies

Exposure Concentration	Exposure Time	End Point	Reference
1.0-11 ppm	Unknown	Odor threshold	Hellman and Small 1974[a]
100 ppm	5-10 sec	Inoffensive	Pozzani and Carpenter 1954
200 ppm	5-10 sec	Slight tingling of face and nasal mucosa	
400 ppm	5-10 sec	Intolerably irritating to nasal mucosa	
0.4 ppm	Not specified (≤8 h)	Background maximal concentration; effects on workers were not addressed.	Hansen et al. 1984
<1 to >10 ppm	<8 h	Asthmatic symptoms in 38 EDA-sensitized workers	Aldrich et al. 1987
Unknown (TLV=10 ppm)	20 min	Delayed (2.5-4 h) asthmatic symptoms in 2 sensitized workers from workplace exposure	Nakazawa and Matsui 1990
30 ppm	15 min	Severe asthmatic reaction 3 and 12 h after exposure of sensitized worker (24-33% ↓ in FEV_1)	Ng et al. 1991
Not stated; in area had 4.8, 10.5 ppm	<8 h	Cough, phlegm, wheezing in 12 sensitized workers; diurnal expiratory flow rate variation	Ng et al. 1995
0.804 mg/m^3 (vapor/aerosol)	1 min	Irritation threshold for the most "sensitive" individuals tested.	Dubinina et al. 1997

[a]Same values were reported in Amoore and Hautala 1983, Verschueren 1996, and Ruth 1986.

and may mask an asthmatic reaction. However, neither source cites specific studies from which this information was obtained. Cary et al. (1999) conclude that there is insufficient data to define the dose-response for an EDA-induced asthmatic response or an exposure level "without adverse effect."

2.2.1. Odor Threshold/Odor Awareness

The odor detection threshold for ethylenediamine was reported to be 1.0 ppm and the 50% and 100% odor recognition thresholds were given as 3.4 ppm and 11.2 ppm, respectively by Hellman and Small (1974). The same values were listed subsequently by Amoore and Hautala (1983), Verschueren (1996), and Ruth (1986). The latter also listed the odor detection threshold as 1-11 ppm and the human irritation threshold alternately as 250 and 500 mg/m^3 (102 and 204 ppm). Union Carbide Corp. (1971) reported that "workers will not stay in concentrations of 2,000 ppm."

2.2.2. Occupational Exposure

Four laboratory personnel intentionally sniffed 100, 200, or 400 ppm EDA vapor for 5-10 sec (Pozzani and Carpenter 1954). It was not specified if these were nominal or analytical concentrations or how the test atmospheres were generated, although in another experiment described in the same study (rat 7-h exposure), EDA atmospheres were generated using liquid EDA and an evaporator. The test subjects indicated that 100 ppm was inoffensive, 200 ppm caused a slight tingling sensation in the face and slight irritation of the nasal mucosa, and 400 ppm was intolerably irritating to the nasal mucosa.

Air EDA concentration in a Swedish petrochemical plant producing amines in a closed system was 0.4 ppm "only at a site for tanking" (Hansen et al. 1984). The number of samplings was not specified; presumably all other samples were below practical limits of detection (~0.04 ppm for same volume collected by impinger sampling method and analyzed by isotachophoreis).

Air monitoring data was conducted in a manufacturing plant where 38/337 employees who worked with EDA became sensitized: they had rhinitis, coughing, and wheezing that cleared after removal from EDA

exposure (Aldrich et al. 1987). EDA concentrations eliciting the worker responses were not provided. The vast majority of the 1,053 EDA monitoring measurements were <1 ppm (actual data were not given). The exposure period before sensitization occurred was shortest in current smokers (7.0 months) and longest for employees with no previous symptoms (37.3 months). Coater machine operators had the greatest incidence of EDA sensitization (14/54). Aldrich et al. (1987) concluded that "increased risk of EDA sensitization might be expected when workplace air concentrations of EDA exceed 1 ppm" and that perhaps the present 10 ppm EDA TLV should be reconsidered.

Nakazawa and Matsui (1990) described two cases of occupational exposure to EDA in a Japanese chemical factory. An 18-year-old man with a history of urticaria and a 37-year-old man with a history of rhinitis developed symptoms of asthma after 4 and 7 months, respectively, of exposure to unspecified concentrations of EDA (Japanese workplace limits for EDA were 10 ppm at the time). Provocative exposure tests were done on these two men when they were symptom-free: they went to work as usual and after 20 min of exposure to EDA their reactions were monitored. Wheeze and rhonchi were audible in their lungs 2.5-4 h after the 20-min exposure, and both men had ~20-40% decreased FEV_1 (forced expiratory volume in 1 sec) approximately 4 h after exposure. The 18-year-old additionally had cough, wheezing, and chronic dyspnea for ~7 days, and the 37-year-old man had additional symptoms 10-18 h after exposure. A non-sensitized subject did not develop any of these symptoms upon similar EDA exposure. Upon transfer to a new work environment, neither patient showed any asthmatic symptoms. Both men had elevated peripheral blood IgE antibodies to EDA but IgG and plasma histamine levels were unaffected.

A 31-year-old non-smoking male chemical worker in Singapore without a history of asthma developed symptoms of bronchial asthma (frequent coughing, wheezing, and breathlessness) after approximately 3 months of EDA vapor exposure (Ng et al. 1991). He was also exposed to lesser amounts of other amines and organic chemicals. Measurement of his peak expiratory flow every 3 h while awake over 2 weeks showed reduced flow rates in the late mornings and afternoons (~17-24% lower FEV_1), except on Saturdays and Sundays. In a bronchial provocation test, the worker inhaled 30 ppm EDA for 15 min from a respirator. He had no effects immediately after exposure, but 3 h later his peak flow rate fell by about 24% below baseline and he had chest tightness. Twelve hours after exposure, he had a severe bout of coughing, wheezing, and breathless-

ness and his peak flow rate fell another 10%. (He was administered nebulized Ventolin and his peak flow improved.) A histamine challenge test (not described) showed he had a high degree of non-specific bronchial hyperreactivity. His chest x-ray and eosinophil counts were normal. His asthmatic attacks became less frequent and severe when he reduced his EDA exposure.

Twelve men who worked in a Singapore factory manufacturing polyamide resin for a mean of 2.5 years and were exposed primarily to EDA vapor (also to other polyamines and organics) reported significantly more frequent symptoms of chronic cough, chronic phlegm, wheezing, and exertional breathlessness than unexposed workers (Ng et al. 1995). The EDA air concentration and exposure duration that elicited the stated symptoms were not specified. EDA analytical air concentrations of 10.5 and 4.8 ppm were measured in two air samples taken in areas where EDA was manually handled. The four workers who developed wheezing after beginning work at the factory had significantly greater diurnal variation in peak expiratory flow rates than the control group (DV-PEFR; measured every 3 waking hours for a week) but the FEV_1, FVC, and FEV/FVC were unaffected.

Dubinina et al. (1997) determined that the irritation threshold for a 1-min exposure in humans was 0.804 mg/m^3 for the most sensitive individuals tested (not stated whether these were EDA-sensitized workers). The EDA vapor concentration is unknown because it was administered as a mixture of vapor and aerosol.

Several other studies lacked sufficient EDA exposure information but provided useful descriptions of the effects of EDA exposure on humans. A 30-year-old male photography chemical mixer with late-onset asthma challenged for 15 min with an unknown concentration of EDA vapor developed asthmatic symptoms 4 h later (Lam and Chan-Yeung 1980). He had chest tightness, coughing, wheezing, and a 26% decrease in the FEV_1 for 24 h after exposure. Results of a skin test (prick or intradermal with 1:100 EDA) were negative for immediate or type III reaction and precipitating antibodies to EDA were not found (Ouchterlony method). Plasma histamine levels in venous blood were not increased during bronchoconstriction. Dernehl (1951) and Lewinsohn and Ott (1991) examined medical records of approximately 200 workers exposed primarily to ethylene amines at a large chemical company (1947-1983). The concentration of EDA in the air was not reported. The employees had eye, skin, and respiratory symptoms, the latter consisting of rhinitis, congestion, coughing, wheezing, and dyspnea. The workers' pulmonary

function (FEV_1 and FVC) was not related to EDA exposure duration or sensitization status after accounting for height, age, race, cigarette smoking, and examination date. Symptoms resolved in workers transferred from the amines unit. Grant (1986) reported that industrial exposure to EDA vapors for several hours at concentrations too low to cause discomfort or disability (exposure undefined) caused reversible edema of the corneal epithelium that was generally painless and caused colored halos to be seen around lights.

Popa et al. (1969) found that 4/6 workers with EDA-induced bronchial asthma (no prior history of respiratory ailments) had bronchoconstriction immediately following a 5-min challenge with nebulized EDA. The EDA exposure concentration was 2 to 10-fold below concentrations that were non-irritating to control (non-sensitized) asthmatics, although no actual EDA concentrations were reported. The four workers had a 62% reduction in the FEV_1 and a 44% increase in respiratory resistance compared to non-sensitized asthmatic controls when examined 30 or 60 min after exposure, a positive Prausnitz-Kustner IgE test, and eosinophilia in the sputum but no precipitating antibodies to EDA. The other two workers had dyspnea 1-2 h after exposure but all inhalation and immunological tests were negative. None of the workers reacted to common allergens, indicating that EDA induced a state of hypersensitivity in the airways that was specific to EDA.

2.3. Neurotoxicity

No human neurotoxicity studies were located for EDA exposure by any route.

2.4. Developmental/Reproductive Toxicity

No human developmental or reproductive EDA studies were found.

2.5. Genotoxicity

No human genotoxicity data were located.

2.6. Carcinogenicity

No human carcinogenicity studies were located with ethylenediamine exposure by any route. The ACGIH (2004) and EPA (2005) conclude that there is insufficient evidence to implicate EDA as either a human or animal carcinogen (see Section 3.5.)

2.7. Summary

Respiratory irritation and asthma-like symptoms were described in EDA-sensitized individuals exposed to EDA concentrations ranging from <1 ppm during a workday (Aldrich et al. 1987) to 30 ppm for 15 min (Ng et al. 1991). An unusually large fraction of workers exposed to EDA vapor became sensitized and experienced asthmatic symptoms: 33% in a Singapore chemical manufacturing plant (Ng et al. 1995), 11% in a modern U.S. manufacturing facility where it was used as a process chemical (Aldrich et al. 1987), and up 17% at a large U.S. chemical company (Dernehl 1951; Lewinsohn and Ott 1991). No human genotoxicity or oncogenicity studies were located.

3. ANIMAL TOXICITY DATA

The available single- and multiple-exposure animal studies in which the exposure concentration and duration were both specified are summarized in Table 4-4.

3.1. Acute Lethality

3.1.1. Rats

Using the range-finding test that their laboratory developed, Smyth et al. (1951) reported that 0/6 rats exposed to 2,000 ppm for 8 h died but 6/6 died after an 8-h exposure to 4,000 ppm EDA. No experimental details or other results were given in the study report, but subsequent publications by the same laboratory indicated that the observation period was two weeks, that the exposure concentrations were nominal and not ana-

TABLE 4-4 Summary of Quantitative Animal Ethylenediamine Inhalation Studies

Species	Exposure Time	Exposure Conc. (ppm)	End point and Comments	Reference
Single-exposure studies				
Rat	30, 60, 120, 240, 480 min	484 [1,000][a]	0/6 mortality for each exposure time; kidney cloudy swelling and lung edema seen after 8 h	Carpenter et al. 1948
Rat	8 h 8 h	1,000 [2,000][a] 2,000 [4,000][a]	0/6 mortality; no effects data 6/6 mortality; no effects data	Smyth et al. 1951
Guinea pig	30, 60, 120, 240, 480 min	484 [1,000][a]	0/6 mortality for each exposure time; kidney cloudy swelling and lung edema seen after 8 h	Carpenter et al. 1948
Multiple-exposure studies				
Rat	7 h/day for up to 30 days	59 132 225 484	No effects noted Hair loss, small increase in microscopic lesions 16/20 toxic deaths (mean 17.4 days); lower body weights; liver and kidney lesions; alopecia 27/30 toxic deaths (mean 11.4 days); liver, kidney, lung, adrenal effects; alopecia	Pozzani and Carpenter 1954

[a]Study provided nominal concentrations, which are in brackets. The analytical concentrations listed are ~50% of the nominal concentration, based on another study by the same laboratory (Pozzani and Carpenter, 1954).

lytically verified, and that the rats could be either males or females (Smyth et al. 1962).

Sherman rats (15/sex) were exposed 7 h/day for up to 30 days to 484, 225, 132, or 59 ppm EDA (nominal concentrations of 1,000, 500, 250, and 125 ppm, respectively) (Pozzani and Carpenter 1954). Formation of a solid white reactant product on the inlet and outlet pipes and the walls of the exposure chamber was noted by the study authors, who proposed this was the reaction product of EDA with atmospheric CO_2, and was responsible for the 50% discrepancy between the measured and nominal EDA concentrations (20% was a typical discrepancy for other chemicals tested by this laboratory). The EDA atmospheres were generated using liquid EDA and an evaporator and EDA concentration was determined by titration. The four exposure groups were not run concurrently, and a separate control group was provided for each exposure group. Food and water were withheld from all animals during exposure. Animals that survived the entire 30 days were killed immediately after the last exposure and their liver and kidneys were weighed. Microscopic examination was performed on the lungs, heart, liver, kidney, adrenal gland, and spleen in the three highest dose groups, and on the kidneys, lungs, and liver in the 59 ppm group.

At 484 ppm, the earliest deaths occurred on days 3 and 5 (one rat each), and all rats died within 20 days of the first exposure due to compound toxicity (11.4 days mean time to death); no controls died. Hair loss was almost complete by 10-15 exposure days. Most of the animals examined histologically had cloudy swelling in the liver and in the kidney convoluted tubules (some had kidney degeneration), and congested lungs (17/28), and some had congestion of the adrenal cortex (5/28). Of the 30 rats exposed to 225 ppm EDA, 16 had "toxic deaths," 4 survived for 30 days, and 10 deaths were due to lung infections and were considered by the study author to be unrelated to treatment (although only 2 rats in the concurrent control group had lung infections; it was not specified whether these animals died). The mean time to death was 17.4 days, with the first animals dying on exposure days 4, 5, and 9 (2, 1, and 2 rats per day, respectively). The four surviving rats had a significantly lower weight gain and increased liver and kidney weights after 30 days than the controls, some hair loss, and most rats had cloudy swelling of the liver and kidney convoluted tubules. About 1/3 of the rats had congested lungs, however, a similar fraction of the control rats also had congested lungs. Animals exposed to 132 ppm had slight depilation and 1/26 rats (vs. 0/27 for controls) had "major" unspecified histopathological find-

ings; the 4 deaths at 132 ppm were attributed to lung infections and not considered "toxic deaths" (3 control animals had infections; death not specified). All 59 ppm rats survived the 30 exposures with no reported toxic effects.

3.1.2. Mice

Izmerov et al. (1982) reported an inhalation LC_{50} of 300 ppm for the mouse. The exposure duration and other experimental details were not provided.

3.2. Nonlethal Toxicity

3.2.1. Rats

In the multiple-exposure study of Pozzani and Carpenter (1954), and described in section 3.1.1., Sherman rats exposed to 59 ppm 7 h/day for up to 30 days had no toxic effects, those exposed to 132 ppm had hair loss and a slight increase in the incidence of microscopic lesions, and rats exposed to 225 or 484 ppm died and/or had hair loss and liver, kidney, and lung lesions.

Male Wistar albino rats exposed to a nominal concentration of 1,000 ppm EDA for 30, 60, 120, 240, or 480 min (6 rats/exposure time) all survived the 2-week observation period (Carpenter et al. 1948). Histopathological examination of rats exposed for 8 h revealed "light cloudy swelling of the kidney" and bronchiolar edema (results for shorter exposure periods were not given).

Several published rat inhalation studies were poorly reported but help provide an overall picture of EDA acute toxicity. Dubinina et al. (1997) conducted acute and multiple-exposure rat studies in which EDA was administered as a mixture of vapor and aerosol for an unspecified number of hours/day. A single exposure to 1.94 mg/m^3 caused a change in the respiration frequency of rats (faster/ slower not specified), 6.36 mg/m^3 led to changes in blood catalase and peroxidase activities, 20.75 mg/m^3 increased body temperature and lung lesions, and 430 mg/m^3 caused mortality. Rats inhaling 2.43 mg/m^3 EDA for $\geq$4 months had lowered body weight gains, altered CNS activity, increased eosinophil counts, catalase activity, and liver, lung, and kidney lesions; rats inhaling

0.814 mg/m^3 EDA had less frequent changes in behavior, transiently elevated eosinophils and gamma-globulins, and reversible alterations in the organ histology; and rats inhaling 0.2 mg/m^3 had no toxicity. Fukalova and Dubinina (1992) found that male rats exposed to 0.7 mg/m^3 EDA for 2 weeks to 4 months had altered substrate specificity of monoamine oxygenase (MAO) enzymes after 2 months but no pronounced signs of toxicity.

3.2.2. Guinea Pigs

Guinea pigs (mixed sex) were exposed to a nominal concentration of 1,000 ppm EDA for 30, 60, 120, 240, or 480 min (six pigs/exposure time) by Carpenter et al. (1948) (study described in Section 3.2.1.). All the animals survived the 2-week observation period, and microscopic examination of animals exposed for 8 h revealed "light cloudy swelling of the kidney" and bronchiolar edema of unspecified severity.

Dubinina et al. (1997) exposed guinea pigs to 2.43, 0.814, or 0.2 mg/m^3 EDA vapor/aerosol for ≥4 months (hours/day not given), as described for rats in Section 3.2.1. High-dose animals had lower total body weight gain, increased relative lung and kidney weights, and microscopic lesions in the liver, lungs, and kidneys. Mid-dose animals had reversible histopathological changes, and the low-dose animals had no toxicity. A one-month exposure to 1.21 mg/m^3 EDA (hours/day not given) caused "significant reorganization of the immune system," as characterized by skin tests and by in vitro assays for immune cells (protocols not described).

3.3. Neurotoxicity

No animal neurotoxicity studies were located with EDA exposure by any route.

3.4. Developmental/Reproductive Toxicity

In the study by Dubinina et al. (1997) in which rats were exposed for ≥4 months to 2.43, 0.814, or 0.2 mg/m^3 EDA vapor/aerosol (procedure and numerous deficiencies of this study were described in Sections

3.2.1.), the reproductive and embryotoxicity of EDA were also assessed. A statistically significant decrease in the number of spermatogonia was observed in the high-dose males ($p<0.01$). There were no changes in ovarian function, or in the pre- and postimplantation fetal morbidity, the number of progeny per female, or the body weight of the offspring. However, the offspring of exposed males and unexposed females had changes in leukocyte counts, whereas offspring of exposed females and unexposed males had a delay in body mass increase, changes in CNS characteristics, and decreased levels of peripheral blood hemoglobin, erythrocytes and leukocytes. Exposure to 0.814 mg/m^3 EDA led to no gonad morphofunctional changes, although minor changes in the progeny of the experimental animals (behavior, levels of blood eosinophils and gamma-globulins) were observed. The lowest exposure concentration caused no toxicological effects.

Several developmental or reproductive studies were conducted on animals by oral EDA exposure. No teratogenic effects were found in fetuses of pregnant female F344 rats given 50, 250, or 1,000 mg EDA-2HCl/kg/day in the diet during gestation days 6-15 in a conventional teratogenicity study, or given 0 or 1,000 mg EDA/kg/day in a pair-feeding study (DePass et al. 1987). No reproductive toxicity was seen in a two-generation study in which F344 rats were given 50, 150, or 500 mg EDA dihydrochloride/kg/day in the diet (Yang et al. 1984a). Parameters examined included the fertility index, days from mating to parturition, the fraction of pregnancies resulting in litters with live pups, fraction of pups alive at birth, litter size, and 0-4 day, 4-14 day, and 4-21 day pup survival indices and body weight. Both sexes of the high dose F_0 and F_1 parents, however, had toxic effects (lowered weight gain, decreased liver weight, increased kidney weight, and hepatocellular pleiomorphism). No maternal or fetal toxicity occurred at gestational day 30 in pregnant NZW rabbits gavaged with 0, 10, 40, or 80 mg EDA/kg/day (as aqueous EDA-2HCl) on gestational days 6-19 (Price et al. 1993). Conversely, EDA (400 mg/kg/day) given to 50 pregnant CD-1 mice by gavage on days 6-13 of gestation caused reduced birth weights and weight gains in the offspring, but no maternal toxicity (Hardin et al. 1987).

3.5. Genotoxicity

EDA caused a weakly positive response in *Salmonella typhimurium* TA100 and TA1535, with or without addition of rat liver S9

homogenate (Hedenstedt 1978; Hulla et al. 1981; Haworth et al. 1983). Leung (1994), however, obtained a negative response in the *Salmonella* mutagenicity assay using strains TA98, TA100, TA1535, TA1537, and TA1538 (±S9 homogenate). EDA did not induce sister chromatid exchanges or HGPRT mutations in CHO cells with or without rat liver S9 activation and did not induce unscheduled DNA synthesis in primary rat hepatocytes (Slesinski et al. 1983). EDA was negative in a dominant lethal assay in which male Fischer 344 rats were given 0.05-0.5 mg/kg/day EDA-2HCl in the diet for 23 weeks, and then mated for 3 weeks (Slesiniski et al. 1983). EDA was negative in the *Drosophila* sex-linked recessive lethal assay when administered to adult Canton-S wild-type males in the diet (10,000 or 20,000 ppm) or by injection (1,500 ppm) (Zimmering et al. 1985).

3.6. Carcinogenicity

No inhalation-exposure carcinogenicity studies were located in the literature. No neoplasms were seen in a multi-generation carcinogenicity study in which F344 rats were given 50, 150, or 500 mg EDA dihydrochloride/kg/day in the diet (Yang et al. 1984b). The F_0 parents were given the compound for 100 days before mating, and the F_1 offspring were fed the same dietary concentrations of EDA dihydrochloride. No evidence of epidermal tumors (or life shortening) was seen in a lifetime skin application assay in male C3H/HeJ mice in which 25 µl of 1% EDA in water was applied 3× per week until death (DePass et al. 1984).

The ACGIH (2004) has concluded that there is inadequate evidence in humans and in experimental animals to establish the carcinogenicity of ethylenediamine and places it in carcinogenicity group A4 ("not classifiable as a human carcinogen"). The Environmental Protection Agency (EPA) classifies EDA as carcinogenicity weight-of-evidence group D: not classifiable as to human carcinogenicity, based on no human data and inadequate animal data (EPA 2005).

3.7. Summary

The database for EDA inhalation animal studies is very limited, with many studies missing critical information. Carpenter et al. (1948) showed that one 8-h exposure of rats or guinea pigs to a nominal concen-

tration of 1,000 ppm resulted in no deaths but did cause lung edema and kidney swelling. [A nominal concentration of 1,000 ppm was found to be 484 ppm analytical in another study by the same laboratory (Pozzani and Carpenter, 1954), which showed that analytical EDA concentration is approximately 50% of the nominal concentration.] In a subsequent range-finding study, Smyth et al. (1951) determined that an 8-h exposure to 2,000 ppm EDA (nominal; analytical was likely ~1,000 ppm) caused no deaths whereas 6/6 rats died at 4,000 ppm (nominal; analytical was likely ~2,000 ppm); no effects other than death were described. Pozzani and Carpenter (1954) found that rats exposed 7 h/day for up to 30 days to 59 ppm had no effects, at 132 ppm had hair loss and a slight increase in the incidence of "major" microscopic lesions (types of lesions were not specified), whereas most or all rats exposed to 225 or 484 ppm died and had liver, kidney, and lung lesions. Dubinina et al. (1997) and Fukalova and Dubinina (1992) conducted several acute and multiple-exposure inhalation studies using rats and guinea pigs, although the significance of their results is questionable due to numerous study deficiencies.

EDA showed little genotoxic activity, as most assays yielded negative or weakly positive responses. No inhalation-exposure carcinogenicity studies were located, and animal dietary and skin painting studies yielded negative results (Yang et al. 1984b; DePass et al. 1984).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No human or animal studies were located that described the metabolism or disposition of ethylenediamine following inhalation exposure. Animal and human studies have shown that amines are well absorbed from the gut, respiratory tract, and skin (Benya and Harbison 1994).

The metabolism and pharmacokinetics of EDA were studied in male Hilltop Wistar rats. They were given a single dose of 5, 50, or 500 mg/kg [^{14}C]EDA-2HCl solution orally, intravenously, or endotracheally for 24 or 48 h (Yang and Tallant 1982). The vast majority of radiolabel was excreted within 24 h by all exposure routes, the urine being the primary excretion route and accounting for 42-65% of the given radioactivity. The feces accounted for about 10-12% of the endotracheally administered radiolabel, and for 4.5-16% and 12-31% of the radioactivity given

orally and intravenously, respectively. A substantial amount of radioactivity was found in the expired air as $^{14}CO_2$ (5-8%) and in the major organs and carcass (1.7-2.7% and 9.1-19%, respectively) for all three exposure routes. The thyroid, liver, kidneys, and bone marrow contained the greatest amount of radioactivity on a per gram basis. Bioavailability ($AUC_{oral/endo}/AUC_{iv}$), total clearance, terminal half-life, and AUC were similar for the three exposure routes; minor differences in parameter values were seen among the three doses. AG 50W cation exchange chromatography identified *N*-acetylethylenediamine as the major metabolite in the urine and the feces by all three exposure routes. Yang and Tallant (1982) proposed that *N*-acetylation is the primary metabolic pathway for EDA, with aminoacetaldehyde and ethanolamine also being formed as intermediates before final conversion to CO_2. Based on the pharmacokinetic and metabolic results, the study authors concluded that the fate of EDA was similar following oral and endotracheal administration at 5 and 50 mg/kg.

Hilltop Swiss Webster mice dosed orally with 5 mg/kg [^{14}C]EDA excreted approximately 70% of the radiolabel in the urine, 5% in the feces, and 12% as $^{14}CO_2$ at 48 h after dosing (Yang et al. 1978). The major organs contained a small amount of radioactivity.

Pharmacokinetic studies were conducted using Fischer 344 rats that were part of a two-year chronic toxicity dietary study with EDA dihydrochloride (Yang et al. 1984b). Male and female rats (43 days old) were initially given a single *per os* dose of 50 mg [^{14}C]EDA-2HCl per kg body weight on day 0, prior to EDA dietary treatment. After 6 and 18 months, rats receiving 0 (control) or 350 mg EDA/kg/day (high-dose) in the diets were given a single *per os* dose of 50 mg [^{14}C]EDA-2HCl per kg body weight. The rats showed no sex-related, age-related, or chronic dosing-related differences in the absorption rate or terminal half-life. However, the older rats had 2-3 times greater AUC than the younger rats, which correlated with their smaller volume of distribution (1/4 to ½ that of day 0 rats), and the $^{14}CO_2$ production rate constant (from ^{14}C-EDA) was slightly (≤18%) but statistically significantly greater in the females than males. Approximately 10-22% of the administered radiolabel appeared as expired $^{14}CO_2$, and urinary and fecal excretion accounted for 39-51% and 11-30% of the administered dose, respectively. Most of the excreted radioactivity was as metabolites.

4.2. Mechanism of Toxicity

Ethylenediamine is highly alkaline, water soluble and lipid-soluble skin and respiratory sensitizer and irritant. Its alkalinity is likely responsible for the corneal and skin lesions described in humans and animals, and for respiratory irritation leading to lung edema that may occur in humans. However, respiratory irritation as the sole end point was not reported in any human studies, which only examined asthmatic symptoms in EDA-sensitized workers. Animal inhalation studies also did not report EDA-induced irritation but found liver, kidney, and lung lesions. The mechanism by which EDA sensitizes humans and causes internal organ lesions is unknown.

Several studies examined the mechanism of EDA-induced asthma in humans. Workers with EDA-induced bronchial asthma had notable bronchoconstriction immediately after exposure to EDA at concentrations below those that were non-irritating to unsensitized asthmatics (Popa et al. 1969). A delayed asthmatic response (several hours after exposure) was seen in several studies in EDA-sensitized workers (Lam and Chan-Yeung 1980, Nakazawa and Matsui 1990, and Ng et al. 1991). Histamine did not appear to be an important mediator because plasma histamine levels were unchanged in venous blood during bronchoconstriction in occupationally exposed workers (Lam and Chan-Yeung 1980; Nakazawa and Matsui 1990). Evidence for an immunological mechanism was inconclusive because precipitable EDA antibody was not found in sensitized workers although IgE and eosinophil levels were increased (Popa et al. 1969, Lam and Chan-Yeung 1980, Nakazawa and Matsui 1990).

4.3. Structure-Activity Relationships

Inhalation toxicity information about chemicals related structurally to EDA was very limited. Repeated exposure of rabbits to 100 ppm ethylamine (C_2H_7N) caused lung, liver, and kidney damage, lung irritation, and corneal injury (Benya and Harbison 1994). One worker exposed to up to 28 ppm hexamethylene diamine ($C_6H_{16}N_2$) developed acute hepatitis and dermatitis following an unspecified number of exposures (Benya and Harbison 1994). Asthmatic symptoms were associated with occupational exposure to a TWA of approximately 0.085 and 0.34 ppm piperizine ($C_4H_{10}N_2$) (Hagmar et al. 1982).

Leung and Auletta (1997) compared the allergic contact skin sensitization and cross-reaction potential of EDA and eight other alkyleneamines using the guinea pig maximization test (10 animals/sex). Sensitizing potency was inversely correlated with the number of amine groups. EDA was the most potent skin sensitizer and skin irritant, and elicited the greatest cross-reaction in guinea pigs originally sensitized with the other amines, when tested as either the inducing or challenge agent.

4.4. Other Relevant Information

4.4.1. Species Variability

EDA toxicity in a species other than the rat was examined in only one inhalation study, in which rats and guinea pigs exposed for 8 h to 1,000 ppm EDA (nominal; analytical approximately 484 ppm) did not die but had lung edema and kidney swelling (Carpenter et al. 1948). No differences in the response of the two species were reported, although only a very brief description of the experimental results was provided.

4.4.2. Susceptible Populations

A susceptible human subpopulation exists, consisting of persons who have become sensitized to EDA either through work or by living in a community near a plant that uses EDA. Workers have reported symptoms including chronic cough, phlegm, wheezing, and exertional breathlessness when exposed to EDA, which typically disappear upon cessation of EDA exposure. Aldrich et al. (1987) showed that persons exposed to <1 ppm EDA became sensitized in an occupational setting after exposure for approximately 7 months (smokers) to 37.3 months (nonsmokers). In the case of community residents, people may become sensitized to EDA over time from periodic but persistent exposures resulting from fugitive or routine emissions.

EDA-sensitized people may experience more severe and/or idiosyncratic response to a given concentration and exposure duration compared to non-sensitized people. Popa et al. (1969) showed that EDA-sensitized individuals had an asthmatic response to EDA at concentrations not irritating to unsensitized asthmatics, although exposure concen-

trations were not stated. Because the qualitative and quantitative differences in the response of nonsensitized and sensitized people to EDA are undefined, an uncertainty factor to specifically account for previously sensitized people cannot be determined. The derived AEGL values are for a once-in-a-lifetime exposure and do not consider previous sensitization.

4.4.3. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for EDA toxic effects. Ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5, and n ranged from 1 to 3 for 90% of the chemicals examined. To obtain protective AEGL 30-, 60-, and 240-min values, scaling across time was performed using $n = 3$ and the ten Berge equation, except that the 10-min value was not extrapolated from 8 h (exposure duration in the key studies) because extrapolating from ≥4 h to 10 min is associated with unacceptably large inherent uncertainty, and the 30-min value was adopted for 10 min to be protective of human health (NRC 2001).

4.4.4. Concurrent Exposure Issues

Workers may be exposed to other dermal and/or respiratory sensitizers which could potentially increase susceptibility to EDA, although the degree of cross-sensitization in humans is not defined. EDA-sensitized workers exposed to EDA dermally or by inhalation did not cross-react to aminophylline (molecular combination of EDA and theophylline), ethylenediamine tetraacetate, or procaine (4-aminbenzoic acid-2(diethylanimo)ethyl ester) (Popa et al. 1969). In a guinea pig maximization test (Leung and Auletta 1997), a comparison of the allergic contact skin sensitization and cross-reaction potential of EDA and eight other alkyleneamines showed that EDA was the most potent skin sensitizer and skin irritant. EDA elicited the greatest cross-reaction in guinea pigs originally sensitized with the other alkyleneamines.

5. RATIONALE FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human studies were located with end points consistent with the definition of AEGL-1. In the available studies, the exposure time was either too short (5-10 sec exposure by Pozzani and Carpenter 1954), not given (Aldrich et al. 1987; Ng et al. 1995), or the exposure concentration was not specified (Nakazawa and Matsui 1990).

5.2. Summary of Animal Data Relevant to AEGL-1

In the multiple-exposure study of Pozzani and Carpenter (1954), Sherman rats (15/sex/dose) exposed 7 h/day for up to 30 days to 59 ppm had no toxic effects, rats exposed to 132 ppm had hair loss and a slight increase in the incidence of microscopic lesions, and those exposed to 225 or 484 ppm died and/or had hair loss and liver, kidney, and lung lesions.

5.3. Derivation of AEGL-1

AEGL-1 values, as shown in Table 4-5, were not recommended because none of the available human or animal data were considered adequate. The multiple-exposure study of Pozzani and Carpenter (1954), in which rats exposed to 59 ppm 7 h/day for up to 30 days had no toxic effects, was not used because it was not associated with a specific end point within the scope of the AEGL-1 definition. Absence of AEGL-1 values does not imply that exposure to concentrations below the AEGL-2 is without adverse effects.

TABLE 4-5 AEGL-1 Values for Ethylenediamine

10 min	30 min	1 h	4 h	8 h
Not recommended due to insufficient data.				

6. RATIONALE FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The only human study for which both the exposure concentration and duration were defined was the bronchial provocation test in which a 31-year-old male EDA-sensitized chemical worker exposed to 30 ppm EDA for 15 min had a delayed asthmatic response (Ng et al. 1991). He had decreased peak flow rate 3 h after exposure and coughed, wheezed, was breathless and had a further fall in peak flow rate 12 h after exposure. He improved after treatment with nebulized ventolin (bronchodilator). However, because an asthmatic response can encompass either AEGL-2 or AEGL-3 effects and the response of non-sensitized persons to the same exposure scenario is unknown, this study was not considered appropriate for derivation of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

Two animal studies are potentially useful for AEGL-2 derivation: (1) the single-exposure study in which rats and guinea pigs exposed for 30 min to 8 h to 0 or ~484 ppm EDA (1,000 ppm nominal) all survived and had "light cloudy swelling of the kidney" and bronchiolar edema of unspecified severity (Carpenter et al. 1948), and (2) the 30-day study (7 h/day) by Pozzani and Carpenter (1954) in which rats (15/sex/dose) exposed to 59 ppm had no toxic effects, rats exposed to 132 ppm had hair loss, and one rat had an unspecified microscopic lesion; rats exposed to 225 ppm had fractional mortality (earliest death, day 4) and kidney and liver lesions; and rats exposed to 484 ppm all died from ≤20 exposures (earliest death, day 3) and most had liver, kidney, and/or lung lesions.

6.3. Derivation of AEGL-2

AEGL-2 values were based on the Carpenter et al. (1948) study in which rats and guinea pigs (6/group) exposed for 8 h to approximately 484 ppm EDA (1,000 ppm nominal) had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney" but none died (Carpenter et al. 1948). No studies were available from which to determine the EDA concentration-time relationship, so scaling to exposure

times <8 h was performed with the ten Berge et al. (1986) equation $C^n \times t = k$, where $n = 3$ was used to obtain AEGL values for 30, 60, and 240 min and the 30-min value was adopted as the 10-min value, as discussed in section 4.4.3. An uncertainty factor of 3 was used for interspecies variability because a similar response was seen in two species, and a modifying factor of 3 because the key study did not specify the severity of the bronchiolar edema. An intraspecies uncertainty factor of 10 was applied because the data were insufficient to determine the mode of lung and kidney lesions (or which was the more sensitive end point) in the key study and consequently the potential variability of the human response to EDA. Note that UF (30) × MF (3) is rounded to 100 for simplicity, per Section 2.9.2. of the SOP (NRC 2001). The developed AEGL-3 values are shown in Table 4-6; calculations are detailed in Appendix A. The AEGL-2 values are supported by the Pozzani and Carpenter (1954) study, in which 1/26 rats had unspecified lesions but no mortality after 30 exposures to 132 ppm EDA for 7 h/day.

EDA-sensitized individuals may experience more severe and/or different effects at a given exposure concentration or duration than non-sensitized people. The qualitative and quantitative differences in the response of the two groups are undefined.

7. RATIONALE FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No quantitative information on lethal EDA exposure in humans was located. An EDA-sensitized chemical worker challenged with 30 ppm EDA for 15 min had a delayed asthmatic response (Ng et al. 1991) that was ameliorated by the administration of a bronchodilator. This study was not used for derivation of AEGL-3 values because it is unclear what would have happened to this individual without medical intervention, and an asthmatic response can encompass either AEGL-2 or AEGL-3 effects. Additionally, the quantitative and qualitative differences in the

TABLE 4-6 AEGL-2 Values for Ethylenediamine

10 min	30 min	1 h	4 h	8 h
12 ppm (30 mg/m^3)	12 ppm (30 mg/m^3)	9.7 ppm (24 mg/m^3)	6.1 ppm (15 mg/m^3)	4.8 ppm (12 mg/m^3)

response of non-sensitized persons to the same exposure scenario is unknown.

7.2. Summary of Animal Data Relevant to AEGL-3

Two studies are relevant for deriving AEGL-3 values: (1) the range-finding test of Smyth et al. (1951) in which 0/6 rats exposed to approximately 1,000 ppm (2,000 ppm nominal) for 8 h died but 6/6 died after an 8-h exposure to 2,000 ppm EDA (4,000 ppm nominal). Few experimental details were provided and the effects on the animals (besides death) were not described, and (2) the 30-exposure study (7 h/day) by Pozzani and Carpenter (1954) in which rats (15/sex/dose) exposed to 59 ppm had no toxic effects, rats exposed to 132 ppm had hair loss and one rat had an unspecified microscopic lesion, rats exposed to 225 ppm had fractional mortality (earliest death day 4) and kidney, and lung lesions, and rats exposed to 484 ppm all died from ≤20 exposures (earliest death day 3) and most had liver, kidney, and/or lung lesions.

7.3. Derivation of AEGL-3

AEGL-3 derivation was based on the range-finding study in which 0/6 rats died after an 8-h exposure to ~1,000 ppm (2,000 ppm nominal) but 6/6 died at 4,000 ppm (nominal) (Smyth et al. 1951). Toxic effects (other than death) were not described, and 1,000 ppm was considered to be the lethality threshold. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the equation $C^n \times t = k$ and $n = 3$, as was done for AEGL-2 and is discussed in Section 4.4.3. A total uncertainty factor of 100 was applied: 10 for interspecies variability (cause of death was undefined and there were no studies using other species) and 10 for intraspecies variability (lack of toxicity data in key study precludes definition of the mode or variability of the toxic response in humans). Target organs (liver and kidneys) were identified in a study where rats received 225 ppm EDA 7 h/day for up to 30 days (first deaths on exposure day 4), although the mode of toxicity was unclear (Pozzani and Carpenter 1954). The developed AEGL-3 values are shown in Table 4-7; calculations are detailed in Appendix A.

EDA-sensitized individuals may experience more severe and/or different effects at a given exposure concentration or duration than non-sensitized people. The qualitative and quantitative differences in the response of the two groups are undefined.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for EDA and their relationship to one another are shown in Table 4-8. AEGL-1 values were not developed due to insufficient data. Absence of AEGL-1 values does not imply that exposure to concentrations below the AEGL-2 is without adverse effects. AEGL-2 values were based on the Carpenter et al. (1948) study in which rats and guinea pigs (6/group) exposed for 8 h to approximately 484 ppm EDA (1,000 ppm nominal) had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney" but none died (Carpenter et al. 1948). No studies were available from which to determine the EDA concentration-time relationship, but scaling to exposure times <8 h was performed with the ten Berge et al. (1986) equation $C^n \times t = k$ where n = 3 was used obtain protective AEGL values for 30, 60, and 240 min and the 30-min value was also adopted for 10 min, as discussed in section 4.4.3. An uncertainty factor of 3 was used for interspecies variability because a similar response was seen in two species, and a modifying factor of 3 because the key study did not specify the severity of the bronchiolar edema. An intraspecies uncertainty factor of 10 was applied because the data were insufficient to determine the mode of lung and kidney lesions (or which was the more sensitive end point) in the key study and consequently the potential variability of the human response to EDA.

The AEGL-3 was based on a range-finding study in which 0/6 rats died after an 8-h exposure to ~1,000 ppm (2,000 ppm nominal) but 6/6 died at 4,000 ppm (nominal) (Smyth et al. 1951). Toxic effects (other

TABLE 4-7 AEGL-3 Values for Ethylenediamine

10 min	30 min	1 h	4 h	8 h
25 ppm (62 mg/m^3)	25 ppm (62 mg/m^3)	20 ppm (49 mg/m^3)	13 ppm (32 mg/m^3)	10 ppm (25 mg/m^3)

TABLE 4-8 Summary of AEGL Values for Ethylenediamine

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Non-disabling)	Not recommended due to insufficient data.				
AEGL-2 (Disabling)	12 ppm (30 mg/m^3)	12 ppm (30 mg/m^3)	9.7 ppm (24 mg/m^3)	6.1 ppm (15 mg/m^3)	4.8 ppm (12 mg/m^3)
AEGL-3 (Lethal)	25 ppm (62 mg/m^3)	25 ppm (62 mg/m^3)	20 ppm (49 mg/m^3)	13 ppm (32 mg/m^3)	10 ppm (25 mg/m^3)

than death) were not described, and 1,000 ppm was considered to be the lethality threshold. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the equation $C^n \times t = k$ and $n = 3$, as was done for AEGL-2. A total uncertainty factor of 100 was applied: 10 for interspecies variability (cause of death was undefined and there were no studies using other species) and 10 for intraspecies variability (lack of toxicity data in key study precludes definition of the mode or variability of the toxic response in humans). Kidney and liver toxicity and death occurred in rats given 4 to 30 exposures of 225 ppm EDA for 7 h/day in another study, although the mode of toxicity was unclear (Pozzani and Carpenter 1954).

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for EDA are summarized in Table 4-9.

The ACGIH TLV-TWA of 10 ppm (25 mg/m^3; skin notation) is based on a rat 90-day oral exposure study in which the NOEL was 23 mg/kg/day (Yang et al. 1978) and a 30-day rat inhalation study in which the NOEL was 59 ppm (Pozzani and Carpenter 1954). ACGIH defines the critical toxic EDA effects as irritation, asthma, and sensitization (ACGIH 2004). The OSHA PEL-TWA and NIOSH REL-TWA are also 10 ppm (25 mg/m^3), intended to avert EDA toxic effects including irritation of nose and respiratory system, dermal sensitization, asthma, liver and kidney damage (NIOSH 2005b; OSHA 2005). The NIOSH IDLH for ethylenediamine was lowered from 2,000 ppm to 1,000 ppm in 1994, NIOSH noting that 1,000 ppm may be a conservative value due to the

lack of relevant acute toxicity data for occupational exposure between 1,000 and 2,000 ppm (NIOSH 2005b).

Aldrich et al. (1987) suggested that because there was evidence that EDA sensitization occurred (in coater machine operator) when the EDA concentrations were <1 ppm, the present TLV of EDA of 10 ppm should be reconsidered (study described in Section 2.2).

The 10-ppm occupational exposure limit is also used in other countries including Australia, Belgium, Denmark, Finland (20 ppm STEL), France (15 ppm STEL), Germany, Japan, the Netherlands, the Phillippines, Russia, Sweden (15 ppm STEL), Switzerland (20 ppm STEL), Turkey, and the U.K. (RTECS 2005).

TABLE 4-9 Extant Standards and Guidelines for Ethylenediamine (ppm)

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended due to insufficient data.				
AEGL-2	12	12	9.7	6.1	4.8
AEGL-3	25	25	20	13	10
PEL-TWA (OSHA)[a]					10
IDLH (NIOSH)[b]		1,000			
REL-TWA (NIOSH)[c]					10
TLV-TWA (ACGIH)[d]					10
MAK (Germany)[e]					10
MAK Peak Limit (Germany)[f]	20 (15 min)				
MAC (Netherlands)[g]					7
LLV (Sweden)[h]					10
STV (Sweden)[i]	15				

[a]OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[b]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2005b) represents the maximum concentration from which one could escape within 30 minutes without any escape-

impairing symptoms, or any irreversible health effects. The IDLH for EDA is based on a study in which rats exposed to 2,000 ppm (~1,000 ppm analytical; see text) for 8 h had 0/6 deaths but exposure to 4,000 ppm (~2,000 ppm analytical; see text) for 8 h caused 6/6 deaths (Smyth et al. 1951).

[c]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005a,b) is defined analogous to the ACGIH-TLV-TWA.

[d]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (established 1956, skin notation added 1987; ACGIH 1996) is the time-weighted average concentration for a normal 8 h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (DFG 2002 [Deutsche Forschungs-gemeinschaft or German Research Association]) is defined analogous to the ACGIH-TLV-TWA.

[f]MAK Spitzenbegrenzung (Peak Limit [Category V]) (DFG 2002) constitutes the maximum "momentary value" concentration (monitoring may use an average value) to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift; total exposure may not exceed 8 h MAK.

[g]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers 2000 [under the auspices of the Ministry of Social Affairs and Employment, The Hague, The Netherlands]) is defined analogous to the ACGIH-TLV-TWA. A footnote was present indicating EDA may be a sensitizer.

[h]LLV (Level Limit Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July, 2000. Defined analogous to the ACGIH-TLV-TWA.

[i]STV (Short-Term Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July, 2000. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 minutes.

8.3. Data Quality and Research Needs

Although EDA is a high production volume chemical, very few inhalation toxicity studies were available for deriving AEGL values, and data were insufficient to determine the mode of EDA toxicity. In addition to causing lesions in the lungs, as is typical for respiratory irritants, EDA caused systemic effects including liver and kidney lesions. Studies were not available, and are needed, to determine the most sensitive target organ, including whether irritation occurs at concentrations below those

causing kidney and liver lesions. Studies are also needed that can be used to derive the EDA concentration-time relationship (n in $C^n t = k$), which will ideally include exposure times of ≤1 h. The small database, lack of mechanistic information, and shortcomings of the available studies led to the use of large uncertainty factors in developing AEGL values for EDA.

Studies are needed in which effects within the scope of AEGL-1 occurred, as no adequate human or animal studies were available to derive AEGL-1 values. Only three animal studies (conducted by the same laboratory) were located for the development of AEGL-2 and AEGL-3 values, and additional studies are needed to confirm these values. In the one single-exposure study adequate for AEGL-2 derivation, rats and guinea pigs were exposed for 30 min to 8 h to only one test concentration (~484 ppm EDA). Both species had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney" (Carpenter et al. 1948). Because the key study did not specify the severity of the bronchiolar edema, a modifying factor of 3 was applied in addition to the interspecies UF of 3 (similar response in two species). Because the most sensitive end point and mode of toxicity were unknown, the potential variability of the human response to EDA could not be predicted, and an intraspecies UF of 10 was used. Only one single-exposure study was adequate for AEGL-3 derivation as well, which was a sparsely reported range-finding test (Smyth et al. 1951) in which 0/6 rats died from exposure for 8 h to ~1,000 ppm but 6/6 died from 8 h exposure to ~2,000 ppm. The toxic effects on the animals were not described, which led to the use of a total UF of 100 (10 each for interspecies and intraspecies UF) because the mode and variability of the toxic response in animals and humans was undefined.

Although the key studies used for derivation of AEGL-2 and AEGL-3 values had shortcomings, they were mutually supportive and were consistent with the Pozzani and Carpenter (1954) a multiple-exposure rat study. The consistency between these three studies, together with the use of large uncertainty factors, provides a reasonable degree of confidence in the developed AEGL-2 and AEGL-3 values.

EDA is a respiratory (and skin) sensitizer, but no studies were found to determine the qualitative and quantitative differences in the response of non-sensitized and sensitized people. This lack of data is not considered relevant to the development of AEGL values for EDA because AEGL values are intended for a once-in-a lifetime exposure and do not consider previous sensitization.

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APPENDIX A

Derivation of AEGL Values

Derivation of AEGL-1

AEGL-1 values are not recommended due to insufficient data. Absence of AEGL-1 values does not imply that exposure to concentrations below the AEGL-2 is without adverse effects.

Derivation of AEGL-2

Key study:

> Carpenter et al. 1948. Rats and guinea pigs (6/group) were exposed for 30 min to 8 h to approximately 484 ppm EDA (1,000 ppm nominal). Rats exposed for 8 h had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney."

Toxicity end point:

> Bronchiolar edema and kidney swelling. (Note that EDA-sensitized individuals may experience more severe effects at a given exposure concentration and/or duration.)

Scaling:

> $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n; used $n = 3$ to extrapolate to <8 h to obtain protective AEGL values, except the 30-min value was adopted as the 10-min value because extrapolating from 8 h to 10 min is associated with unacceptably large inherent uncertainty.

Total uncertainty factor: 30

> Interspecies: 3: A similar response was seen in two species in the key study.
> Intraspecies: 10: Data were insufficient to determine the mode of lung and kidney lesions (or which was the more sensitive end point)

in the key study and consequently the potential variability of the human response to EDA.

Modifying factor: 3: The key study did not specify the severity of the bronchiolar edema.

Calculations for <8 h:

$$\frac{\text{Concentration}}{\text{UF} \times \text{MF}} \quad \frac{484\ \text{ppm}^3}{100^*} \times \text{time (8 h)} = k = 907\ \text{ppm}^3\text{-h}$$

$C^3 \times 0.5\ \text{h} = 907\ \text{ppm}^3\text{-h}$
30-min (and 10-min) AEGL-2 = C = 12 ppm [30 mg/m^3]

$C^3 \times 1\ \text{h} = 907\ \text{ppm}^3\text{-h}$
1-h AEGL-2 = C = 9.7 ppm [24 mg/m^3]

$C^3 \times 4\ \text{h} = 907\ \text{ppm}^3\text{-h}$
4-h AEGL-2 = C = 6.1 ppm [15 mg/m^3]

Calculations for 8 h:

8-h AEGL-2 = 484 ppm / 100 = 4.8 ppm [12 mg/m^3]

*Note that UF (30) × MF (3) is rounded to 100 for simplicity, per Section 2.9.2. of the SOP (NRC 2001).

Derivation of AEGL-3

Key study: Smyth et al. (1951). No rats (0/6) died after an 8-h exposure to 1,000 ppm (2,000 ppm nominal) but 6/6 died at 2,000 ppm (4,000 ppm nominal). Toxic effects (other than death) were not described.

Toxicity end point: Lethality threshold at 1,000 ppm. (Note that EDA-sensitized individuals may experience more severe effects at a given exposure concentration and/or duration.)

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n; used $n = 3$ to extrapolate to <8 h to obtain protective AEGL values, except the 30-min value was adopted as the 10-min value because extrapolating from 8 h to 10 min is associated with unacceptably large inherent uncertainty.

Total uncertainty factor: 100
Interspecies: 10: The cause of death was not defined in the key study, and there were no supporting data with AEGL-3 end points from other species.
Intraspecies: 10: Lack of toxicity data in key study precludes definition of the mode or variability of the toxic response in humans.

Calculations for <8 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{1{,}000\ \text{ppm}^3}{100} \times \text{time (8 h)} = k = 8{,}000\ \text{ppm}^3\text{-h}$$

$C^3 \times 0.5\ \text{h} = 8{,}000\ \text{ppm}^3\text{-h}$
30-min (and 10-min) AEGL-3 = C = 25 ppm [62 mg/m^3]

$C^3 \times 1\ \text{h} = 8{,}000\ \text{ppm}^3\text{-h}$
1-h AEGL-3 = C = 20 ppm [49 mg/m^3]

$C^3 \times 4\ \text{h} = 8{,}000\ \text{ppm}^3\text{-h}$
4-h AEGL-3 = C = 13 ppm [32 mg/m^3]

Calculations for 8 h:

8-h AEGL-3 = 1,000 ppm / 100 = 10 ppm [25 mg/m^3]

APPENDIX B

Derivation of the Level of Distinct Odor Awareness

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT_{50}, i.e., concentration at which 50% of the odor panel observed an odor without necessarily recognizing it) of 1.0 ppm was obtained for EDA from Hellman and Small (1974). The same citation listed an OT_{50} of 0.30 for *n*-butanol, as compared to the reference value of 0.04 ppm as the odor threshold provided by van Doorn et al (2002). Based on the differences in *n*-butanol values from the two sources, an "inter-laboratory" correction factor is applied to EDA as follows:

$$\frac{0.04 \text{ ppm } n\text{-butanol}}{0.3 \text{ ppm } n\text{-butanol}} \times 1.0 \text{ ppm } OT_{50} \text{ EDA} = 0.133 \text{ ppm "corrected" } OT_{50} \text{ EDA}$$

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

$$I = k_w \times \log (C / OT_{50}) + 0.5$$

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

$3 = 2.33 \times \log (C / 0.133) + 0.5$, which can be rearranged to
$\log (C / 0.133) = (3 - 0.5) / 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 0.133 = 1.56$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life, factors such as sex, age, sleep, smoking, upper airway infections and allergies, as well as distraction, increase the odor detection threshold by a factor of 4. In addi-

tion, it takes into account that odor perception is very fast (about 5 sec) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

$$LOA = C \times 1.33 = 1.56 \text{ ppm} \times 1.33 = 2.1 \text{ ppm}$$

The LOA for EDA is 2.1 ppm.

APPENDIX C

ACUTE EXPOSURE GUIDELINES FOR ETHYLENEDIAMINE (107-15-3)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended due to insufficient data.				
Key Reference: Not applicable.				
Test Species/Strain/Number: Not applicable.				
Exposure Route/Concentrations/Durations: Not applicable.				
Effects: Not applicable.				
End point/Concentration/Rationale: Not applicable.				
Uncertainty Factors/Rationale: Total uncertainty factor: Not applicable. Interspecies: Intraspecies:				
Modifying Factor: Not applicable.				
Animal to Human Dosimetric Adjustment: Not applicable.				
Time Scaling: Not applicable.				
Data Adequacy: AEGL-1 values were not recommended because none of the available human or animal data were considered adequate. Absence of AEGL-1 values does not imply that exposure to concentrations below the AEGL-2 is without adverse effects.				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
12 ppm	12 ppm	9.7 ppm	6.1 ppm	4.8 ppm
Key Reference: Carpenter, C.P., H.F. Smyth, Jr., and C.B. Shaffer. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30: 2-6.				
Test Species/Strain/Sex/Number: Rats and guinea pigs, 6/group, sex unspecified.				
Exposure Route/Concentrations/Durations: Rats and guinea pigs were exposed to 0 or to approximately 484 ppm EDA (1,000 ppm nominal) for ½, 1, 2, 4, or 8 h.				

(Continued)

AEGL-2 VALUES Continued

Effects: Animals exposed for 8 h had bronchiolar edema of unspecified severity and "light cloudy swelling of the kidney" but none died. Effects for shorter exposure durations were not specified.
End point/Concentration/Rationale: Bronchiolar edema and kidney swelling from 8-h exposure to approximately 484 ppm EDA. Note that persons previously sensitized to EDA may experience more severe effects at a given exposure concentration and/or duration.
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 3: A similar response was seen in two species in the key study. Intraspecies: 10: Data were insufficient to determine the mode of lung and kidney lesions and consequently the potential variability of the human response to EDA.
Modifying Factor: 3: The key study did not specify the severity of the organ lesions.
Animal to Human Dosimetric Adjustment: Not performed.
Time Scaling: $C^n \times t = k$; no data were available to derive n, so used n = 3 to extrapolate to <8 h to obtain protective AEGL values, except the 30-min values were adopted as 10-min values to be protective of human health (NRC 2001; see Section 4.4.3.).
Data Adequacy: Key study tested only one EDA concentration but at a number of time intervals. AEGL values are supported by a study in which 1/26 rats had unspecified lesions after 30 exposures of 7 h/day but none died (Pozzani and Carpenter, 1954).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
25 ppm	25 ppm	20 ppm	13 ppm	10 ppm
Key Reference: Smyth, H.F., C.P. Carpenter, and C.S. Weil. 1951. Range-finding toxicity data: List IV. AMA Arch. Ind. Hyg. Occup. Med. 4: 119-122.				
Test Species/Strain/Sex/Number: Sprague-Dawley rats; 6/concentration (sex not specified).				
Exposure Route/Concentrations/Duration: Inhalation for 8 h to ~1,000 ppm (2,000 ppm nominal).				
Effects: Death was the only stated effect: 0/6 deaths at 2,000 ppm; 6/6 deaths at 4,000 ppm.				

End point/Concentration/Rationale: 1,000 ppm (2,000 ppm nominal) is the estimated lethality threshold for an 8-h exposure in rats. Note that EDA-sensitized persons may experience more severe and/or different effects at a given exposure concentration and/or duration.
Uncertainty Factors/Rationale: Total uncertainty factor: 100 Interspecies: 10: The cause of death was not defined in the key study, and there were no supporting data with AEGL-3 end points from other species. Intraspecies: 10: Lack of toxicity data in key study precludes definition of the mode or variability of the toxic response in humans.
Modifying Factor: None.
Animal to Human Dosimetric Adjustment: Not performed.
Time Scaling: $C^n \times t = k$; no data were available to derive n, so used n = 3 to extrapolate to <8 h to obtain protective AEGL values, except the 30-min values were adopted as 10-min values to be protective of human health (NRC 2001; see Section 4.4.3.).
Data Adequacy: Key study lacked a description of toxic effects other than death. An uncertainty factor of 100 is intended to account for the lack of supporting data from other species and an unknown mode of toxicity. Target organs (liver and kidneys) are identified in another rat study in which fractional mortality resulted from 30 exposures of 7 h/day to 225 ppm (first deaths on exposure day 4; Pozzani and Carpenter, 1954).

APPENDIX D

Category Plot for Ethylenediamine

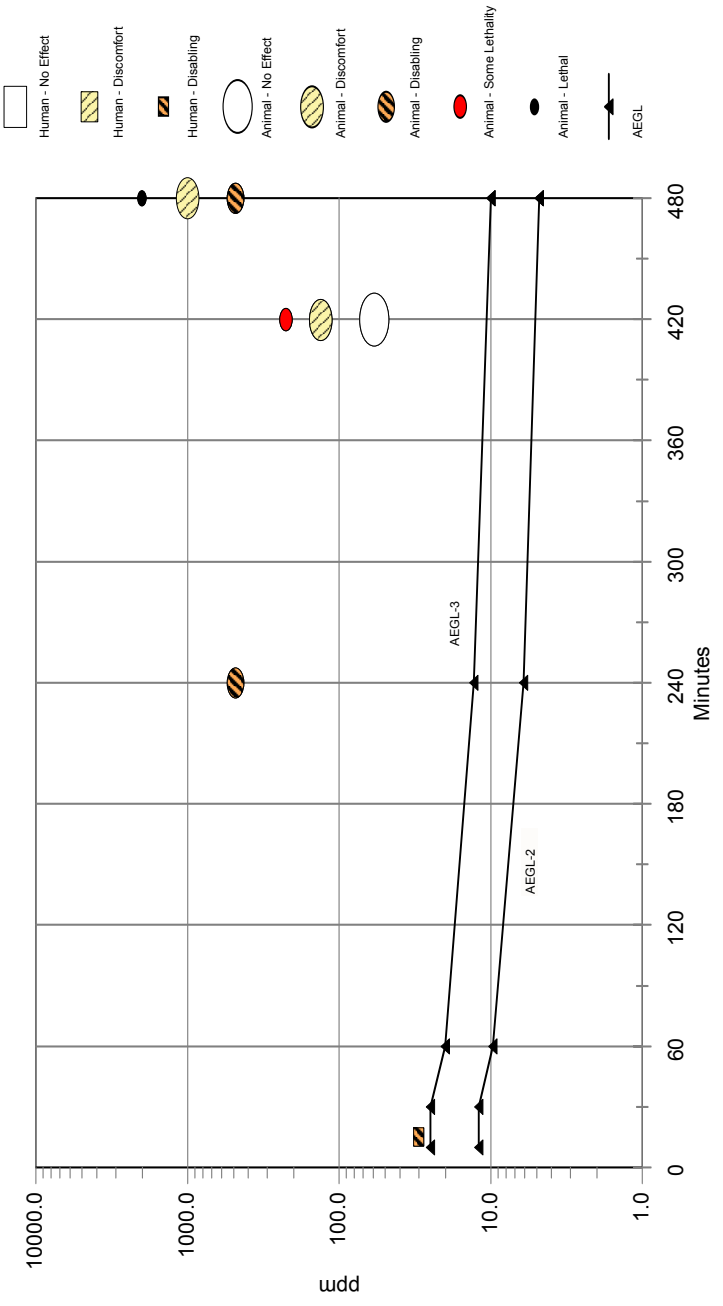

FIGURE D-1 Chemical toxicity—TSD all data, ethylenediamine.

5

HFE-7100: Methyl Nonafluorobutyl Ether (40%) (CAS Reg. No. 163702-07-6) plus Methyl Nonafluoroisobutyl Ether (60%) (CAS Reg. No. 163702-08-7)[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrofluoroether-7100 (HFE-7100) is a mixture of methyl nonafluorobutyl and nonafluoroisobutyl ethers in ratios of 30-50 and 50-70%, respectively. This mixture has been developed as a replacement for presently used chlorofluorocarbons and other ozone-depleting chemicals. It is used in industrial situations as a cleaning agent, lubricant carrier, drying

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory) and the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member George Rusch (Chemical Manager). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

agent, specialty solvent, and heat transfer medium. It is a volatile liquid with a slight ethereal odor. No information on production was located.

Except for a single monitoring study conducted by 3M Company and reported by AIHA (1999) in which exposures were noted to be below 50 ppm, no information was located on human exposure. Animal data using the rat as the model addressed anesthetic properties, acute oral, dermal, and inhalation toxicity; neurotoxicity, and genotoxicity. A study with the beagle dog addressed cardiac sensitization. HFE-7100 is of low acute oral and inhalation toxicity. It does not have anesthetic properties, is not neurotoxic or genotoxic, and is not a cardiac sensitizer. In developmental studies with the rat, the fetal effect of an increase in supernumerary ribs was observed only in conjunction with slight maternal toxicity. No information useful for time scaling across the AEGL exposure durations was available.

The AEGL-1 value is based on a subchronic study with the rat (Coombs et al. 1996a). In this study, groups of 20 male and female rats were exposed to concentrations up to 15,159 ppm for 6 h/day, 5 days/week for 13 weeks. This concentration was not neurotoxic. Reversible increases in weight of the liver, kidney, and spleen were observed, and these were considered a natural adaptation to chemical treatment. An interspecies uncertainty factor of 1 was applied because the concentration was basically a NOAEL, the exposures were repeated, and uptake is greater in the rodent than in primates (based on the higher respiratory rate and cardiac output of rodents compared with primates). Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied. A modifying factor of 2 was applied because human data are very limited and because some of the key studies used limited numbers of animals. The resultant value is 2,500 ppm. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. The presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Furthermore, the repeated number of the exposures in the key study supports the use of the same value across all time points. Therefore, the 2,500 ppm concentration is applicable for all AEGL-1 time points.

The AEGL-2 value is based on a 5-min no-adverse-effect exposure prior to a cardiac sensitization test with beagles (Kenny et al. 1996) and is supported by a 4-week repeat exposure study with the rat (Coombs et

al. 1996b). Six male beagles exposed to 48,900 ppm for 5 min prior to a cardiac sensitization test showed no response to exposure. Although the beagles did exhibit clinical signs following a challenge dose of epinephrine, there was no cardiac sensitization. The beagles fully recovered and were used in subsequent tests. One of two beagles exposed to the next highest concentration, 89,300 ppm for 5 min (prior to the cardiac sensitization test), became slightly agitated and exhibited tremors and stiff limbs. This response might impair the ability to escape. Therefore, according to the definition of the AEGL-2 in the Standing Operating Procedures for developing AEGLs (NRC 2001), the 48,900 ppm was considered a NOAEL. In a second study, groups of 10 male and female rats were exposed to concentrations up to 30,000 ppm for 6 h/day, 5 days/week for 4 weeks (Coombs et al. 1996b). At 30,000 ppm, the majority of rats exhibited reversible centrilobular hepatocyte hypertrophy which is a normal adaptive response to chemical treatment.

Although of short duration, the 5-min study with beagles, supported by the 4-week repeat study with rats, was used to derive the AEGL-2. Beagles were considerably more sensitive to the effects of HFE-7100 than rats. Both beagles and rats have higher respiratory rates and cardiac output than humans, resulting in greater chemical uptake. Therefore, an interspecies uncertainty factor of 1 was applied. Studies with rats, including neurotoxicity and developmental studies, failed to identify significant toxicological end points. HFE-7100 was not a cardiac sensitizer; therefore, heart patients should not be at added risk. An intraspecies uncertainty factor of 3 was considered sufficient to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resulting value is 8,200 ppm. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Furthermore, the presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. The repeat nature of the rat study also supports the use of a single value across the AEGL exposure durations. Therefore, the 8,200 ppm concentration is applicable for all AEGL-2 time points.

The AEGL-3 value is based on the same study with beagles (Kenny et al. 1996) and is supported by an acute inhalation study with the rat (3M Company 1995). One of two beagles inhaling 89,300 ppm for 5 min became slightly agitated, and showed clinical signs of tremors and stiffness of the limbs. The second beagle, administered a challenge dose

of adrenaline during a second 5-min exposure exhibited severe clinical signs including whole-body tremors. Although the 89,300 ppm exposure for 5 min was a clear NOAEL for death, the challenge dose of epinephrine to the second dog (during continuing exposure) with the resulting severe clinical signs is applicable to an emergency situation and can be considered life-threatening in susceptible individuals. However, in a 4-h study with rats inhaling 100,000 ppm, clinical signs were slight, consisting of slightly lowered respiration and sluggishness in one of three rats (3M Company 1995). Convulsions leading to death occurred only in rats inhaling 214,000 ppm for 40 min or more (Eger 1998).

The more conservative NOAEL for lethality in the study with beagles was used to develop AEGL-3 values. Beagles were considerably more sensitive to the effects of HFE-7100 than rats. Both beagles and rats have higher respiratory rates and cardiac output than humans, resulting in greater chemical uptake. Therefore, an interspecies uncertainty factor of 1 was applied. Studies with rats, including neurotoxicity and developmental studies, failed to identify significant toxicological end points. HFE-7100 was not a cardiac sensitizer; therefore, heart patients should not be at added risk. An intraspecies uncertainty factor of 3 was considered sufficient to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. Time scaling may not be relevant for anesthetics and halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Therefore, the resulting 15,000 ppm concentration is applicable for all AEGL-3 time points. The 89,300 ppm concentration may be a conservative estimate of the threshold for lethality as rats survived a 4-h exposure to 100,000 ppm (3M Company 1995) and the dose-response curve for convulsions and death (ED_{50} of 214,000 ppm) is predicted to be steep (Eger 1998).

The calculated values are listed in the Table 5-1.

1. INTRODUCTION

HFE-7100 is composed of a combination of methyl nonafluorobutyl and nonafluoroisobutyl ethers in ratios of 30-50 and 50-70%, respectively. Animal toxicity tests were generally performed using a 40:60

TABLE 5-1 Summary of AEGL Values for HFE-7100

Classification	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL–1 (Nondisabling)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	Reversible organ weight changes, repeated exposures, rat (Coombs et al. 1996a)
AEGL–2 (Disabling)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	NOAEL for clinical signs, dog (Kenny et al. 1996); NOAEL for clinical signs-repeat exposures, rat (Coombs et al. 1996b)
AEGL–3 (Lethal)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	Severe clinical signs, dog (Kenney et al. 1996); no deaths, rat (3M Company 1995)

mixture of the *n*-butyl and isobutyl isomers (AIHA 1999). HFE-7100 has been developed as a replacement for chlorofluorocarbons, hydrochlorofluorocarbons, hydrofluorocarbons and perfluorocarbons for use as a cleaning and rinsing agent, lubricant carrier, drying agent, specialty solvent, and heat transfer medium (AIHA 1999). The Environmental Environmental Protection (EPA) has listed 3M HFE-7100 as an acceptable substitute for ozone depleting substances in specific solvent cleaning and aerosol industry applications under its Significant New Alternatives Program. No information on the manufacturing process or production was located.

HFE-7100 is a highly volatile liquid with a slight ethereal odor. No information on the odor threshold was located. Chemical and physical data are listed in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. General Toxicity

No data on human toxicity were located. Air monitoring conducted by the 3M Company (1997) and reported by AIHA (1999) indicates that concentrations are generally less than 50 ppm near vapor degreasers where HFE-7100 was being used as a solvent. No adverse health effects were reported from workers engaged in this process.

2.2. Neurotoxicity

No information was located on neurotoxicity of HFE-7100 to humans.

2.3. Developmental/Reproductive Toxicity

No information was located on the developmental or reproductive toxicity of HFE-7100 to humans.

2.4. Genotoxicity

No information was located on the genotoxicity of HFE-7100 to humans.

2.5. Carcinogenicity

No information was located on the carcinogenicity of HFE-7100 to humans.

TABLE 5-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Methyl nonafluorobutyl ether: 1-methoxy-1,1,2,2,3,3,4,4,4-nonafluorobutane; 1-methoxyperfluorobutane; 1,1,1,2,2,3,3,4,4-nonafluoro-4-methoxybutane Methyl nonafluoroisobutyl ether: 1-methoxy-2-trifluoromethyl-1,1,2,3,3,3-hexafluoropropane; 1-methoxyperfluoroisobutane; 2-(difluoromethoxymethyl)-1,1,1,2,3,3,3-heptafluoropropane	3M Company 2000
Chemical formula	$C_5H_3F_9O$ Methyl nonafluorobutyl ether: CF_3-CF_2-CF_2-CF_2-O-CH_3 (31.0%) Methyl nonafluoroisobutyl ether: $(CF_3)_2$-CF-CF_2-O-CH_3 (68.7%)	AIHA 1999; Coombs et al. 1996b
Molecular weight	250	AIHA 1999
CAS Reg. No.	Methyl nonafluorobutyl ether: 163702-07-6 Methyl nonafluoroisobutyl ether: 163702-08-7	3M Company

(Continued)

TABLE 5-2 Continued

Parameter	Value	Reference
Physical state	Clear, colorless liquid	3M Company 2000
Solubility in water	<12 ppm	3M Company 2000
Oil/gas partition coefficient	9.66	Eger et al. 1999
Saline/gas partition coefficient	0.0050	Eger et al. 1999
Vapor pressure	202 mm Hg at 25°C 0.26 atmospheres	3M Company 2000 Eger et al. 1999
Saturated vapor pressure	2.24×10^5 ppm at 20°C	3M Company 2000
Vapor density (air = 1)	8.6	3M Company 2000
Flammable Limits LEL UEL	 None None	3M Company 2000
Specific gravity	1.5 g/mL	3M Company 2000
Melting point	−135°C	3M Company 2000
Boiling point	61°C	3M Company 2000
Conversion factors	1 ppm = 10.22 mg/m^3 1 mg/m^3 = 0.0978 ppm	AIHA 1999

2.6. Summary

HFE-7100 is a newly developed ether with a slight ethereal odor that is intended for use as a cleaning agent and speciality solvent. No information was located on toxicity, developmental or reproductive effects, genotoxicity, or carcinogenicity in humans. The only monitoring report indicates that workplace exposures were less than 50 ppm.

3. ANIMAL TOXICITY DATA

Orally, HFE-7100 is practically non-toxic. A dose of 5 g to 5 male and 5 female adult Sprague-Dawley rats produced no clinical signs (one animal exhibited soft stool on the day of treatment) and had no effect on mortality, morbidity, body weight, or gross pathology after 14 days (Hazleton Wisconsin, Inc. 1995a). Repeated (28-day) oral doses of 0, 8, 40, 200, or 1,000 mg/kg to male and female Sprague-Dawley rats produced irregular respiration and salivation at the high dose, but no deaths (Mitsubishi Chemical Safety Institute 1996a). Increased liver and thymus weights accompanied by cellular hypertrophy and increased blood albumin were observed, primarily in the 1,000 mg/kg/group. These effects were reversible during a 14-day recovery period. When tested on the skin or eyes of New Zealand white rabbits, HFE-7100 was minimally irritating to the skin (score of 0.7 out of 8 at the 4-h observation) and practically non-irritating to the eye (score or 2.0 out of 110 at the 1-h observation and 0 out of 110 at the 24-h observation) (Hazleton Wisconsin, Inc. 1995b; 1995c). HFE-7100 was not a dermal sensitizer when tested on the skin of guinea pigs (Hazleton Wisconsin, Inc. 1996a). When applied to the skin of rabbits for 5 days, absorption was minimal (Corning Hazleton 1996a).

3.1. Acute Lethality

The convulsive and anesthetic properties of HFE-7100 were studied using four adult male Sprague-Dawley rats (Eger 1998). The rats were placed in individual tubes within a larger flow-through chamber. Chamber atmospheres were monitored by gas chromatography. Chamber atmospheres were increased in steps beginning with 25-50% of the predicted minimum alveolar anesthetic concentration (MAC; calculated by

dividing two atm by the oil/gas partition coefficient) and continuing until the animals exhibited clonic convulsions. Animals were observed for 20 min at each concentration. HFE-7100 was not anesthetic, as defined by movement in response to a painful stimulus, at any partial pressure applied, up to 0.24-0.26 atm, the vapor pressure, nor did it decrease the requirement for anesthesia for a known anesthetic when given concurrently with that anesthetic. With increasing partial pressures, the rats became increasingly excited and at slightly more than 0.2 atm, 3 of 4 exhibited convulsions. The convulsive ED_{50} was 0.214 atm (214,000±1,000 ppm). Convulsions were associated with an increase in body temperature. The three rats that exhibited convulsions subsequently died. No exposure durations were provided, but the stepwise increments in concentration leading up to the convulsive concentration would indicate an exposure of at least 40 min.

3.2. Nonlethal Toxicity

3.2.1. Dogs

During cardiac sensitization studies, six beagles were exposed to 0, 10,000, 18,800, or 48,900 ppm for 5 min before administration of exogenous epinephrine. Two beagles were successfully exposed to 89,300 ppm for 5 min. No clinical signs were described at the lower concentrations. During the 5-min exposure to 89,300 ppm, one beagle became slightly agitated and exhibited signs of tremors and stiff limbs. Signs were not described in the second dog prior to administration of a challenge dose of epinephrine.

3.2.2. Rats

The remaining studies used the rat as the test species. Only one study with acute exposure was located. Additional studies with repeated and subchronic exposures are included in the following discussion.

Three male Sprague-Dawley rats were exposed in a 40 L flow-through chamber at a nominal concentration of 100,000 ppm which was regularly monitored (3M Company 1995). Oxygen concentration was maintained near 20%. The exposure period was 4 h. The animals were active near the start of exposure, although one animal appeared slightly

sluggish approximately 30 min into the exposure. At 3 h into the exposure, respirations ranged from 60-80/min which was described as slightly depressed. All animals survived the exposure and recovery period (undefined). Therefore, the 4-h LC_{50} is greater than 100,000 ppm. No further details were provided in this unpublished memo.

Groups of 5 male and 5 female Crl:CD BR Sprague-Dawley rats were exposed to 0 (air) or targeted concentrations of 1,500, 3,000, 9,500, or 30,000 ppm for 6 h/day, 5 days/week, for 4 weeks (Coombs et al. 1996b). Measured concentrations, analyzed by gas chromatography, were 1,489, 2,935, 9,283, and 28,881 ppm, respectively. The study generally followed EPA guidelines for subchronic studies in that body weight was monitored, blood was collected to monitor effects on hematology and clinical chemistry, and urine was collected for urinalysis. Following exposure, major organs were weighed and tissues were examined microscopically. There were no treatment-related clinical signs during the exposures and there were no toxicologically significant effects on body weight, food consumption, hematology parameters, or gross pathology. A liver weight increase in male rats in the 28,881 ppm group was accompanied by centrilobular hepatocyte hypertrophy in 3 of 5 males. Hepatocyte hypertrophy was observed in 4 of 5 females in the 28,881 group although liver weight was not affected. Hepatocyte hypertrophy was also observed in 1 of 5 males and 2 of 5 females in the 9,283 ppm group. Hepatocyte hypertrophy was generally scored as minimal. Focal necrosis was not observed. Changes in clinical chemistry parameters involved increased serum glucose and decreased serum cholesterol in males in the 28,881 ppm group. Palmitoyl CoA oxidase activity was non-significantly increased in male rats in the 28,881 ppm group. Urinary protein was increased in males in the 9,283 and 28,881 ppm groups, and urinary fluoride was increased in rats of both sexes in all but the 1,489 ppm group.

Groups of 10 young male and 10 young female Sprague-Dawley rats were exposed to target concentrations of 1,500, 4,500, 7,500, or 15,000 ppm for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1996a). Mean analyzed concentrations were 1,502, 4,550, 7,533, and 15,159 ppm, respectively. Isomer ratios by weight were stated as being 68.7% methyl nonafluoroisobutyl ether and 31.0% methyl nonafluorobutyl ether. The study generally followed EPA guidelines for subchronic studies in that clinical signs and body weight were monitored, blood was collected for hematology and clinical chemistry measurements, and urine was collected for urinalysis. Following exposure, a necropsy was per-

formed, major organs were weighed, and tissues and organs were examined microscopically. There were no treatment-related clinical signs or effects on body weight, food consumption, or hematology, clinical chemistry, or urine parameters (with the exception of a dose-related increase in urinary fluoride excretion). Liver, spleen, and kidney weights were minimally, but statistically significantly increased in males receiving 15,159 ppm. This effect was not evident in female rats. Microscopically, minimal to moderate centrilobular hepatocyte hypertrophy was observed in males (9/10) and females (6/10) that were exposed to 15,159 ppm. There were no increases in serum enzyme activities including alkaline phosphatase, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, gamma-glutamyl transferase, or creatinine phosphokinase, and focal necrosis of the liver was not observed. There were no treatment-related microscopic liver changes in the lower dose groups. Palmitoyl CoA activity was increased in male rats in the 15,159 ppm group, and there was evidence that HFE-7100 acted as a peroxisome proliferator in male rats, also at 15,159 ppm. There were no histological correlates for the minimal increases in kidney and spleen weights. In light of the lack of effect on relevant clinical chemistry and hematology parameters and histopathology, the increased organ weights are considered an adaptive response to chemical treatment.

3.3. Neurotoxicity

A functional observational battery (FOB) of tests (a neurobehavioral screening) composed of the following observations and tests were taken or administered in the 28-day and 13-week studies: observations of posture, salivation, vocalizing, tremors, grooming activity, arousal, rearing counts, bolus and urine count, and gait; reactions to approach, touch, noise, tail pinch, light (pupillary reaction); righting reflex; forelimb and hindlimb grip strength; footsplay; body temperature; and body weight. A FOB was administered to groups of five male and five female Sprague-Dawley rats following exposure to measured concentrations of 0, 1,489, 2,935, 9,283, or 28,881 ppm for 6 h/day, 5 days/week for 28 days (Coombs et al. 1996b). Compared with preexposure observations and results, there were no treatment-related clinical signs and no effects on behavior following these exposures.

A functional observational battery was also administered pretest and during weeks 4, 8, and 12 during exposure of groups of 10 male and

10 female Sprague-Dawley rats to measured concentrations of 1,502, 4,550, 7,533, or 15,159 ppm for 6 h/day, 5 days/week, for 13 weeks (Coombs et al. 1996a). There were no effects of treatment on activity, rearing, grip strength, hind limb splay, body temperature, or body weight. During weeks 8 and 12 there were slightly increased incidences of vocalizations in male rats in the 15,159 ppm group compared with the controls (controls, 0/10; 15,159 ppm, 4/10 [week 8] and 3/10 [week 12]). Soft stools were also observed in two males in this group during week 8. Hair loss was greater in females in the 15,159 ppm group during week 12 (7/10) than in the control group (2/10). According to the authors, these observations do not indicate a neurotoxic effect.

3.4. Cardiac Sensitization

Kenny et al. (1996) evaluated the cardiotoxicity of HFE-7100 in six male beagles according to the method of Reinhardt (1971). The dogs were restrained and the test material was administered via a face mask. Electrocardiograms were recorded during the exposures. Epinephrine (adrenaline) doses were individualized to each dog so that the response to epinephrine alone produced a clear but minimal effect on the electrocardiogram, ideally a few ectopic beats. Dogs were categorized as weak to strong responders depending on the dose of epinephrine (1-12 μg/kg) that elicited a baseline response. The 17-min exposure procedure consisted of exposure to air for 2 min followed by an epinephrine challenge, a 5-min recovery period, and a 10-min exposure to the test material (beginning at 7 min) with administration of a second epinephrine challenge at 5 min into the exposure, i.e., the epinephrine challenge was administered at 12 min followed by a 5-min observation period. A positive cardiac sensitization test was characterized by a burst of multifocal ventricular ectopic activity or ventricular fibrillation during exposure to HFE-7100. Each of the dogs was exposed to 0 (air only), 10,000, 18,800, or 48,900 ppm with at least a day of rest between exposures. Only one dog was successfully exposed and tested at 89,300 ppm as clinical signs were severe following the second challenge dose of epinephrine. None of the exposures produced cardiac effects in any of the dogs. However, concentration-related signs of exposure in response to the second challenge dose of epinephrine were observed, particularly at the 48,900 and 89,300 ppm concentrations (Table 5-3).

TABLE 5-3 Response of Dogs during a Cardiac Sensitization Test[a,b,c]

Concentration (ppm)	Response
10,000	Struggling and slight salivation (1 dog) negative for cardiac sensitization (6 dogs)
18,800	Licked lips when mask removed (3 dogs) salivation (2 dogs) forelimbs cold to touch (1 dog) negative for cardiac sensitization (6 dogs)
48,900	Agitation, restlessness (6 dogs) head and body tremors, arched back, rigid body (4 dogs) ears and neck cold to touch (1 dog) negative for cardiac sensitization (6 dogs)
89,300	Restlessness, forepaws and ears cold to touch, tremors, agitation, arched back, excessive salivation; cardiac sensitization not measured due to struggling (1 dog); additional dogs not tested

[a]Dogs received individualized epinephrine doses of 1-12 µg/kg.
[b]Six dogs tested at each concentration except at 89,300 ppm.
[c]Data from Kenny et al. 1996.

The cardiac sensitization test involves only a 10-min exposure because exposure duration is not relevant to eliciting an effect. Concentrations of halocarbons that do not produce a positive response in this short-term test generally do not produce the response when exposures are continued for 6 h (Reinhardt et al. 1971; NRC 1996).

3.5. Developmental/Reproductive Toxicity

In a range-finding study, groups of 10 time-mated Crl:CD BR VAF Plus Sprague-Dawley female rats were exposed to nominal concentrations of 0, 3,000, 9,500, or 30,000 ppm for 6 h/day on days 6-19 of gestation (Huntingdon Life Sciences 1996a). A reduction in body weight gain was observed in the 30,000 ppm group during the first 2 days of treatment. A recovery was apparent beginning on day 8 when body weight gain was similar to that of the controls. On day 20, dams were sacrificed, litter values were determined, and fetuses were examined for gross abnormalities. There were no treatment-related effects on the litters or on gross appearance of the fetuses. No histopathologic examinations

were conducted. This study was used to set exposure concentrations for further studies.

In a second study, groups of 25 pregnant Crl:CD BR VAF Plus (Sprague-Dawley) rats were exposed whole-body to 0 (air), 4,500, 7,500, or 15,000 ppm for 6 h/day, on days 6 through 19 of pregnancy (Huntingdon Life Sciences 1996b). Measured concentrations were 4,629, 7,538, and 15,076 ppm, respectively. Dams were monitored for clinical signs, body weight, and food and water consumption. On day 20 of pregnancy, dams were sacrificed and examined. The ovaries were checked for corpora lutea and the uteri were weighed and examined for number and distribution of young and number and distribution of embryofetal deaths, both early and late; individual fetuses were sexed and weighed. Half of the fetuses of each litter were examined for visceral malformations and half were examined for skeletal malformations. In addition to malformations, anomalies (minor frequently detected differences) and variants (alternative structures that regularly occur in a population) were scored.

In dams in the high-dose group there was a slight and gradual reduction in mean body weight compared with the control group. Final mean body weight and body weight gain in the high-dose group were lower than the mean control weight by 2 and 5%, respectively. Food consumption was also slightly reduced in the high-dose dams. These effects were not present in the lower dose groups. Live young were produced by 24, 24, 22, and 24 dams in the control, low, mid, and high-dose groups, respectively. The total number of fetuses in the control through high-dose groups were 281, 307, 268, and 291, respectively. There were no differences among the groups in pre-implantation losses, implantation rate, or incidence and distribution of embryofetal deaths. Total litter weights were similar, but the mean fetal weight was slightly lower (by 4%) in the high-dose group compared with the control group. This effect was attributed to the increased litter size in the high-dose group. There were no dose or treatment-related visceral or skeletal malformations. Incomplete ossification of the skeleton was higher in the control group fetuses (both by litter and number of fetuses) than in any treatment group. This effect resulted in a higher incidence of skeletal anomalies in the control group than in the treated groups. The incidence of lumbar ribs, a commonly observed skeletal variant, was higher in the high-dose group than in the control group. The percent of fetuses with 14 ribs in the control through high-dose groups were 10.5, 13.5, 17.6, and 22.5. Litter incidences for 14 ribs in the control through dose group were 7/24, 12/24, 12/22, and 13/24, respectively. An associated finding in the high-dose

group was two fetuses in two litters with one extra thoracolumbar vertebra. In the 7,538 ppm group, a single fetus was observed with a complete lumbar rib. Visceral anomalies included dilated renal pelvis/ureter in the high-dose group (seven fetuses in five litters and none in the control group). Dilated renal pelvis/ureter is a common finding in control fetuses and is considered an anomaly rather than a malformation. The study authors note the possible effect of non-specific maternal stress on the formation of supernumerary lumbar ribs in rats. According to the authors the increased incidences of supernumerary ribs in test animals is equivocal.

The relationship of exposure concentration to the presence of supernumerary ribs was further studied by exposing pregnant rats to a higher concentration. Groups of 25 time-mated Crl:CD BR VAF Plus Sprague-Dawley female rats were exposed to nominal concentrations of 0 or 30,000 ppm on days 6-19 of gestation (Huntingdon Life Sciences 1998). At 30,000 ppm, dams exhibited a reduction in weight gain between days 10 and 12 of pregnancy compared with the control group, but recovery occurred by day 20. The number of supernumerary ribs was increased in fetuses in the 30,000 ppm group (25.8%) compared with the control group (15.1%). No other anomalies were observed.

3.6. Genotoxicity

Three mutagenicity/genotoxicity studies were located. HFE-7100 was not mutagenic to several strains of *Salmonella typhimurium* in a test conducted with and without metabolic activation (Mitsubishi Chemical Safety Institute 1996b). HFE-7100 tested negative in a chromosomal aberration assay in cultured Chinese hamster lung cells (Mitsubishi Chemical Safety Institute 1996c). In vivo, HFE-7100 was negative in a mouse micronucleus assay at dose levels up to 5,000 mg/kg (Huntingdon Life Sciences 1996c).

3.7. Chronic Toxicity/Carcinogenicity

No chronic toxicity or carcinogenicity studies with HFE-7100 were located. No tumors or biochemical changes indicative of carcinogenicity were apparent in a subchronic study with rats (Coombs et al. 1996a).

3.8. Summary

The animal inhalation data involving HFE-7100 are summarized in Table 5-4. Only at concentrations high enough to involve some oxygen deprivation are toxic effects observed. In a study with rats, the EC_{50} for convulsions was 214,000 ppm and 3 of 4 rats died following the exposure (Eger 1998). However, no rats died following a 4-h exposure to 100,000 ppm (3M Company 1995). Prior to administration of the challenge dose of epinephrine in a cardiac sensitization test, no clinical signs were described in dogs inhaling concentrations up to 48,900 ppm for 5 min. Signs of tremors and stiff limbs were observed in one of two dogs inhaling 89,300 ppm for 5 min. Following the second challenge dose of epinephrine during a cardiac sensitization test, one dog exposed to 89,300 ppm for at least 5 min exhibited severe clinical signs including restlessness, cold extremities, limb rigidity, head and whole-body tremors, head shaking, arched back, agitation, and salivation (Kenny et al. 1996). Tests for cardiac sensitization with dogs were negative.

Following repeat exposures to concentrations up to 30,000 ppm and subchronic exposures to concentrations up to 15,159 ppm, HFE-7100 had no effect on neurobehavioral parameters in rats (Coombs et al. 1996a; 1996b). These repeated dose studies resulted in reversible organ weight changes, primarily an increase in liver weight, and were accompanied by hepatocyte hypertrophy. These effects are considered an adaptative response to chemical exposure and are not considered adverse (the reversibility of both the hepatocyte hypertrophy and associated liver weight increase in rats was shown in the oral study by Mitsubishi Chemical Safety Institute 1996a). HFE-7100 was not teratogenic in a series of studies in which dams were administered concentrations of approximately 5,000 to 30,000 ppm during gestation days 6 to 19 (Huntingdon Life Sciences 1996a; 1996b; 1998).

Data on developmental toxicity were limited to studies with the rat. The data indicated that concentrations up to 30,000 ppm were slightly stressful to pregnant dams as indicated by slightly lower weight gain. The primary finding in fetuses was supernumerary ribs. Although incidences were increased in the treated group when both fetuses and litters were considered, there was no clear dose-response, especially considering the more than 6-fold difference in concentrations between the low and high concentrations. There was no indication of treatment-related growth retardation which is usually observed as delayed ossifica-

TABLE 5-4 Summary of Animal Toxicity Data for HFE-7100

Concentration (ppm)	Exposure Duration	Species (number)	Effect	Reference
214,000 ± 1,000	—	Rat (4)	Convulsions, death (3 of 4 rats); not anesthetic	Eger 1998; Eger et al. 1999
100,000	4 h	Rat (3)	No deaths; few signs	3M Company 1995
89,300	5 min	Dog (1)	Slightly agitated, tremors, stiff limbs (1 dog tested)[a]	Kenny et al. 1996
48,900 18,800 10,000	5 min 5 min 5 min	Dog (6) Dog (6) Dog (6)	No signs described No signs described No signs described	
30,000 15,056 7,538 4,629	Gestation days 6-19, 6 h/day	Rat (groups of 25)	Slight stress of dams at two higher Concentrations; no visceral or skeletal malformations	Huntingdon Life Sciences 1996b; 1998
28,881 9,283 2,935 1,489	4 weeks: 6 h/day, 5 days/week	Rat (groups of 10)	No clinical signs at any exposure; minimal, reversible hepatocellular hypertrophy in some animals at two higher exposures; no toxicologically significant	Coombs et al. 1996b

			effects; not neurotoxic	
15,159 7,533 4,550 1,502	13 weeks: 6 h/day, 5 days/week	Rat (groups of 20)	No clinical signs at any exposure; no toxicologically significant effects; reversible hepatocyte hypertrophy at high concentration; not neurotoxic	Coombs et al. 1996a

[a]The described signs were observed prior to administration of the second challenge dose of epinephrine.

tion and reduced body weight. Thus, the increased incidence of supernumerary ribs in the treated rats is of questionable biological significance. It should be noted that the historical control data on Sprague Dawley rats shows mean fetal and litter incidences of bilateral supernumerary ribs of 1% (maximum, 16%) and 5% (maximum, 55%), respectively (Charles River Laboratories 1996). From this study there was no indication that the fetus is more sensitive to HFE-7100 than the dam as fetal effects were observed only in conjunction with slight maternal toxicity.

Mutagenicity and genotoxicity assays with HFE-7100 were negative. No chronic studies or studies addressing carcinogenicity were located. Orally, HFE-7100 is considered practically nontoxic (LD_{50} > 5 g/kg).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Groups of 4 male and 4 female rabbits were administered single intravenous injections of 0, 1, 2, 5, or 10 mg/kg HFE-7100 in DMSO (Corning Hazleton, Inc. 1996b). Blood samples were collected prior to exposure, at 4, 8, 12, 24, and 48 h post-exposure, and on days 8 and 16 post-exposure. Heptafluorobutyric acid was detected in the serum from 4 to 48 h post-exposure, indicating cleavage of the ether group. No quantitative data were provided.

Increased urinary inorganic fluoride in Sprague-Dawley rats treated subchronically with HFE-7100 at concentrations of 0, 1,500, 4,500, 7,500, and 15,000 ppm (Coombs et al. 1996a) indicates that additional biotransformation of the parent molecule(s) takes place with release of free inorganic fluoride and its subsequent elimination by the kidneys. Urinary fluoride concentrations during week 13 of the study were 1.5, 5.1, 12.8, 21.5, and 39.8 µg/mL for males in the control through high-dose group and 1.5, 3.3, 9.6, 13.5, and 22.5 µg/mL for females in the control through high-dose group. Using a polynomial regression model (r^2 = 0.82), the AIHA (1999) calculated that an HFE-7100 concentration of 2,400 ppm corresponded to a urinary fluoride level of 5 mg/L. As noted by AIHA (1999), this compares well with the ACGIH (2002) end of shift biological exposure index for urinary fluoride of 12 mg/L.

4.2. Mechanism of Toxicity

No information on the mechanism of toxicity was located. HFE-7100 did not have anesthetic properties up to its known vapor pressure (Eger 1998). HFE-7100 is not an anesthetic but a "nonimmobilizer" (see Section 4.3). Nonimmobilizers may produce clonic convulsions by two interrelated mechanisms: one correlates with lipophilicity (nonpolarity), implying an action in a nonpolar phase, and the second correlates with an action on the neurotransmitter GABA (γ-aminobutyric acid), perhaps by modifying the action of GABA on $GABA_A$ receptors. Anesthetics generally have an affinity for both polar and nonpolar phases, whereas, HFE-7100 has a low affinity for the polar phase.

4.3. Structure Activity Relationships

HFE-7100 is a hydrofluoroether. Fluorine forms the strongest single bond to carbon encountered in organic chemistry. The "per"fluoroethers or highly fluorinated ethers are poorly water soluble.

The convulsive property of volatile polyhalogenated compounds generally correlates with lipophilicity. Of 42 volatile compounds studied in rats, the convulsive ED_{50} of 80% of the compounds (including HFE-7100) correlated with lipophilicity ($r^2 = 0.99$). The oil/gas partition coefficient for HFE-7100 of 9.66 is low for an anesthetic, predicting an anesthetizing concentration of perhaps 10-20% of an atmosphere (22,400-44,800 ppm). However, HFE-7100 is not an anesthetic compound but a "nonimmobilizer." Nonimmobilizers are perfluorinated compounds that deviate from the Meyer-Overton hypothesis, i.e., their MAC × oil/gas partition coefficients exceed those of conventional inhaled anesthetics of 1.8 atm. Nonimmobilizers are compounds whose lipophilicity predicts an anesthetic effect but have no such effect, either when given alone or when added to a known anesthetic. The butanes will be taken up, but primarily in nonpolar phases. They will be eliminated very rapidly, with one pass through the lungs. This elimination is orders of magnitude more rapid than the elimination of a typical ether such as diethyl ether (Eger 2002; see also Koblin et al. 1994).

Similar to HFE-7100, the hydrofluorocarbon, 1,1,1,2-tetrafluoroethane (HFC-134a) and the hydrochlorofluorocarbon 1,1-dichloro-1-fluoroethane (HCFC-141b) are low in toxicity (NRC 2002). These chemicals also rapidly reach equilibrium in the blood. However, in con-

trast to HFE-7100, both of these chemicals exhibit anesthetic properties. Although HFE-7100 is an ether, the perfluoro group limits its solubility in biological fluids. Storage in adipose tissue is expected to be minimal based on its poor solubility in biological fluids and the elimination of the heptafluorobutyric acid metabolite within 48 h of an intravenous dose (Corning Hazleton, Inc. 1996b).

4.4. Other Relevant Information

4.4.1. Species Variability

Few data on different species were available. Based on clinical signs observed during exposure to high concentrations, 89,300-100,000 ppm, the dog appears to be more susceptible to HFE-7100 toxicity than the rat (Kenny et al. 1996; 3M Company 1995).

4.4.2. Susceptible Populations

No information on susceptible populations was located. In studies of a hydrofluorocarbon (HFC-134a) and a hydrochlorofluorocarbon (HCFC-141b), asthmatics were not identified as a susceptible population; HFC-134a is inert and has been used as a carrier in inhalers for asthmatic individuals. HFE-7100 also appears to be practically nontoxic. It is not a cardiac sensitizer. Therefore, neither asthmatics nor individuals with heart problems would be a particularly susceptible population. In the developmental studies with the rat, the pregnant dams and fetuses represent potentially susceptible populations. There were no adverse effects on either population.

4.4.3. Concentration-Exposure Duration Relationship

No information on the concentration-exposure relationship for a single end point was located. When considering the cardiac sensitization test with beagles, the National Research Council (Bakshi 1998) states that, “Because blood concentrations of halogenated hydrocarbons are not likely to increase when exposure time is increased beyond 5-10 min, the NOAEL identified for cardiac sensitization following a 10-min exposure

can be used without time extrapolation to set a 1-h EEGL." The rapid attainment of equilibrium in the blood reasonably holds true for halogenated hydrocarbons that are not cardiac sensitizers.

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues were apparent.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No information on toxicity to humans was located.

5.2. Summary of Animal Data Relevant to AEGL-1

HFE-7100 is of low toxicity to rats and dogs. No acute studies with end points relevant to deriving AEGL-1 values were located. In the absence of acute studies, the 13-week repeated dose study with the rat (Coombs et al. 1996a) can be considered for development of AEGL-1 values. In this study, rats were exposed to concentrations up to 15,159 ppm for 6 h/day, 5 days/week for 13 weeks. Increased but reversible organ weight changes were attributed to the repeated nature of the exposures and are not predicted to occur following a single exposure. Except for hepatocyte hypertrophy, which is reversible, there were no histological correlates. There were no neurotoxic signs. The 15,159 ppm concentration in this repeated dose study can be considered a no-observed-effect-level (NOAEL) according to the definition of the AEGL-1, i.e., transient, asymptomatic effects.

5.3. Derivation of AEGL-1

The repeated exposure of the rat to 15,159 ppm (Coombs et al. 1996a) was used as the basis for development of AEGL-1 values. Because the concentration was basically a NOAEL, the exposures were repeated, and initial uptake would be more rapid in rodents than in pri-

mates (based on the higher respiratory rate and cardiac output of rodents compared with primates, equilibrium would be reached more rapidly in rodents), an interspecies uncertainty factor of 1 was applied. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resultant value is 2,500 ppm. Time scaling may not be relevant for anesthetics and halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased (NRC 1996). The presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Furthermore, the repeated nature of the exposures in the key study support the use of the same value across all time points. Therefore, the 2,500 ppm concentration is applicable for all AEGL-1 time points. Values appear in Table 5-5.

It should be noted that if the NOAEL for tremors in dogs (see AEGL-2 derivation below) were used as the basis for the AEGL-1 with application of interspecies and intraspecies uncertainty factors of 3 each and a modifying factor of 2, the same AEGL-1 value, 2,500 ppm, would be derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No information on toxicity to humans was located.

6.2. Summary of Animal Data Relevant to AEGL-2

Several studies can be considered appropriate for derivation of AEGL-2 values. In the first study, six beagles were exposed to 48,900

TABLE 5-5 AEGL-1 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)

ppm for 10 min. No clinical signs were described during the 5-min exposure prior to the second challenge dose of epinephrine. Clinical signs were observed during the second 5 min (of the 10-min exposure) following a challenge dose of epinephrine (Kenny et al. 1996). Therefore, 48,900 ppm for 5 min was a NOAEL for clinical signs in the absence of exogenous epinephrine. HFE-7100 was not a cardiac sensitizer at this concentration or at the higher concentration of 89,300 ppm.

A study with the rat used repeated exposures (Coombs et al. 1996b). Exposure to the highest concentration, 30,000 ppm for 4 weeks, resulted in only hepatocyte hypertrophy, a reversible effect when exposure is discontinued. This concentration was not neurotoxic as functional observational battery observations were negative. In a developmental study, exposure of pregnant rats to 30,000 ppm did not result in severe adverse effects to either the dams or fetuses.

6.3. Derivation of AEGL-2

The exposure of beagles to 48,900 ppm was chosen as the basis for the AEGL-2. No clinical signs were described during the 5-min exposure prior to the challenge dose of epinephrine. The NOAEL of 48,900 ppm was chosen as the basis for the AEGL-2 because at the next highest exposure, 89,300 ppm, the severe clinical signs of agitation, tremors, and stiff limbs might impair the ability to escape. An interspecies uncertainty factor of 1 was applied to the 48,900 ppm for several reasons: when considering clinical signs, the dog was shown to be more sensitive than the rat, and the respiration rate of dogs and rodents is greater than that of humans, resulting in greater uptake. Although exposures were at a lower concentration, the no-effect concentrations of 30,000 ppm in well-conducted repeat exposure and developmental studies support the interspecies uncertainty factor of 1. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Furthermore, the chemical is poorly soluble in biological fluids. Therefore, an intraspecies uncertainty factor of 3 was applied to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resulting value is 8,200 ppm.

Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do

not greatly increase as exposure duration is increased (NRC 1996). Furthermore, the presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Therefore, the 8,200 ppm concentration is applicable for all AEGL-2 time points. The use of the same value across all exposure durations is supported by the study in which rats were exposed to concentrations up to 30,000 ppm for 6 h/day, 5 days/week for four weeks. These rats exhibited reversible liver hypertrophy which is attributed to the repeated nature of the exposures (Coombs et al. 1996b). The use of repeated exposures in this study supports using a single value across the AEGL-2 timepoints. Values appear in Table 5-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were located.

7.2. Summary of Animal Data Relevant to AEGL-3

In a study with rats, the EC_{50} for convulsions was 214,000 ppm and 3 of 4 rats died following the exposure (Eger 1998). However, no rats died following a 4-h exposure to 100,000 ppm (3M Company 1995). Prior to the second challenge dose of epinephrine during a cardiac sensitization test, one of two dogs exposed to 89,300 ppm exhibited severe clinical signs including agitation, tremors, and stiff limbs (Kenny et al. 1996). The second dog survived the second challenge dose of epinephrine but exhibited extremely severe clinical signs.

TABLE 5-6 AEGL-2 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)

7.3. Derivation of AEGL-3

Taken together, the animal data indicate that the threshold for lethality in both the rat and dog lies above 89,300 ppm. Because the data are insufficient for calculating the exact threshold for lethality in either species, the 5-min exposure of the dog to 89,000 ppm was used as the basis for the AEGL-2 values. Although the tremors in dogs are rapidly reversible and do not cause lasting effects, they may have a severe effect on populations such as patients with heart disease. An interspecies uncertainty factor of 1 was applied to the 48,900 ppm for several reasons: when considering clinical signs, the dog was shown to be more sensitive than the rat, and the respiration rate of dogs and rodents is greater than that of humans, resulting in greater uptake. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Therefore, the resulting 15,000 ppm concentration is applicable for all AEGL-3 time points. The 89,300 ppm concentration may be a conservative estimate of the threshold for lethality as rats survived a 4-h exposure to 100,000 ppm (3M Company 1995). Application of the same uncertainty and modifying factors to the 100,000 ppm concentration results in a slightly higher value, 17,000 ppm. Values appear in Table 5-7.

The 15,000 ppm concentration is supported by the repeated exposure of pregnant rats to 30,000 ppm (Huntingdon Life Sciences 1998). No adverse effects other than a transient lower weight gain were observed in dams exposed from days 6 through 19 of gestation. Pregnant rats represent a susceptible animal population. Furthermore, humans have a much lower respiratory rate and cardiac output than rodents.

TABLE 5-7 AEGL-3 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)

These are the two primary determinants of systemic uptake of volatile chemicals. Therefore, at similar concentrations, rodents will absorb substantially more of a chemical than primates.

The use of the 5-min value for all time periods is supported by fact that the exposures were repeated in the study with the rat above, a conservative approach to developing AEGL values was used, and there were no deaths in rats exposed to 100,000 ppm for 4 h (3M Company 1995). The only observed adverse effect in the latter study was mild—a slightly lower respiratory rate.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values and their relationship to each other are summarized in Table 5-8.

8.2. Comparison with Other Standards and Guidelines

HFE-7100 is a newly developed chemical and only a Workplace Environmental Exposure Level (WEEL) has been developed. The WEEL for an 8-h workday is 750 ppm (AIHA 1999). The WEEL was based on the NOEL of 7,500 ppm in the 90-day toxicity study with rats (Coombs et al. 1996a).

8.3. Data Adequacy and Research Needs

Human data are lacking. Recent animal studies were well conducted and addressed multiple end points; however several of the key studies used limited numbers of animals.

TABLE 5-8 Summary of AEGL Values (ppm)

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	2,500	2,500	2,500	2,500	2,500

AEGL-2 (Disabling)	8,200	8,200	8,200	8,200	8,200
AEGL-3 (Lethal)	15,000	15,000	15,000	15,000	15,000

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APPENDIX A

ACUTE EXPOSURE GUIDELINE LEVELS FOR HFE-7100 (CAS Reg. No. 163702-07-6 and 163702-08-7)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
2,500 ppm	2,500 ppm	2,500 ppm	2,500 ppm	2,500 ppm

Key Reference: Coombs, D.W., C.K. Shepherd, M. Bannerman, C.J. Hardy, D. Cook, M. Hall and G.F. Healy. 1996a. T-6334: 13 Week repeat dose inhalation toxicity study in rats. MIN 196/961181, Huntingdon Life Sciences, Huntingdon, Cambridgeshire, England.

Test Species/Strain/Number: Rats/Sprague-Dawley/20 males and 20 females.

Exposure Route/Concentrations/Durations: Inhalation: 1,502, 4,550, 7,533, 15,159 ppm, 6 h/day, 5 days/week for 13 weeks.

Effects:
1,502, 4,550, 7,533 ppm - no effects
15,159 ppm - reversible liver weight increase, minimal organ weight changes.

End point/Concentration/Rationale: Reversible organ weight changes/15,159 ppm/no adverse effect with repeated exposures (changes attributed to repeat exposures).

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, uptake would be similar in primates and rodents, although based on higher respiratory rates and cardiac output, equilibrium would be reached more rapidly in rodents than primates.
Intraspecies: 3, no significant toxicological end points identified; poor solubility in biological fluids.

Modifying Factor: 2, limited data on humans; limited number of animals in several studies.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: Repeated nature of the exposures allows use of a single value across all timepoints.

Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies, but minimal human data and limited number of animals in several studies.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
8,200 ppm	8,200 ppm	8,200 ppm	8,200 ppm	8,200 ppm

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited, Huntingdon, Cambridgeshire, England.
Support: Coombs, D.W., C.K. Shepherd, M. Bannerman, C.J., Hardy, D. Crook, M. Hall, E.W. Hughes, and C. Gopinath. 1996b. T-6334: 28-Day repeat dose inhalation toxicity study in rats. MIN 181/952688, Huntingdon Life Sciences, Huntingdon, Cambridgeshire, England.

Test Species/Strain/Number: Dog/beagle/6 (Kenny et al. 1996).
Rat/Sprague-Dawley/10 (Coombs et al. 1996b).

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,000, 48,900, and 89,300 ppm/5 min prior to cardiac sensitization test (Kenny et al. 1996).
Inhalation/0, 1,500, 3,000, 9,500, or 30,000 ppm for 6 h/d, 5 d/wk, for 4 wk (Coombs et al. 1996b).

Effects:
Kenny et al. 1996:
10,000 ppm: no effects
18,800 ppm: minimal effects
48,900 ppm: no clinical signs prior to administration of epinephrine; signs of stress following second dose of epinephrine (restlessness, trembling, limb rigidity).
89,300 ppm: severe signs of stress (salivation, tremors, limb rigidity)
All dogs recovered; not a cardiac sensitizer when concurrently injected with epinephrine.
Coombs et al. 1996b:
No clinical signs at any concentration.

End point/Concentration/Rationale: No signs of stress in dogs; not a cardiac sensitizer, 48,900 ppm

(Continued)

AEGL-2 VALUES Continued

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, both beagles and rats have higher respiratory rates and cardiac output than humans.
Intraspecies: 3, no significant toxicological end points identified in other studies; poor solubility in biological fluids for all species.

Modifying Factor: 2, limited data on humans, limited number of animals in several studies.

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: Not applied; low solubility of test compound in blood, rapidly reaches equilibrium; cardiac response does not change when chemical is administered for hours.

Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies. Limited human data; limited number of animals in some key studies.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
15,000 ppm	15,000 ppm	15,000 ppm	15,000 ppm	15,000 ppm

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited, Huntingdon, Cambridgeshire, England.
Support: 3M Company. 1995. Acute inhalation toxicity for HFE-7100 in the rat. Unpublished memo, 3M Company, Toxicology Services, 3M Center, St. Paul, MN.

Test Species/Strain/Number: Dog/beagle/6 (only 1 of 2 dogs observed 89,300 ppm) (Kenny et al. 1996).
Rat/Sprague-Dawley/3 (3M Company 1995).

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,800, 48,900, and 89,300 ppm/5 min (Kenny et al. 1996).
Inhalation/100,000 ppm/4 h (3M Company 1995).

Effects:
Kenny et al. 1996.
10,000 ppm: no clinical signs.
18,800 ppm: no clinical signs.
48,900 ppm: no clinical signs prior to administration of epinephrine
89,300 ppm: severe clinical signs.

3M Company 1995. 100,000 ppm for 4 h: no deaths.
End point/Concentration/Rationale: Severe clinical signs/89,300 ppm/considered lethal threshold due to severity of signs. Supported by no deaths in rats at 100,000 ppm (3M Company 1995).
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1—respiratory rate and cardiac output higher in beagles and rats than in humans. Intraspecies: 3—no significant toxicological end points identified in other studies; poor solubility in biological fluids for all species.
Modifying Factor: 2—limited data on humans; limited number of animals in several studies.
Animal to Human Dosimetric Adjustment: Not applied.
Time Scaling: Not applied; low solubility of test compound in blood, rapidly reaches equilibrium; cardiac response does not change when chemical is administered for hours.
Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies. Limited human studies; limited number of animals in this and several support studies. The 89,300 ppm may be a conservative estimate of a lethal concentration as no rats died after a 4-h exposure to 100,000 ppm.

6

Tetranitromethane[1]

Acute Exposure Guideline Levels

SUMMARY

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 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory) and National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member Kyle Blackman (Chemical Reviewer). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

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, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

EXECUTIVE SUMMARY

Tetranitromethane (TNM) is a highly explosive chemical used as an oxidizer in rocket propellants, to increase the cetane number of diesel fuels, and as a reagent to detect double bonds in organic molecules. TNM is formed as an impurity during the manufacture of trinitrotoluene (TNT). Inhaled TNM caused respiratory and ocular irritation in humans and animals, and lung tumors in rats and mice.

AEGL-1 values were not developed due to insufficient data. No studies were located with end points clearly within the scope of AEGL-1.

AEGL-2 values were derived from a 4-h rat LC_{50} study (Kinkead et al. 1977), in which rats exposed to 10 ppm (lowest concentration tested) had mild lung congestion whereas 3/10 died with lung lesions at the next higher concentration tested of 15 ppm. Because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 was applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation. Scaling across time was performed using the exponential equation $C^n \times t = k$, which has been shown to describe the concentration-exposure time relationship for many irritant and systemically acting vapors and gases, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable to derive n empirically for TNM, and $n = 3$ and $n = 1$ were used to extrapolate to <4 h and >4 h, respectively, except that the 30-min value was adopted as the 10-min value, to provide AEGL values protective of human health (NRC 2001). A total uncertainty factor of 10 was used: 3 for interspecies extrapolation because the key study tested the most sensitive species, and 3 to account for sensitive humans because mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.

AEGL-3 values were derived from the same 4-h rat LC_{50} study as the AEGL-2 values (Kinkead et al. 1977). The point of departure for AEGL-3 was the calculated lethality $BMDL_{05}$ of 11 ppm, which is consistent with the empirical lethality NOEL of 10 ppm in the key study and in a repeat-exposure study with rats and mice (6 h/day for 14 days; NTP 1990). Scaling across time was performed as for the AEGL-2, i.e., using $C^n \times t = k$, where $n = 3$ or $n = 1$. A total uncertainty factor of 10 was applied: 3 for interspecies extrapolation (key study tested the most sensitive species), and 3 for human variability (NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans).

A cancer inhalation slope factor was derived for TNM and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure, as shown in Appendix B. TNM concentrations associated with a 10^{-4} excess cancer risk were 2.5 to 10-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were considered to be more appropriate for AEGL-2 derivation because (1) they appeared to be the more sensitive end points, (2) AEGL values are

applicable to rare events or single, once-in-a-lifetime exposures, and the data indicate that TNM neoplasms resulted from chronic exposure, and (3) a direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in methodology used to obtain these numbers.

The calculated values are listed in the Table 6-1.

1. INTRODUCTION

Tetranitromethane (TNM) is a highly explosive liquid not known to occur naturally. It is prepared by the nitration of acetic anhydride with anhydrous nitric acid (Budavari et al. 1996; IARC 1996). TNM is also formed as an impurity during the manufacture of TNT (trinitrotoluene) and up to 0.12% may be present in crude TNT (Sievers et al. 1947). TNM is used as an oxidizer in rocket propellants, to increase the cetane number of diesel fuels, as a reagent to detect double bonds in organic molecules, and for the nitration of tyrosine in proteins and peptides (Budavari et al. 1996; ACGIH 1996). HSDB (2005a) lists only one current U.S. producer of TNM, although the amount produced was not available. U.S. production of TNM was reported to be >1,000 pounds in 1977 (HSDB 2005a).

TABLE 6-1 Summary of AEGL Values for Tetranitromethane (TNM)

Level	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL-1[a] (Nondisabling)	Not recommended due to insufficient data.					
AEGL-2 (Disabling)	0.66 ppm (5.3 mg/m^3)	0.66 ppm (5.3 mg/m^3)	0.52 ppm (4.2 mg/m^3)	0.33 ppm (2.6 mg/m^3)	0.17 ppm (1.4 mg/m^3)	Mild reversible lung irritation in rats (Kinkead et al. 1977).
AEGL-3 (Lethal)	2.2 ppm (18 mg/m^3)	2.2 ppm (18 mg/m^3)	1.7 ppm (14 mg/m^3)	1.1 ppm (8.8 mg/m^3)	0.55 ppm (4.4 mg/m^3)	NOEL for lethality in rats (Kinkead et al. 1977).

[a]A value for the human odor threshold was not located.

In humans, exposure to impure TNM has been reported to cause irritation of the eyes, nose, throat, dizziness, chest pain, dyspnea, methemoglobinuria, and cyanosis (Budavari et al. 1996). In animals, TNM caused respiratory and eye irritation and lung vascular congestion, pulmonary edema, bronchopneumonia, and lung tumors in rats and mice (Kinkead et al. 1977; NTP 1990). The NTP (2002) *Report on Carcinogens, Tenth Edition* states that TNM is "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals." The ACGIH places TNM in carcinogenicity class A3, i.e. a "confirmed animal carcinogen with unknown relevance to humans" (ACGIH 2004). IARC considers TNM to be "possibly carcinogenic to humans" and places it in group 2B, based on sufficient evidence in experimental animals and inadequate evidence in humans (IARC 1996). A carcinogenicity risk assessment of TNM is currently (July 2005) not listed on the Environmental Protection Agency (EPA) online IRIS database. Chemical and physical properties of TNM are listed in Table 6-2.

TABLE 6-2 Physical and Chemical Data of TNM

Parameter	Value	Reference
Synonyms	TNM; NCI-C55947	HSDB 2005a
Chemical formula	$C(NO_2)_4$	Budavari et al. 1996
Molecular weight	196.03	Budavari et al. 1996
CAS Registry Number	509-14-8	Verschueren 1996
Physical state	Liquid	Budavari et al. 1996
Solubility in water	Insoluble (soluble in alcohol, ether)	Budavari et al. 1996
Vapor pressure	13 mm Hg at 25°C	Verschueren 1996
Vapor density (air = 1)	6.8; 0.8	Verschueren 1996; HSDB 2005a
Liquid density (water = 1)	1.65 at 13/4°C	Verschueren 1996
Melting point	13.8°C	Budavari et al. 1996
Boiling point	126°C at 760 mm	Budavari et al. 1996
Flammability/ explosive limits	Limits not found; combustible liquid, difficult to ignite	NIOSH 2005a
Conversion factors	1 mg/m^3 = 0.125 ppm; 1 ppm = 8.02 mg/m^3	ACGIH 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Koelsch (1917) described three cases of occupational exposure to high, undefined concentrations of TNM (fumes evolved during TNT production) in one plant; two of the exposures proved fatal. A man who had worked for 14 days with impure TNT containing TNM developed severe chest pains during the night, and the next day at work had respiratory distress, chest tightness, and foamy sputum. The following day he died of pulmonary edema and had methemoglobinemia. A second worker in the same plant developed marked respiratory tract irritation after 14 days of exposure and subsequently developed fatal pneumonia. In the third case, a female worker inhaled a large amount of TNM and ran out of the room, fell unconscious, and was revived several hours later after treatment with oxygen and skin stimulation. The next day, recovery was almost complete.

2.2. Nonlethal Toxicity

Workers exposed to undefined concentrations of TNM that were emitted as fumes from crude TNT complained of nasal irritation, burning of the eyes, dyspnea, expectoration, coughing, chest tightness, and dizziness, with continued exposure leading to drowsiness, headache, anemia, marked cyanosis, respiratory distress, and bradycardia (Sievers et al. 1947).

A survey of workers exposed to unknown concentrations of TNM found it was irritating to the mucous tissue of the eyes, nose, and respiratory passages, but was seldom irritating to the skin (Hager 1949). Symptoms from acute exposure included salivation and upper respiratory passage irritation, whereas prolonged exposure resulted in headaches, weariness, sleepiness, slowed pulse, "formation of hemoglobin (not further details provided)", disturbance of internal respiration, and effects (not specified) on the CNS and heart.

The AIHA (1964), in its recommendation for industrial hygiene practice, stated that "concentrations in excess of 1 ppm will cause lacrimation and upper respiratory irritation" and "concentrations as low as 0.4 ppm may cause mild irritation," and cited Sievers et al (1947) as the

source of this information. The data in Sievers (1947), however, were obtained with cats using impure TNM (see Section 3.1.3), and it is unclear whether humans would be similarly sensitive as cats.

2.2.1. Odor Threshold/Odor Awareness

No data was found regarding the human odor threshold for TNM, or of concentrations that are detected by humans.

2.3. Neurotoxicity

No human neurotoxicity studies were located with TNM exposure by any route.

2.4. Developmental/Reproductive Toxicity

No human genotoxicity data were located.

2.5. Genotoxicity

No human genotoxicity data were located.

2.6. Carcinogenicity

No human carcinogenicity data were located.

2.7. Summary

No quantitative human TNM inhalation exposure studies, including an odor threshold, were located. Based on animal studies using impure TNM, the AIHA (1964) stated that "concentrations in excess of 1 ppm will cause lacrimation and upper respiratory irritation" and "concentrations as low as 0.4 ppm may cause mild irritation." Symptoms experi-

enced by workers exposed to unknown concentrations of impure TNM (emitted during TNT production) included irritation to the mucous tissue of the eyes, nose, and respiratory passages, dyspnea, expectoration, coughing, chest tightness, and dizziness (Sievers et al. 1947; Hager 1949). Continued exposure led to drowsiness, headache, anemia, marked cyanosis, respiratory distress, and bradycardia. Two workers exposed for several weeks to a high, undefined concentration of impure TNM had respiratory irritation and distress, chest tightness, foamy sputum, and methemoglobinemia, and shortly thereafter died of pneumonia or pulmonary edema (Koelsch 1917). It is unclear whether TNM inhalation caused methemoglobinemia since exposure was to impure TNM containing TNT; the latter has been reported to cause similar effects in humans (fatigue, weakness, eye irritation, anorexia, nausea, methemoglobinemia) (HSDB 2005b). Kinkead et al. (1977) showed that oral, but not intravenous, administration of TNM caused methemoglobinemia in rats and mice, indicating that metabolism of TNM to nitrite ion by intestinal bacteria was necessary for methemoglobin formation.

No human developmental or reproductive studies, genotoxicity data, or oncogenicity data were located with TNM exposure by any route.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Fischer 344/*N* rats (5/sex/dose) were exposed (whole body) 6 h/day for 2 weeks (5 days/week) to 2, 5, 10, or 25 ppm TNM in a study conducted by the National Toxicology Program (NTP 1990). TNM vapor was generated from a gas dispersion bottle by bubbling nitrogen through liquid TNM. TNM concentration in the exposure chambers was monitored every 10-15 min with a Miran Infrared Gas Analyzer. All animals were observed, weighed, and necropsied. The lung, heart, liver, spleen, trachea, thymus, testes, ovary, kidney, and brain were examined microscopically in 1 rat/sex at 5, 10, and 25 ppm, no rats at 2 ppm, and 2 rats/sex of the control group. All rats exposed to 25 ppm died on the first day and had grossly visible yellow exudate around the mouth and nose,

edematous and/or reddened lungs, and microscopic diffuse lung edema. At 10 ppm, one male died on day 8 and had diffuse pneumonitis. The 10 ppm rats lost weight (males, 34%; females, 21% loss of their initial body weights), were lethargic (2 males, days 1 and 2), had rough coats (2 males, 2 females, day 7), lacrimation (1 male, day 1), conjunctivitis (2 females, day 1), and nose bleed (1 female, day 14). Reddened lungs were found in one (1/1) male. No clinical observations or pathology were reported at 0, 2, or 5 ppm.

The U.S. Army sponsored a series of inhalation studies of atmospheric pollutants generated from the manufacture of munitions, including TNM (Kinkead et al. 1977). Male Sprague-Dawley CFE rats (10/concentration) were exposed for 4 h to 10-23 ppm TNM and were observed for 2 weeks and then sacrificed. All animals were grossly examined. TNM concentrations were monitored by a colorimetric method and a Technicon AutoAnalyzer I system. The mortality results are summarized in Table 6-3 (Section 3.6.). The exposure concentrations and [death rates] were as follows: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10]. The LC_{50} was calculated by the authors to be 17.5 ppm (using the probit method of Finney 1952). Deaths typically occurred within 12 h of exposure. The severity of toxic responses increased with exposure concentration. The rats were lethargic, had a noticeably slowed rate and depth of respiration, and had nose and eye irritation "at the toxic levels" (not specified). Animals exposed to 10 ppm lost weight the first 4 days after exposure but thereafter recovered, whereas rats exposed to greater TNM concentrations had poor weight gain throughout the study. Rats that died prematurely had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion.

Kinkead et al. (1977) also exposed male rats (100/group) to 0, 3.5, 5, or 7.5 ppm TNM continuously for 2 weeks. TNM concentrations were initially measured by a colorimetric method and a Technicon AutoAnalyzer I system, but after 2 days were instead continuously monitored with a Wilkes Miran IR infrared analyzer. Rats exposed to all concentrations were lethargic and had dyspnea, kyphosis (abnormal backward curvature of the spine), lowered body weight gains, and yellowed fur, with severity of effects increasing with exposure concentration. TNM did not alter blood methemoglobin levels. At 3.5 ppm, no rats died; at 5.0 ppm, two rats died after 7 days and 16 died after 2 weeks; and at 7.5 ppm one rat

TABLE 6-3 Tetranitromethane Single-Exposure Animal Studies

Species	Exposure Time	Exposure Conc. (ppm) [mortality]	End Points and Comments	Reference
Rat	36.3 min 60 min 5.8 h	1,320 300 33	Estimated time at which 50% of rats will not survive given concentration (ET_{50}). Rats had closed eyes, gasping, lacrimation, rhinorrhea, red lungs with epithelial cell destruction, vascular congestion, edema	Horn 1954
Rat	2 weeks continuous	3.5 [0/100] 5.0 [16/100] 7.5 [65/100]	Dose-related increase in bronchitis and lung edema; other non-specific lung (irritation) lesions; kyphosis	Kinkead et al. 1977
Rat	4 h	23 [10/10] 21 [10/10] 19 [6/10] 18 [3/10] 15 [3/10] 10 [0/10]	LC_{50} = 17.5 ppm. Males only. Most deaths occurred within 12 h. Rats were lethargic, had slowed respiration, nose and eye irritation, poor weight gain, and lung congestion and hemorrhage; severity increased with test concentration	Kinkead et al. 1977
Mouse	4 h	76 [10/10] 63 [5/10] 55 [4/10] 47 [3/10] 42 [3/10] 32 [1/10] 17 [0/10] 14 [0/10]	LC_{50} = 54.4 ppm. Males only. Most deaths occurred within 12 h. Mice were lethargic and had slowed respiration and nose and eye irritation, lung congestion and hemorrhage, and poor weight gain	Kinkead et al. 1977

(Continued)

TABLE 6-3 Continued

Species	Exposure Time	Exposure Conc. (ppm) [mortality]	End Points and Comments	Reference
Mouse	2 h	75 114	LC_{50} (no further information available) LC_{100} (no further information available)	Korbakova 1960
Cat	6 h 4-5.5 h 1-2.25 h	0.1-0.4 7.2-5.2 7	TNM was emitted during TNT production and possibly contained impurities. At 0.1-0.4 ppm cats had slight lacrimation. At higher concentrations, cats were irritated, restless, dyspneic, weak, and had hemorrhagic and edematous lungs, congested kidneys and liver, ~5-20% methemoglobin; death occurred at end of stated exposure time	Sievers et al. 1947
Cat	20 min	10 100	"Seriously ill;" died after 10 days Death 1 h after exposure	Flury and Zernik 1931

died after 3 days, 3 died after 7 days, and 65 died after 2 weeks. Pathological changes reflecting pulmonary irritation occurred at all doses of TNM: pneumonitis, bronchitis, tracheitis, bronchopneumonia, histiocytic pneumonia, and edema (manifest as increased wet lung/body weight ratios). The two lesions that were clearly dose-related and attributed specifically to TNM were lung edema and tracheitis; edema was considered the most severe primary lesion and was closely related to mortality. The liver, heart, and kidneys had distended vasculature, which were likely associated with death of the animals or were a secondary effect of the lung pathology.

Groups of 20 rats/dose (sex not specified) were exposed to 0, 33, 300, or 1,230 ppm TNM until death or for a maximum of 6.5 h (Horn 1954). Animals were exposed in a 500 L stainless steel chamber and the test atmospheres were generated by flowing air through liquid TNM. Air samples were analyzed for TNM concentration with a spectrophotometer (Beckman Model DU). The exposure time required for 50% of the animals to die was 5.8 h, 60 min, and 36.3 min at 33, 300, and 1,230 ppm TNM, respectively. At 33 ppm, only 65% of the animals had died at the end of the 6.5-h exposure period. Rats exposed to each of the three concentrations exhibited preening, closed eyes, gasping, lacrimation, rhinorrhea, salivation and a short clonic convulsion prior to death. The signs developed more slowly at the lower doses, and lacrimation, rhinorrhea, and salivation were mild at 33 ppm. Necropsy revealed that all groups of treated animals had large amounts of exudate around the nose and mouth, and dark red lungs with epithelial cell destruction, marked vascular congestion, pulmonary edema, and compensatory emphysema. The gastrointestinal tract of some animals was hyperemic.

3.1.2. Mice

B6C3F1 mice (5/sex/dose) were exposed 6 h/day for 2 weeks (5 days/week) to 2, 5, 10, 25, or 50 ppm TNM, followed by microscopic examination of 1/5 rats/sex at 5, 10, and 25 ppm, 0/5 at 2 ppm, and 2/5 controls/sex (NTP 1990; see Section 3.1.1 for experimental methods). All mice exposed to 50 ppm died on day 2, and most males (3/5) and all females (5/5) exposed to 25 ppm died on day 3-7. Body weight gains of mice treated with ≥5 ppm were lower than of controls (dose-related), and mice exposed to ≥10 ppm TNM lost weight, were lethargic starting on day 1, and had polypnea and/or ataxia starting on day 1 at 50 ppm and

starting on day 2 at 10 and 25 ppm. Histopathology revealed bronchopneumonia at 10 and 25 ppm, reddened lungs at 25 and 50 ppm, and yellow nasal exudate at 50 ppm.

Male CF-1 mice (10/concentration) were exposed for 4 h to 14-76 ppm TNM and were observed for 2 weeks and then sacrificed (Kinkead et al. 1977; methods as described for rats in Section 3.1.1.). Deaths typically occurred within 12 h of exposure (see Table 6-3), and the exposure concentrations [mortality rates] were as follows: 76 ppm [10/10]; 63 ppm [5/10]; 55 ppm [4/10]; 47 ppm [3/10]; 42 ppm [3/10]; 32 ppm [1/10]; 17 ppm [0/10]; and 14 ppm [0/10]. The LC_{50} was calculated as 54.4 ppm using the probit method of Finney (1952). The mice were lethargic and had slowed respiration and nose and eye irritation. TNM-treated mice that survived the 14-day observation period had "scattered weight losses" and mild lung congestion; mice that died prematurely had moderate to severe lung congestion and areas of hemorrhage.

Korbakova (1960) conducted an acute exposure study using mice and determined that the 2-h LC_{50} was 75 ppm, whereas there was 100% mortality at 114 ppm. No further information was available.

3.1.3. Cats

A cat exposed to 10 ppm TNM for 20 min became ill and died 10 days later, and another cat exposed to 100 ppm TNM for 20 min died an hour after exposure (Flury and Zernik 1931). TNM analysis was by absorption on 0.1 *N* potassium hydroxide and determination of the reaction products. Further experimental details and other results were not reported.

Fumes given off from 10-15 g TNM (liquid) in a small container or narrow-necked glass flask placed in a "moderate size" exposure chamber (0.022 or 0.4 m^3) were fatal in 2-4.25 h to two cats (Koelsch 1917). TNM concentration was not measured; air circulation was provided through two coin-sized air holes. Prior to death, the animals were restless, lacrimated, sneezed, coughed, foamed at the mouth, and gasped. Exposure of a cat for ½ h to 1-2 drops of TNM on filter paper piece(s) (number not specified) hung inside a similar exposure chamber caused marked irritation and lowered food intake. Subsequent exposure of this cat to filter paper piece(s) with 4 drops of TNM caused death after 15 min (Koelsch 1917) and tracheitis, bronchopneumonia, pulmonary edema, and "oxyhemoglobin" (translation from German) of unspecified

level. A cat exposed in a closed tub (0.022 m^3) for 10 min to vapor emitted from 10 drops TNM had foaming at the mouth, lacrimation, restlessness, tracheitis, and severe pneumonia and died 1¼ h later. Koelsch (1917) stated that methemoglobin formation was not found in these acute experiments because it was preempted by fatal lung edema.

Sievers et al. (1947) conducted a series of experiments in which cats were exposed to TNM fumes emitted from impure TNT samples obtained during various steps of TNT production. These studies have the drawback that the cats were likely simultaneously exposed to other chemicals besides TNM; this was not addressed by Sievers et al. (1947). In one study, cats were placed in a cage within a 30"× 30"× 30" exposure chamber and 700-800 g of the impure TNT/TNM was placed in a tray on top of the cage inside the chamber and air (5-6 L/min) was passed over the test material. Air samples were taken in the chamber during exposure and TNM concentration was measured by a colorimetric method. Two cats exposed to a TNM concentration of 25.2 ppm (measured after 1 h) and 7.2 ppm (measured after 3.5 h) had signs of irritation (ptyalism, lacrimation, sternutation) during the first hour, restlessness and rapid breathing during the second hour, and dyspnea, weakness, unconsciousness, and death after 4 or 5.5 h. The lungs of these cats were slate-colored, hemorrhagic, and contained alveolar and bronchiolar serocellular exudate (serous fluid, degenerating epithelial cells, and some leukocytes). Their kidneys were congested, liver cells contained fine fat droplets and/or were slightly congested, and approximately 11% of the total hemoglobin was converted to methemoglobin. Similar clinical signs and microscopic pathology were found in three cats similarly exposed to 7 ppm TNM fumes from TNT (measured 2¼ h after start of experiment), with death occurring after 1, 1½, and 2¼ h after exposure; their blood contained 5-20% methemoglobin.

Sievers et al. (1947) also exposed two cats 6 h/day for 3 days to TNM emitted from a TNT sample; the TNM concentration after 1 h was 9.2 ppm (3.3 ppm after 5 h), 9.5 ppm, and 5.7 ppm on days 1, 2, and 3, respectively. The cats had irritation, lacrimation, and salivation within 5 min, and were breathing rapidly by the end of the second day. On the third day one of the cats was dyspneic and appeared to be near death. Autopsy revealed slate-colored, congested, and hemorrhagic lungs and discolored kidneys. Both cats had slight methemoglobinemia. Cats exposed to lower concentrations of TNM fumes (0.4 and 0.1 ppm measured after 1 and 5 h) from TNT production wastewater for 6 h had slight lacrimation. These cats were exposed for 6 h the next day as well, when

there was only a trace of TNM in the air (not specified), and the animals behaved normally during exposure and for the following week of observation. No changes were found in the blood determinations at 0.4 or 0.1 ppm.

3.1.4. Rabbits

One rabbit exposed for 4 h to the fumes given off from ~10 g (liquid) TNM in a beaker in a 0.4 m^3 exposure chamber died 24 h after the start of the experiment (Koelsch 1917). The TNM concentration was not reported. The rabbit was constantly falling to one side and breathed rapidly. Necropsy showed lung edema and blood suffusion of the lungs, heart, and all internal organs.

3.1.5. Guinea Pigs

Fumes given off from ~10 g (liquid) TNM in a beaker in a 0.4 m^3 exposure chamber were fatal within 3½ h to one guinea pig (Koelsch 1917). The TNM concentration was not reported. The animals became increasingly weak and quiet until death.

3.2. Nonlethal Toxicity

Grant and Schuman (1993) stated that "Animals show evidence of irritation of the eyes rather quickly at concentrations from 3.3 to 25.2 ppm in air." No further information was provided.

3.2.1. Rats

Fischer 344/*N* rats (10/sex/dose) were exposed by inhalation to 0.2, 0.7, 2, 5, or 10 ppm TNM for 6 h/day for 13 weeks (5 days/week) (NTP 1990). All animals were necropsied and the 5 and 10 ppm group tissues were examined histologically; see Section 3.1.1 for further methods details. The 10 ppm rats had low body weight gains, lethargy, serous nasal exudate, chronic lung inflammation, and metaplasia of the nasal mucosa (females). One 10 ppm female was accidentally killed during

week 2. No effects were seen in animals exposed to ≤5 ppm other than slightly (10%) decreased body weight gain in 5 ppm females. The observed liver weight changes lacked a clear dose-response and correlating histopathology.

3.2.2. Mice

B6C3F1 mice (10/sex/dose) were exposed by inhalation to 0.2, 0.7, 2, 5, or 10 ppm TNM for 6 h/day for 13 weeks (5 days/week) (NTP 1990). All animals were necropsied and their tissues were examined histologically; see Section 3.1.1 for further methods details. One male died at 0.7 ppm (week 4), one male at 5 ppm (day 35), and one female died at 10 ppm (day 77). Necropsy indicated that these deaths were not treatment-related: the 5 ppm mouse had skin lesions at the base of the tail, and the 10 ppm female had an ovarian cyst (necropsy results were not provided for the 0.7 ppm mouse). No clinical signs were noted at ≤5 ppm. Mice inhaling 10 ppm had lethargy, choppy breathing, and slight Cheyne-Stokes (not further defined). Dose-related decreases in body weight gains relative to the controls occurred in both sexes (6.8-55% lower for 0.2-10 ppm males; 12-51% lower for 2-10 ppm females). Bronchiole epithelial hyperplasia occurred at ≥0.7 ppm (possibly at 0.2 ppm), acute serous inflammation of the nasal turbinates and nasal epithelial squamous metaplasia were seen at 10 and 25 ppm. [Note that the NTP (1990) pathology results differ somewhat with those reported by the contract laboratory; the latter reports higher incidences of nasal mucosal inflammation and bronchiolar epithelial hyperplasia (including at 0.2 ppm), and nasal epithelial squamous metaplasia is reported as a lesion only in the NTP report.] Males had increased absolute and relative liver weight at all test concentrations; the lack of a clear dose-response and of accompanying microscopic changes indicated the liver weight increases were not toxicologically significant.

3.2.3. Dogs

Horn (1954) exposed two dogs (strain not specified) to 0 or 6.35 ppm TNM for 6 months (6 h/day, 5 days/week). TNM vapor was generated and measured as described in Section 3.1. Neither animal died dur-

ing the study. Signs of toxicity, observed only during the first two exposure days, included occasional coughing, lethargy, an "unthrifty" appearance, and refusal to eat. The fur of the TNM-treated dog became yellowish by the 6th exposure day. One of the TNM-treated dogs gave birth to a litter of puppies on the 36th day of the experiment (see Section 3.3.). Measurement of hematology, biochemistry, and urinalysis parameters periodically throughout the experiment and terminal necropsy and histopathology revealed no treatment-related findings in the mother dog.

3.2.4. Cats

Cats exposed to approximately 0.1-0.4 ppm impure TNM (fumes from TNT production wastewater) 6 h/day for two days had slight lacrimation during the first day and no effects the second day at barely detectable TNM concentrations (Sievers et al. 1947). This study is described in greater detail in Section 3.1.3.

3.3. Neurotoxicity

No studies were located assessing the neurotoxicity of TNM exposure in animals.

3.4. Developmental/Reproductive Toxicity

A pregnant dog (strain not specified) that participated in a 6-month inhalation study (TNM at 6.35 ppm, 6 h/day, 5 days/week) (Horn 1954) had occasional coughing, lethargy, an "unthrifty" appearance, refused to eat during the first two exposure days and its fur became yellowish by the 6th exposure day. The dog gave birth to a litter of puppies on the 36th day of the experiment, approximately halfway through the daily exposure period. The puppies were exposed for the remainder of that period and the next exposure day without any signs of toxicity or effect on subsequent growth and development. Analysis of the mother dog's hematology, biochemistry, and urinalysis parameters periodically throughout the experiment revealed no treatment-related findings.

3.5. Genotoxicity

TNM was strongly mutagenic in *Salmonella typhimurium* in most conducted assays. Positive responses were obtained with as little as 1.0 μg/plate without S9 activation, and 10 μg/plate with activation using TA97, TA98, TA100, TA102, and/or TA1535 (Würgler et al. 1990; Kawai et al. 1987; Zeiger et al. 1987). Negative results were obtained using in TA1537 up to a cytotoxic concentrations irrespective of activation (Zeiger et al. 1987; NTP 1990) and in some assays using TA98 and TA102 (Kawai et al. 1987; Würgler et al. 1990). TNM (≥1.7 μg/mL) induced chromosome aberrations in the absence but not in the presence of metabolic activation in CHO cells (NTP 1990). Sister chromatid exchanges, however, were increased weakly by TNM (≥20 μg/mL) only in the presence of S9 (NTP 1990). Chronic inhalation exposure to TNM by mice (0.5, 1.0 ppm) and rats (2.0, 5.0 ppm) in a 2-year NTP bioassay (NTP 1990) caused a high incidence of lung tumors (see Section 3.6.): all the tested lung tumors had a GC → AT transition in the second base of codon 12 of the *K-ras* oncogene (Stowers et al. 1987).

3.6. Chronic Toxicity/Carcinogenicity

IARC (1996) classified TNM as possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals. The ACGIH places TNM in carcinogenicity category A3 (confirmed animal carcinogen with unknown relevance to humans) in the current TLV-BEI listing (ACGIH 2004), but classifies TNM as carcinogenicity class A2 (suspected human carcinogen) in the IDLH documentation (ACGIH 1996); no information was found to resolve this discrepancy. EPA has not yet (July 2005) assigned TNM to a carcinogenicity weight-of-evidence group.

3.6.1. Rats

In a lifetime (103 weeks) inhalation NTP bioassay, Fischer 344/*N* rats were exposed for 103 weeks (6 h/day, 5 days/week) to 0, 2, or 5 ppm TNM (NTP 1990; Bucher et al. 1991). The generation of TNM vapor and its measurement are described in Section 3.1.1. No clinical signs of irritation were reported. Mortality was increased at 5 ppm due to lung tumors:

in males starting at week 80 and in females starting at week 100. Both sexes had 7-17% lower body weight gains after week 84. There were marked increases in the incidence of nasal and lung lesions at 2 and/or 5 ppm in both sexes. Incidences for rats at 0, 2, and 5 ppm, respectively, for chronic mucosal inflammation were 12/48, 20/49, 37/59 for males and 13/49, 9/50, 31/50 for females; for respiratory epithelium hyperplasia were 7/48, 15/49, 29/50 for males and 5/49, 3/50, 22/50 for females; of respiratory epithelium squamous metaplasia were 0/48, 1/49, 13/50 for males and 0/49, 0/50, 1/50 for females; of alveolar epithelium hyperplasia were 1/50, 44/50, 50/50 for males and 1/50, 43/50, 50/50 for females; and of bronchiolar hyperplasia were 1/50, 23/50, 45/50 for males and 0/50, 28/50, 40/50 for females. All TNM-treated groups had increased incidences of alveolar-bronchiolar adenomas and carcinomas (0, 2, and 5 ppm: 1/50, 33/50, 46/50 for males; 0/50, 22/50, 50/50 for females). High-dose rats also had an increased incidence of lung squamous-cell carcinomas (0, 2, and 5 ppm: 0/50, 1/50, 19/50 for males; 0/50, 1/50, 12/50 for females).

Horn (1954) exposed 19 rats (sex and strain not specified) to 0 or 6.35 ppm TNM for 6 months (6 h/day, 5 days/week). TNM vapor was generated by slowly dropping liquid TNM into a carburetor attached to the chamber inlet, and air TNM concentrations were measured spectrophotometrically. Eleven rats died over the 6-month period and half the animals had died after 133 days compared to one death in the control group. The rats had yellow discoloration of the fur from the 6th day on, occasional blood-tinged nasal exudate, and some were lethargic. Animals that died prematurely or were sacrificed after 6 months had lungs that were dark red, distended, and edematous; the cause of death appeared to be overwhelming pneumonia. Several rats had hyperemic intestines. Microscopic examination of the lungs of animals that died on study showed bronchial constriction, mucosal degeneration, purulent bronchitis, hemorrhage, congestion, edema, and pneumonitis; there was also some degeneration of the kidneys and liver. TNM-treated rats that survived the 6-month exposure had milder lung pathology.

3.6.2. Mice

B6C3F1 mice (50/sex/dose) were exposed to 0, 0.5 or 2 ppm TNM for 103 weeks (6 h/day, 5 days/week) in an NTP carcinogenicity bioassay (NTP 1990; Bucher et al. 1991). An additional 6 male mice were ex-

posed for 52 weeks to 0 or 2 ppm, and 10 male mice were exposed to 0.5 ppm; only the lung histopathology results were presented in the NTP (1990) report for these animals. The generation of TNM vapor and its measurement are described in Section 3.1.1. Animals exhibited no signs of irritation. Body weights were within 10% of controls for the females throughout the study and for the first 18 months in males, but were 11-19% lower in males after week 88. The 2-year survival was decreased in both groups of TNM-treated males due to lung tumors. Microscopic analysis of the lungs showed increased incidences of nasal and lung lesions at 0.5 and/or 2 ppm in both sexes. The incidence in rats at 0, 0.5, and 2 ppm, respectively, of nasal lumen exudate was 1/49, 1/50, 29/49 in males and 3/49, 30/50, and 33/50 for females; of respiratory epithelium hyperplasia was 3/49, 6/50, 5/49 in males and 2/49, 5/50, and 17/50 for females; of respiratory epithelium squamous metaplasia was 0/49, 0/50, 0/49 in males and 0/49, 2/50, and 8/50 in females; of chronic mucosal inflammation was 1/49, 2/50, 5/49 in males and 11/49, 11/50, and 23/50 in females; of alveolar epithelium hyperplasia was 2/50, 21/50, 46/50 in males and 2/50, 20/50, 41/50 in females; of alveolar histiocytic cellular infiltration was 7/50, 5/50, 22/50 in males and 3/50, 10/50, 32/50 in females; and of bronchiole hyperplasia was 0/50, 9/50, 40/50 in males and 0/50, 7/50, 41/50 in females. Examination of the nasal passages showed no primary neoplasms, but the incidence of alveolar-bronchiolar adenoma was increased at 0.5 and 2 ppm in both sexes, and of carcinoma was increased at 0.5 and 2 ppm in males and at 2 ppm in females. The total incidence of adenoma or carcinoma at 0, 0.5, and 2 ppm was 12/50, 27/50, 47/50 in males and 4/49, 24/50, 49/50 in females. Of the mice exposed to 2 ppm for only 52 weeks, one had multiple alveolar-bronchiolar adenomas, five had alveolar epithelium hyperplasia, and two had bronchiolar epithelium hyperplasia. At 0.5 ppm, four mice had hepatocellular adenomas and one had hyperplasia of the respiratory epithelium after 52 weeks; an increased incidence of hepatocellular adenomas was not seen in the 2-year study.

3.7. Summary

TNM was shown to be a severe respiratory irritant, causing lung edema and hemorrhage, in acute inhalation studies with cats, dogs, rabbits, rats, and mice. Rats appeared to be the most sensitive species in the acute lethality studies. Kinkead et al. (1977) obtained 4-h LC_{50} values of

17.5 ppm for rats and 54.4 ppm for mice, whereas a 2-week NTP (1990) study found that a single exposure to 25 ppm caused 100% mortality in rats and 3-7 exposures to 25 ppm caused 80% mortality in mice. Repeated inhalation exposure of rats and mice caused lung metaplasia and hyperplasia after 13 weeks (at ≥10 ppm and ≥2 ppm, respectively) and lung tumors after 2 years (at ≥2 ppm and ≥0.5 ppm, respectively) (NTP 1990).

Ocular irritation, lethargy, and methemoglobinemia were reported in acute exposure studies with cats exposed to impure TNM, possibly containing TNT. Since TNT is associated with methemoglobinemia, it is unclear which was the causative agent. In any case, formation of methemoglobin (highest level was 20%) did not appear to significantly contribute to animal death, which was due to lung edema and hemorrhage. Kinkead et al. (1977) showed that TNM caused methemoglobinemia in rats and mice when administered orally, but not by inhalation or intravenously.

TNM was mutagenic in most strains of *Salmonella typhimurium* with or without addition of S9 homogenate and induced chromosome aberrations and sister chromatid exchanges in CHO cells (Kawai et al. 1987; Zeiger et al. 1987; Würgler et al. 1990; IARC 1996). The ability of TNM to induce neoplasms in animals was demonstrated in the NTP (1990) study, in which lifetime exposure of mice to 0.5 or 2 ppm and rats to 2 ppm clearly increased the incidence of lung tumors in both species. No complete developmental or reproductive studies were located; dog pups exposed to up to 6.25 ppm for 6 h/day during the last 36 days of gestation and for one subsequent day had no signs of toxicity or effects on postnatal growth and development. TNM is generally recognized as an animal carcinogen although its carcinogenicity in humans is unknown.

TNM single-exposure and multiple-exposure studies are summarized in Tables 6-3 and 6-4.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No human or animal studies were located that described the metabolism or disposition of TNM following inhalation exposure. The demonstration that TNM caused methemoglobinemia in rats and mice

TABLE 6-4 Tetranitromethane Multiple-Exposure Animal Studies

Species, (Reference)	Exposure Time	Exposure Conc. (ppm)	End Points and Comments
Rat (Horn 1954)	6 h/day for 6 months (5 days/wk)	6.35	11/19 died. Yellow fur, bloody nasal exudate, lethargy, lung hemorrhage, edema, congestion, some degeneration of the kidneys and liver.
Rat (NTP 1990)	6 h/day for 2 weeks (5 days/wk) (5/sex/dose)	2, 5	No effects reported
		10	1/5 males died on day 8 (pneumonitis); lethargy (day 1-2), conjunctivitis (day 1), lacrimation (day 1), rough coats (day 7), nose bleed (day 14); decreased BW; reddened lungs
		25	All died on day 1 (pulmonary edema, red lungs)
	6 h/day for 13 weeks (5 days/wk)	0.2, 0.7, 2, 5	No adverse effects noted; decreased BW gain at 5 ppm
		10	Lethargy, decreased BW, nasal exudate and metaplasia (females), lung inflammation, fibrosis
	6 h/day for 103 weeks (5 days/wk)	2	Lung neoplasia
		5	Nasal mucosa inflammation; lung hyperplasia, neoplasia; lowered BW
Mouse (NTP 1990)	6 h/day for 2 weeks (5 days/wk) (5/sex/dose)	2	No adverse effects noted
		5	Decreased BW
		10	Decreased BW; lethargy (day ≥1), bronchopneumonia
		25	8/10 died on day 3-7, lethargy (day ≥1), polypnea (day ≥2), ataxia (day ≥2); reddened lungs, bronchopneumonia
		50	All died on day 2; lethargy, ataxia, polypnea (day ≥1), reddened and/or edematous lungs, yellow nasal exudate
	6 h/day for 13 weeks (5 days/wk) (10/sex/dose)	0.2, 0.7	Bronchiole epithelial hyperplasia (BEH); 1unrelated death at 0.7 ppm, decreased BW gain
		2	BEH with increased incidence, nasal inflammation and squamous metaplasia As at 2 ppm but greater incidence; 1 unrelated death
		5	Decreased BW gain, lethargy, choppy breathing, slight Cheyne-Stokes, nasal inflammation and metaplasia, lung hyperplasia
		10	

(Continued)

TABLE 6-4 Continued

Species, (Reference)	Exposure Time	Exposure Conc. (ppm)	End Points and Comments
	6 h/day for 103 weeks (5 days/wk)	0.5, 2	Lung metaplasia, hyperplasia, neoplasia; lowered BW; nasal exudate
Cat (Sievers et al. 1947)	6 h/day for 3 days	~3.3-9.5	Irritation, lacrimation, rapid breathing, slate-colored, hemorrhagic, and congested lungs, discolored kidneys, slight methemoglobinemia; half were moribund after 3 days. Impure TNM used.
Dog (Horn 1954)	6 h/day for 6 months (5 days/wk)	6.35	Coughing, lethargy, "unthrifty" appearance, refusal to eat first two days; yellowed fur.

BW = body weight.

when administered orally, but not by inhalation or intravenously, indicated that metabolism of TNM to nitrite ion by intestinal bacteria was necessary for methemoglobin formation (Kinkead et al. 1977). Sakurai et al. (1980) showed that rat hepatic microsomes catalyze denitrification of TNM to nitrile and formaldehyde.

4.2. Mechanism of Toxicity

TNM is a severe respiratory and eye irritant in humans and animals, although its precise mechanism of toxicity is unknown. In two well-conducted rat and mouse studies (Kinkead et al. 1977; NTP 1990), TNM toxicity occurred predominantly in the respiratory tract, where it caused pulmonary edema, hemorrhage, and death at sufficiently high concentrations.

Kinkead et al. (1977) compared the effects in rats of continuous exposure to TNM for 2 weeks with exposure to NO_2 gas at four times the (molar) concentration of TNM (because TNM contains four NO_2 groups, and the LC_{50} of NO_2 was approximately 4 times the LC_{50} of TNM). Both compounds caused lethargy, dyspnea, kyphosis, general poor health, and lung irritation leading to edema, but effects were more severe for TNM. Qualitative and quantitative differences in body weight decreases, lung weight increases, and mortality curves suggested a different mode of toxicity for the two compounds. TNM has been shown that TNM selectively binds tyrosine residues in proteins and peptides and can inactivate various enzymes. In vitro data using rat alveolar macrophages (inhibition by TNM of lipopolysaccharide/interferon stimulated production of nitric oxide) suggested that nitration of cell membrane tyrosine residues and subsequent inhibition of tyrosine kinase pathways may be a mechanism of TNM toxicity (Morgan 2000).

4.3. Structure Activity Relationships

Animals studies indicate that TNM is notably more toxic than a number of structurally similar compounds. The rat 4-h LC_{50} of methyl nitrate (CH_3NO_3) vapor was determined to be 1,275 ppm for rats and 5,742 ppm for mice (Kinkead et al. 1977). The animals were lethargic, cyanotic, had slowed respiration, and pulmonary congestion with focal hemorrhage. The rats died within 12 h of exposure whereas mouse deaths typically occurred 3-11 days after exposure.

Rabbits and guinea pigs survived 15-min and 1-h exposures, respectively, to 30,000 ppm nitromethane (CH_3NO_2) vapor, but all tested rabbits died from a 2-h exposure and all guinea pigs died from a 1-h exposure (Davis 1993). The animals had mild narcosis, weakness, and slight respiratory irritation but no eye irritation. One monkey was able to survive a 140-h exposure to 500 ppm nitromethane but exposure to 1,000 ppm for 48 h caused death (Davis 1993). Histopathological findings were primarily in the liver and kidneys, but there was no evidence of methemoglobinemia.

Nitroethane and 1-nitropropane did not induce cancer in animal inhalation studies, whereas 2-nitropropane and tetranitropropane caused liver and lung cancer, respectively (Davis 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The limited available data indicated that, for acute TNM exposure, rats were somewhat more sensitive than mice, as the two species had 4-h LC_{50} values of 17.5 and 54.4 ppm, respectively (Kinkead et al. 1977). Additionally, a single 6 h exposure to 25 ppm caused 100% death in rats but it took 3-7 successive daily 6-h exposures to 25 ppm to kill 8/10 mice (NTP 1990). In multiple-exposure studies using lower exposure concentrations (10 days or 13 weeks, 6 h/day; NTP 1990), however, the difference in sensitivity between rats and mice was less clear: at 5 ppm after 10 days or 13 weeks rats had no adverse effects (possibly lethargy) but mice after 10 days had lower body weight gain and after 13 weeks had nasal inflammation, metaplasia, and lung hyperplasia.

Dogs were less sensitive than rats or mice, as exposure for 6 months to 6.35 ppm (6 h/day; 5 days/week) caused only coughing, lethargy, and inappetence for the first two days (Horn 1954).

The relative susceptibility of cats to TNM vapor is unknown. Cats appeared to be more sensitive than either rodents or dogs (exposure to ≥7 ppm TNM caused death within 1-5 1/2 h), although exposure was to impure TNM (vapor emitted from a TNT production sample).

4.4.2. Susceptible Populations

No studies were located identifying populations susceptible to TNM toxicity.

4.4.3. Concentration-Exposure Duration Relationship

Exposure duration-specific values (for 30, 60, 240, and 480 min) were obtained by exponential scaling using the equation $C^n \times t = k$. This equation, where the exponent n ranges from 0.8 to 3.5, has been shown to describe the concentration-exposure time relationship for many irritant and systemically acting vapors and gases (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n, and in the absence of chemical specific data, an n of 3 was applied to extrapolate to shorter time periods, and an n of 1 was applied to extrapolate to longer time periods than the exposure duration in the key study (i.e., 4 h). This procedure is considered to provide AEGL values protective of human health (NRC 2001). The 10-min values were not extrapolated from 4 h because the NAC has determined that extrapolating from ≥4 h to 10 min is associated with unacceptably large inherent uncertainty, in which case the 30-min value is adopted for 10 min to be protective of human health.

4.4.4. Concurrent Exposure Issues

Several early TNM toxicity studies (e.g., Koelsch 1917; Sievers et al. 1947) reported effects resulting from exposure to impure TNM, i.e., vapors emitted from TNT or during TNT production. The impure TNM therefore likely contained some TNT, and it is unknown which entity caused resulting effects in humans or animals. One effect ascribed to TNM in studies using impure TNM, i.e., the formation of methemoglobin, was shown to be unlikely due to TNM in subsequent rat and mouse studies (Kinkead et al. 1977). It is unknown, however, whether TNM potentiates any toxic effects caused by TNT.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human studies with quantitative exposure concentration data were located.

5.2. Summary of Animal Data Relevant to AEGL-1

No single-exposure studies were located that met the definition of

AEGL-1. AEGL-1 values could potentially be derived from the NTP (1990) study in which Fischer 344/*N* rats were exposed to 2-25 ppm TNM and B6C3F1 mice were exposed to 2-50 ppm TNM for 6 h/day for 2 weeks (5 days/week). At 2 ppm there were no effects in either species, and at 5 ppm, mice had slightly lowered body weight gains. However, since 10 ppm caused significant lung lesions and was a NOEL for lethality in rats and mice, and only a small fraction of the 5 ppm animals were examined histologically, it is unclear if exposure to 2 ppm is within the scope of AEGL-1.

Another study for possible use in AEGL-1 derivation is one where cats exposed for 6 h to approximately 0.1-0.4 ppm impure TNM had slight lacrimation (Sievers et al. 1947). It is unknown, however, whether the lacrimation was due to TNM or an impurity, since the exposure was actually to fumes emitted from TNT production wastewater.

5.3. Derivation of AEGL-1

AEGL-1 values were not developed due to insufficient data. No studies were located with end points clearly within the scope of AEGL-1 in Table 6-5.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No useful human studies were located.

6.2. Summary of Animal Data Relevant to AEGL-2

Three studies were considered potentially useful for AEGL-2 derivation, only one of which was a single-exposure study. These studies were (1) the 4-h rat LC_{50} study conducted by Kinkead et al. (1977), in which male Sprague-Dawley CFE rats were exposed to 10-23 ppm, and

TABLE 6-5 AEGL-1 Values for Tetranitromethane (TNM)

10 min	30 min	1 h	4 h	8 h
Not recommended due to insufficient data.				

mortality was seen at all concentrations except 10 ppm; because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 could be applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation; (2) the NTP (1990) study, in which mice exposed to 5 ppm TNM for 6 h/day for 2 weeks (5 days/week) had slightly lowered body weights, whereas the next higher concentration tested caused significant lung lesions, and (3) a 2-week continuous exposure study in which male rats exposed to 3.5 ppm were lethargic and had dyspnea, decreased body weights, pneumonitis, bronchitis and tracheitis, and lung edema (Kinkead et al. 1977). However, the exposure duration in this study (336 h) was considered too long for extrapolation to ≤8 h with a reasonable degree of confidence.

6.3. Derivation of AEGL-2

AEGL-2 values were based on the 4-h rat LC_{50} study (Kinkead et al. 1977), in which 10 ppm was the NOEL for lethality from extreme lung irritation and was the lowest concentration tested. Because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 was applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation. Scaling across time was performed using the exponential equation $C^n \times t = k$, which has been shown to describe the concentration-exposure time relationship for many irritant and systemically acting vapors and gases, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable to derive n empirically for TNM, and $n = 3$ and $n = 1$ were used to extrapolate to <4 h and >4 h, respectively, except that the 30-min value was adopted as the 10-min value, to be protective of human health (NRC 2001; see Section 4.4.3.). A total uncertainty factor of 10 was used: 3 for interspecies extrapolation because the key study tested the most sensitive species, and 3 to account for sensitive humans because mild lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans. The resulting AEGL-2 values are shown in Table 6-6; calculations are detailed in Appendix A.

A cancer inhalation slope factor was derived for TNM and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure, as shown in Appendix B. TNM concentrations associated with a 10^{-4} excess cancer risk were 2.5 to 10-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were

TABLE 6-6 AEGL-2 Values for Tetranitromethane

10 min	30 min	1 h	4 h	8 h
0.66 ppm (5.3 mg/m^3)	0.66 ppm (5.3 mg/m^3)	0.52 ppm (4.2 mg/m^3)	0.33 ppm (2.6 mg/m^3)	0.17 ppm (1.4 mg/m^3)

considered to be more appropriate for AEGL-2 derivation because (1) they appeared to be the more sensitive end points, (2) AEGL values are applicable to rare events or single, once-in-a-lifetime exposures, and the data indicate that TNM neoplasms resulted from chronic exposure, and (3) a direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in methodology used to obtain these numbers.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No quantitative information on lethal TNM exposure in humans was located.

7.2. Summary of Animal Data Relevant to AEGL-3

Two rat and mouse studies were considered potentially useful for AEGL-3 derivation: (1) the 4-h rat LC_{50} study (Kinkead et al. 1977) where mortality from extreme lung irritation occurred at all concentrations except 10 ppm, using the calculated lethality $BMDL_{05}$ of 11 ppm, and (2) the NTP (1990) study, in which rats and mice were exposed 6 h/day for 2 weeks (5 days/week) to 2, 5, 10, 25, or 50 ppm; lung lesions occurred at 10 ppm in mice and one male rat died on day 8 (pneumonitis), and at 25 ppm all rats died on the first day and 8/10 mice died on days 3-7; 10 ppm can be used as a lethality NOEL for the rat and possibly the mouse.

7.3. Derivation of AEGL-3

AEGL-3 values were derived from the Kinkead et al. (1977) 4-h rat LC_{50} study, which was considered more relevant for AEGL derivation than the NTP (1990) study because it was a single-exposure protocol.

The AEGL-3 point of departure was the lethality $BMDL_{05}$ of 11 ppm, which was calculated using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2. with the Kinkead et al. (1977) lethality data. The $BMDL_{05}$ of 11 ppm is consistent with the empirical lethality NOEL of 10 ppm found in the key study and in a repeat-exposure study with rats and mice (6 h/day for 14 days; NTP 1990). Scaling across time was performed as for the AEGL-2, i.e., using $C^n \times t = k$, where $n = 3$ or $n = 1$, and the 30-min value was adopted as the 10-min value. A total uncertainty factor of 10 was applied: 3 for interspecies extrapolation (key study tested the most sensitive species), and 3 for human variability (NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans). The resulting AEGL-3 values are shown in Table 6-7; calculations are detailed in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not developed due to insufficient data. No studies were located with end points clearly within the scope of AEGL-1.

AEGL-2 values were derived from a 4-h rat LC_{50} study (Kinkead et al. 1977), in which rats exposed to 10 ppm (lowest concentration tested) had mild lung congestion whereas 3/10 died with lung lesions at the next higher concentration tested of 15 ppm. Because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 was applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation. Scaling across time was performed using the exponential equation $C^n \times t = k$, which has been shown to describe the concentration-exposure time relationship for many irritant and systemically acting vapors and gases, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable to derive n empirically for TNM, and $n = 3$ and $n = 1$ were used to extrapolate to <4 h and >4 h, respectively, except that the

TABLE 6-7 AEGL-3 Values for Tetranitromethane (TNM)

10 min	30 min	1 h	4 h	8 h
2.2 ppm (18 mg/m^3)	2.2 ppm (18 mg/m^3)	1.7 ppm (14 mg/m^3)	1.1 ppm (8.8 mg/m^3)	0.55 ppm (4.4 mg/m^3)

30-min value was adopted as the 10-min value, to provide AEGL values protective of human health (NRC 2001). A total uncertainty factor of 10 was used: 3 for interspecies extrapolation because the key study tested the most sensitive species, and 3 to account for sensitive humans because mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.

AEGL-3 values were derived from the same 4-h rat LC_{50} study as the AEGL-2 values (Kinkead et al. 1977). The AEGL-3 point of departure was the calculated lethality $BMDL_{05}$ of 11 ppm, which is consistent with the empirical lethality NOEL of 10 ppm found in the key study and in a repeat-exposure study with rats and mice (6 h/day for 14 days; NTP 1990). Scaling across time was performed as for the AEGL-2, i.e., using $C^n \times t = k$, where $n = 3$ or $n = 1$, and the 30-min value was adopted as the 10-min value. A total uncertainty factor of 10 was applied: 3 for interspecies extrapolation (key study tested the most sensitive species), and 3 for human variability (NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans).

A cancer inhalation slope factor was derived for TNM and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure, as shown in Appendix B. TNM concentrations associated with a 10^{-4} excess cancer risk were 2.5 to 10-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were considered to be more appropriate for AEGL-2 derivation because (1) they appeared to be the more sensitive end points, (2) AEGL values are applicable to rare events or single, once-in-a-lifetime exposures, and the data indicate that TNM neoplasms resulted from chronic exposure, and (3) a direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in methodology used to obtain these numbers.

The AEGL values for TNM and their relationship to one another are shown in Table 6-8.

8.2. Comparison with Other Standards and Guidelines

The available existing standards and guidelines for TNM are summarized in Table 6-9.

The ACGIH lowered their recommended TLV from 1 ppm to 0.005 ppm in 1993 to protect workers from the risk of lung cancer, which was seen in the NTP (1990) study in mice exposed for a lifetime to 0.5 ppm TNM. The NIOSH IDLH for TNM was changed from 5 ppm to 4

ppm in 1994 based on acute inhalation toxicity data in humans and animals (NIOSH 2005b).

TABLE 6-8 Summary of AEGL Values for Tetranitromethane (TNM)

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	Not recommended due to insufficient data.				
AEGL-2 (Disabling)	0.66 ppm (5.3 mg/m^3)	0.66 ppm (5.3 mg/m^3)	0.52 ppm (4.2 mg/m^3)	0.33 ppm (2.6 mg/m^3)	0.17 ppm (1.4 mg/m^3)
AEGL-3 (Lethal)	2.2 ppm (18 mg/m^3)	2.2 ppm (18 mg/m^3)	1.7 ppm (14 mg/m^3)	1.1 ppm (8.8 mg/m^3)	0.55 ppm (4.4 mg/m^3)

TABLE 6-9 Extant Standards and Guidelines for Tetranitromethane (ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended due to insufficient data.				
AEGL-2	0.66	0.66	0.52	0.33	0.17
AEGL-3	2.2	2.2	1.7	1.1	0.55
PEL-TWA (OSHA)[a]					1
IDLH (NIOSH)[b]		4			
REL-TWA (NIOSH)[c]					1
TLV-TWA (ACGIH)[d]					0.005
MAK (Germany)[e]					(None)[e]
MAC (Netherlands)[f]					0.005
LLV (Sweden)[g]					0.05
STV (Sweden)[h]	0.1				

[a]OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (in effect since at least 1989) (NIOSH 2005a,b) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[b]IDLH (Immediately Dangerous to Life and Health, National Institute of Occu-

(Continued)

pational Safety and Health) (NIOSH 2005a,b) 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 TNM is based on irreversible lung and systemic damage and death in animals.

[c]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005a,b) is defined analogous to the ACGIH-TLV-TWA.

[d]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2004) 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. TNM is placed in carcinogenicity category A3: "confirmed animal carcinogen with unknown relevance to humans." The TLV documentation (ACGIH 1996), however, classifies TNM as carcinogenicity class A2 (suspected human carcinogen).

[e]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA. No MAK value was given but TNM was placed in Carcinogen Category 2 ("substances which should be regarded as if they are carcinogenic for man").

[f]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA. A skin notation was present, indicating a danger of percutaneous absorption.)

[g]LLV (Level Limit Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July 2000. Defined analogous to the ACGIH-TLV-TWA.

[h]STV (Short-Term Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 28th July 2000. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 min.

8.3. Data Adequacy and Research Needs

The database for development and support of values was limited, with no quantitative human data or odor threshold available. No single-exposure studies were available for derivation of AEGL-1 values, or for deriving the concentration-time relationship for TNM (n in $C^n \times t = k$). Studies are needed to fill these data gaps.

However, the key study used to derive the AEGL-2 and AEGL-3 values was well-conducted (Kinkead et al. 1977), and the developed AEGL values were supported by the NTP (1990) 2-week repeat-exposure study with rats and mice. Use of the same species and method-

ology for both AEGL-2 and AEGL-3 raises the confidence in the derived values and their relationship to one another across time.

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APPENDIX A

Derivation of AEGL Values

AEGL-1

AEGL-1 values were not developed due to insufficient data. No studies were located with end points clearly within the scope of AEGL-1.

AEGL-2

Key study: Kinkead et al. (1977). Male Sprague-Dawley CFE rats (10/concentration) were exposed for 4 h and observed for 2 weeks. The exposure concentrations and [death rates] were: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10]. The rats were lethargic, had a noticeably slowed rate and depth of respiration, nose and eye irritation, and weight loss. The severity of toxicity increased with exposure concentration. Rats that died prematurely had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion. Because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 was applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation.

Toxicity end point: Mild reversible lung irritation from a 4-h exposure to 3.3 ppm.

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n empirically for TNM, so used $n = 3$ and $n = 1$ to extrapolate to <4 h and >4 h, respectively, except adopted 30-min value as 10-min value to protect human health (see Section 4.4.3.).

Uncertainty factors: Total Uncertainty Factor: 10
Interspecies: 3: Key study tested most sensitive species.
Intraspecies: 3: Mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.

Calculations:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{3.3 \text{ ppm}}{10}^{3} \times \text{time (4 h)} = k = 0.144 \text{ ppm}^3\text{-h for } <4 \text{ h}$$

$C^3 \times 0.5$ h = 0.144 ppm^3-h
30-min (and 10-min) AEGL-2 = C = 0.66 ppm [5.3 mg/m^3]

$C^3 \times 1$ h = 0.144 ppm^3-h
1-h AEGL-2 = C = 0.52 ppm [4.2 mg/m^3]

4-h AEGL-2 = C = 0.33 ppm [2.6 mg/m^3]

Calculations:

$$\text{Concentration} \; \frac{3.3 \text{ ppm}}{\text{UF}}{}^{1} \times \frac{\text{time (4 h)}}{10} = k = 1.32 \text{ ppm-h for} > 4 \text{ h}$$

$C^1 \times 8$ h = 1.32 ppm-h
8-h AEGL-2 = C = 0.17 ppm [1.4 mg/m^3]

AEGL-3

Key study: Kinkead et al. (1977). Male Sprague-Dawley CFE rats (10/concentration) were exposed for 4 h and observed for 2 weeks. The exposure concentrations and [death rates] were: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10]. The rats were lethargic, had a noticeably slowed rate and depth of respiration, nose and eye irritation, and weight loss. The severity of toxicity increased with exposure concentration. Rats that died prematurely had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion. A $BMDL_{05}$ of 11 ppm was calculated using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2. with the Kinkead et al. (1977) lethality data.

Toxicity end point: NOEL for lethality (from extreme lung irritation), based on the calculated lethality $BMDL_{05}$ of 11 ppm.

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n empirically for TNM, so used $n = 3$ and $n = 1$ to extrapolate to <4 h and >4 h, respectively, except adopted 30 min value as 10-min value to protect human health (see Section 4.4.3.).

Uncertainty factors: Total Uncertainty Factor: 10
Interspecies: 3: Key study tested most sensitive species

Intraspecies: 3: NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.

Calculations:

$\underline{\text{Concentration}}^{3} \times \text{time (4 h)} = k = 5.32\ \text{ppm}^3\text{-h for} < 4\ \text{h}$
$\underline{\text{UF}} \quad \underline{10}$

$C^3 \times 0.5\ \text{h} = 5.32\ \text{ppm}^3\text{-h}$
30-min (and 10-min) AEGL-3 = C = 2.2 ppm [18 mg/m^3]

$C^3 \times 1\ \text{h} = 5.32\ \text{ppm}^3\text{-h}$
1-h AEGL-3 = C = 1.7 ppm [14 mg/m^3]

$C^3 \times 4\ \text{h} = 5.32\ \text{ppm}^3\text{-h}$
4-h AEGL-3 = C = 1.1 ppm [8.8 mg/m^3]

Calculations:

$\underline{\text{Concentration}}^{1} \times \text{time (4 h)} = k = 4.4\ \text{ppm}^1\text{-h for} > 4\ \text{h}$
$\underline{\text{UF}} \quad \underline{10}$

$C^1 \times 8\ \text{h} = 4.4\ \text{ppm-h}$
8-h AEGL-3 = C = 0.55 ppm [4.4 mg/m^3]

APPENDIX B

CANCER ASSESSMENT

A preliminary cancer assessment of tetranitromethane (TNM) was performed using the NTP (1990) study, in which male and female mice were exposed to 0, 0.5, or 2 ppm TNM and male and female rats were exposed to 0, 2, or 5 ppm TNM for 6 h/day, 5 days/week, for 103 weeks. All TNM exposures caused alveolar/bronchiolar adenoma or carcinoma, and 5 ppm rats also had squamous cell carcinoma. The highest tumor incidence was alveolar/bronchiolar adenoma or carcinoma in female mice (4/49, 24/50, 49/50 for 0, 0.5, and 2 ppm TNM), which was used to generate the inhalation unit risk after adjusting for discontinuous exposure (6 h/day, 5 day/week), converting to mg/m^3, and extrapolating to a human equivalent concentration (HEC) using the relationship below (EPA 1994, pp. 44 and 50), where MV = min volume and SA = lung alveolar plus bronchiolar surface area, M = mouse, and H = human:

$$\text{HEC } (mg/m^3) = mg/m^3 \text{ mouse} \times \frac{(34.9 \text{ L/min } MV_M) \times (54.32 \text{ m}^2 \text{ } SA_H)}{(13{,}800 \text{ L/min } MV_H)\ (0.05035 \text{ m}^2 \text{ } SA_M)}$$

The resulting HEC of 1.95 mg/m^3 and 7.82 mg/m^3 (for 0.5 and 2 ppm, respectively) were used to calculate the $BMDL_{10}$ of 0.255 mg/m^3 using EPA's Benchmark Dose Software, Version 1.3.2. and the multistage model (EPA 1999). The inhalation unit risk (or slope factor, i.e. q_1*) of 0.392 per (mg/m^3) was obtained by dividing 0.10 (i.e., 10% risk) by the $BMDL_{10}$.

For a lifetime cancer risk of 10^{-4}, air concentration is

$10^{-4}/0.392\ (mg/m^3)^{-1} = 2.55 \times 10^{-4}\ mg/m^3$. For 10^{-4} risk from lifetime (24-h/day) exposure, total TNM exposure would be:

$$(2.55 \times 10^{-4}\ mg/m^3)\ (25{,}600 \text{ days}) = 6.53\ mg/m^3$$
$$\text{(Risk) (70-year life)}$$

An additional adjustment factor of 6 is applied to allow for uncertainties in assessing potential cancer risks under short term exposures with the multistage model (Crump and Howe 1984):

$6.53\ mg/m^3 \div 6 = 1.09\ mg/m^3$ or 0.14 ppm for 24 h exposure

For exposures less than 24 h, the fractional exposure (f) becomes 1/f × 24 h (NRC 1985) (extrapolation to 10 min was not performed due to unacceptably large inherent uncertainty):

Exposure Duration	AEGL-2 Values (ppm) Based on Toxicity End Points	TNM Exposure Conc. (ppm) with an Excess Cancer Risk of		
		10^{-4}	10^{-5}	10^{-6}
0.5 h	0.66	6.72	0.67	0.067
1 h	0.52	3.36	0.34	0.0336
4 h	0.33	0.84	0.084	0.0084
8 h	0.17	0.42	0.042	0.0042

Because animal doses were converted to an air concentration that results in an equivalent human inhaled dose for the derivation of the cancer slope factor, no reduction of exposure levels is applied to account for interspecies variability.

TNM concentrations associated with a 10^{-4} excess cancer risk for a single 30 to 480 min exposure were 2.5 to 10-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were considered to be more appropriate for AEGL-2 derivation because AEGL values are applicable to rare events or single, once-in-a-lifetime exposures, and the data indicate that TNM neoplasms resulted from chronic exposure. A direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in methodology used to obtain these numbers (the TNM concentration with a 10^{-4} excess cancer risk was estimated by linearly extrapolating from lifetime exposure [25,600 days] to 0.5-8 h, whereas the AEGL-2 values were based on results from a single exposure for 10 min to 4 h).

APPENDIX C

ACUTE EXPOSURE GUIDELINES FOR TETRANITROMETHANE (CAS Reg. No. 107-15-3)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended due to insufficient data.				
Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
End point/Concentration/Rationale:				
Uncertainty Factors/Rationale: Total uncertainty factor: Interspecies: Intraspecies:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy:				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.66 ppm	0.66 ppm	0.52 ppm	0.33 ppm	0.17 ppm
Reference: Kinkead, E.R., J.D. MacEwen, C.C. Haun, et al. 1977. Toxic hazards evaluation of five atmospheric pollutants from Army ammunition plants. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory Technical Report AMRL-TR-77-25.				
Test Species/Strain/Number: Male Sprague-Dawley CFE rats (10/concentration).				
Exposure Route/Concentrations/Durations: Inhalation of 10, 15, 18, 19, 21, or 23 ppm for 4 h.				
Effects: Mortality: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10]. The rats were lethargic, had slowed rate and depth of respiration, and had nose and eye irritation.				

All groups had weight loss, which was reversible only at 10 ppm. Rats that died prematurely had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion. The severity of toxicity increased with exposure concentration. Because 10 ppm is a lethality NOEL in this study and is near the point of departure for AEGL-3, a modifying factor of 3 was applied to 10 ppm obtain a concentration (3.3 ppm) that would cause only mild reversible lung irritation.

End point/Concentration/Rationale: Mild reversible lung irritation from exposure to 3.3 ppm for 4 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3—Key study tested most sensitive species
Intraspecies: 3—Mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.

Modifying Factor: 3—applied to 10 ppm to obtain a concentration (3.3 ppm) causing only mild reversible lung irritation.

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n empirically for TNM, so used $n = 3$ and $n = 1$ to extrapolate to <4 h and >4 h, respectively, except adopted 30-min value as 10 min value to be protective of human health (see section 4.4.3.).

Data Adequacy: The relevant data set was small but contained two mutually supportive and well-conducted studies (Kinkead et al. 1977 and NTP 1990). Use of 3.3 ppm as the Point of departure was supported by the repeat-exposure study with rats and mice (6 h/day for 14 days; NTP 1990) in which 2 ppm caused no effects in either species and 5 ppm caused no effects in rats and only decreased body weights in mice (no histopath at 2 ppm and only for 1/5 animals/sex at 5 ppm, however).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.2 ppm	2.2 ppm	1.7 ppm	1.1 ppm	0.55 ppm

(Continued)

AEGL-3 VALUES Continued

Reference: Kinkead, E.R., J.D. MacEwen, C.C. Haun, et al. 1977. Toxic ammunition plants. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory Technical Report AMRL-TR-77-25.
Test Species/Strain/Number: Male Sprague-Dawley CFE rats (10/concentration).
Exposure Route/Concentrations/Durations: Inhalation of 10, 15, 18, 19, 21, or 23 ppm for 4 h.
Effects: Mortality: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10]. The rats were lethargic, had slowed rate and depth of respiration, and had nose and eye irritation. All groups had weight loss, which was reversible only at 10 ppm. Rats that died prematurely had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion. The severity of toxicity increased with exposure concentration.
End point/Concentration/Rationale: The calculated lethality $BMDL_{05}$ of 11 ppm was the NOEL for lethality (from extreme lung irritation).
Uncertainty Factors/Rationale: Uncertainty factors: Total Uncertainty Factor: 10 Interspecies: 3—Key study tested most sensitive species. Intraspecies: 3—NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans.
Modifying Factor: None.
Animal to Human Dosimetric Adjustment: Not performed.
Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n empirically for TNM, so used $n = 3$ and $n = 1$ to extrapolate to <4 h and >4 h, respectively, except adopted 30-min value as 10-min value to be protective of human health (see section 4.4.3.).
Data Adequacy: The relevant data set was small but contained two mutually supportive and well-conducted studies (Kinkead et al. 1977 and NTP 1990). Use of the calculated lethality $BMDL_{05}$ of 11 ppm as the Point of departure was supported by the empirical lethality NOEL of 10 ppm in the key study and in a repeat-exposure study with rats and mice (6 h/day for 14 days; NTP 1990).

APPENDIX D

Category Plot for Tetranitromethane

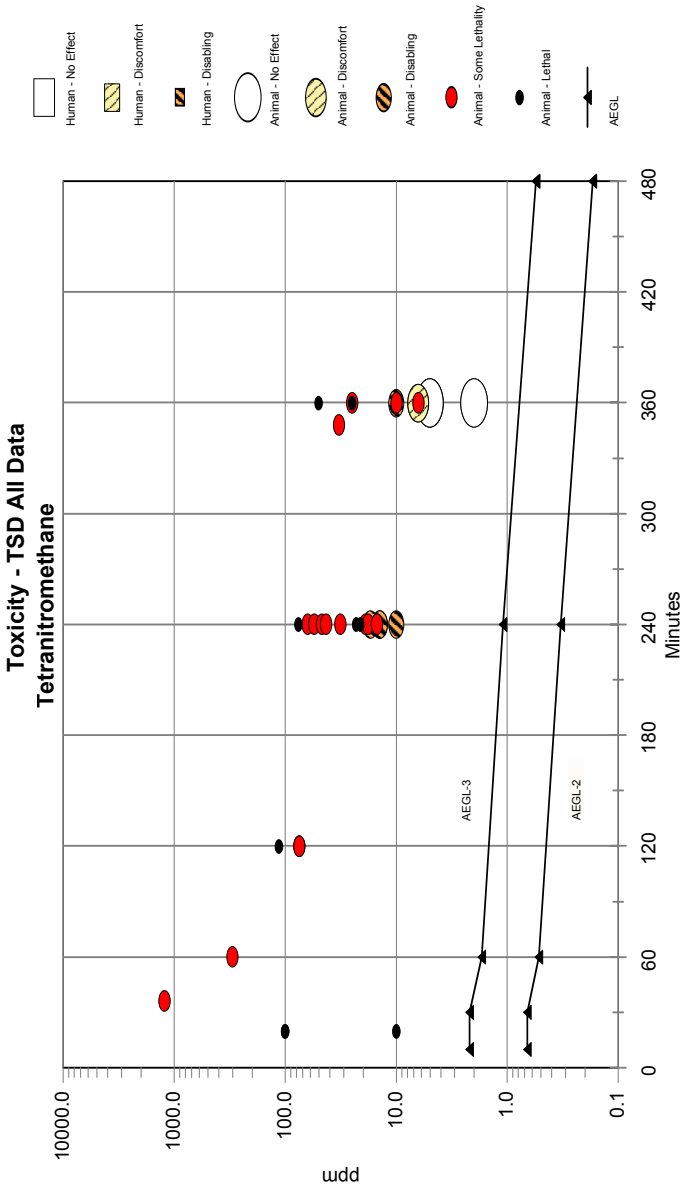

FIGURE D-1 Chemical toxicity—TSD all data, tetranitromethane. Note that the above plot includes several multiple-exposure (6 h/day, 5 days/week) studies for which a single 6 h/day exposure was input into the table (the NTP [1990] 2-week rat and mouse studies, and the Horn [1954] 6-month rat and dog studies).