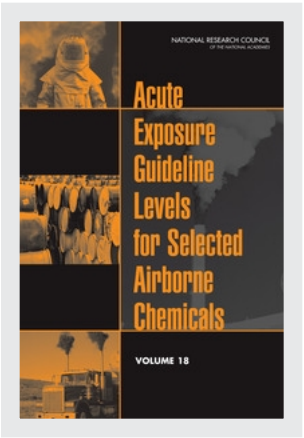

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 18

DETAILS

178 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-31189-2 | DOI 10.17226/18941

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 18

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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This project was supported by Contract No. W81K04-11-D-0017 and EP-W-09-007 between the National Academy of Sciences and the U.S. Department of Defense and the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-31189-2
International Standard Book Number-10: 0-309-31189-6

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu/.

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Preface

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

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

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

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

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

ume in that series. AEGL documents for bromine chloride, carbonyl fluoride, selected halogen fluorides, and oxygen difluoride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bromine chloride (interim report 22), carbonyl fluoride (interim report 22), selected halogen fluorides (interim reports 16, 18, and 22), and oxygen difluoride (interim report 22): Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim reports was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowl-

edges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 18

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

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

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

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

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

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

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

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

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

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

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared seventeen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014a,b). This report is the eighteenth volume in that series. AEGL documents for bromine chloride, carbonyl fluoride, selected halogen fluorides, and oxygen difluoride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

Bromine Chloride[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

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

SUMMARY

Bromine chloride is a red-brown liquid. It is formed when bromine and chlorine react reversibly in the liquid and vapor phases. When equimolar amounts of the halogens are reacted, about 60% of the mixed halogens are present as bromine chloride (about 40% is dissociated). The interhalogen compounds are very reactive and hydrolyze readily.

Bromine chloride is used as a water-treatment biocide and in organic synthesis involving addition across olefinic double bonds to produce bromochloro compounds and for aromatic brominations, where an aromatic bromide and hydrogen chloride are produced. Bromine chloride also has application as a brominating agent in the preparation of fire-retardant chemicals, pharmaceuticals, high-density brominated liquids, agricultural chemicals, dyes, and bleaching agents.

No data relevant to deriving AEGL-1 values for bromine chloride were found. Thus, AEGL-1 values are not recommended.

Relevant data for deriving AEGL-2 values for bromine chloride were also not found. However, in accordance with the standing operating procedures for developing AEGL values (NRC 2001), AEGL-2 values were determined by dividing the AEGL-3 values by 3, because the dose-response curve for bromine chloride is steep (0% lethality at 40 ppm and almost 100% lethality at 120 ppm).

For AEGL-3 values, the point-of-departure was the threshold for lethality estimated from a study by Dow Chemical (1977). In that study, the mortality rate in rats exposed to bromine chloride at 20, 40, 80, or 120 ppm for 7 h was 0/6, 0/6, 1/6, and 5/6, respectively. Benchmark concentration analysis was used to estimate the no-observed-adverse-effect level (NOAEL) for lethality (NRC 2001). The 7-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) was 39.4 ppm. A total uncertainty factor of 10 was applied; a factor of 3 for interspecies differences and a factor of 3 for intraspecies variability. The effects of direct-acting irritants like bromine chloride are not expected to differ significantly between species or among individuals (NRC 2001). In addition, a modifying factor of 3 was applied to account for the sparse data on bromine chloride and the uncertainty in the exposure concentrations in the Dow Chemical study. Time scaling was performed using the equation $C^n \times t = k$. Data on bromine chloride were inadequate to derive an empirical value for n, so default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 7-h point-of-departure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min value.

The AEGL values for bromine chloride are presented in Table 1-1.

1. INTRODUCTION

Bromine chloride is a red-brown liquid (Lang 2006). It is formed when bromine and chlorine react reversibly in the liquid and vapor phases. When equimolar amounts of the halogens are reacted at room temperature, about 60% of the mixed halogens are present as bromine chloride (about 40% is dissociated) (Dagani et al. 2000).

TABLE 1-1 AEGL Values for Bromine Chloride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	1.1 ppm (5.2 mg/m^3)	1.1 ppm (5.2 mg/m^3)	0.83 ppm (3.9 mg/m^3)	0.53 ppm (2.5 mg/m^3)	0.37 ppm (1.7 mg/m^3)	One-third of the AEGL-3 values.
AEGL-3 (lethal)	3.2 ppm (15 mg/m^3)	3.2 ppm (15 mg/m^3)	2.5 ppm (12 mg/m^3)	1.6 ppm (7.6 mg/m^3)	1.1 ppm (5.2 mg/m^3)	Threshold for lethality in the rat (Dow Chemical Co. 1977).

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

The physical properties of mixed halogens are generally intermediate between those of the component halogens (Lang 2006; Frim and Ukeles 2011); however, mixed halogens are polar while single halogen molecules are not (Cotton and Wilkinson 1980). Bromine chloride is a strong oxidizing agent (Dagani et al. 2000). In general, interhalogen compounds are more chemically reactive than elemental halogens due to the weakness of the interhalogen bond (Cotton and Wilkinson 1980; Barrie et al. 2012). Among the diatomic interhalogens, bromine chloride is the least stable, dissociating reversibly to its elemental components (Cotton and Wilkinson 1980; Lang 2006).

The mixed halogen compounds readily hydrolyze (Cotton and Wilkinson 1980). Bromine chloride and its dissociation products may react with water to form a variety of weak and strong acids, including hydrochloric, hypochloric, hydrobromic, and hypobromous acids. The relative proportions of the products depend on pH, but have little dependence on temperature (Liu and Margerum 2001). The following equations show some of the primary reactions (Liu and Margerum 2001; Frim and Ukeles 2011):

$$2BrCl \leftrightarrow Br_2 + Cl_2$$

$$BrCl + H_2O \leftrightarrow HCl + HOBr$$

$$Cl_2 + H_2O \leftrightarrow HOCl + HCl$$

$$Br_2 + H_2O \leftrightarrow HOBr + HBr$$

Ions (e.g., Br^-, Cl^-) may also exist in equilibrium with the molecules presented above (Liu and Margerum 2001). As a result of the numerous chemical species that may be formed on contact with water, a release of bromine chloride into the atmosphere may result in human exposure to mixtures of varying composition, depending on the environmental humidity and its pH; physiologic sources of moisture (e.g., sweat, moisture in the upper respiratory tract) may also create localized exposures to mixtures including hydrolysis products.

The vapor density of bromine chloride has not been determined; however, on the basis of molecular weight (115.36 g/mol), bromine chloride vapor is approximately four times heavier than dry air (average molecular weight of 28.96 g/mol at standard temperature and pressure). The chemical and physical properties of bromine chloride are presented in Table 1-2.

Bromine chloride is used as a water-treatment biocide. Its advantages over chlorine include activity over a wider pH range, more rapid disinfection, effectiveness at lower residual concentrations, and lower aquatic toxicity (Frim and Ukeles 2011). Bromine chloride is used in organic synthesis involving addition across olefinic double bonds to produce bromochloro compounds, and for aromatic brominations, where an aromatic bromide and hydrogen chloride are produced. Bromine chloride is also used as a brominating agent in the preparation of fire-retardant chemicals, pharmaceuticals, high density brominated liquids, agricultural chemicals, dyes, and bleaching agents (Frim and Ukeles 2011).

TABLE 1-2 Chemical and Physical Properties of Bromine Chloride

Parameter	Value	References
Synonyms	Bromochloride	HSDB 2011
CAS registry no.	13863-41-7	HSDB 2011
Chemical formula	BrCl	HSDB 2011
Molecular weight	115.36	HSDB 2011
Physical state	Red-brown liquid at ≤5ºC	HSDB 2011
Melting point	-66ºC	HSDB 2011
Boiling point	5ºC (decomposes)	HSDB 2011
Solubility in water	Reacts with water	HSDB 2011
Density (water =1)	2.32 g/L at 25ºC	IPCS 2009
Vapor pressure	2.368 kPa (17.8 mm Hg) at 25ºC	IPCS 2009
Conversion factors	1 ppm = 4.72 mg/m^3 1 mg/m^3 = 0.212 ppm	

2. HUMAN TOXICITY DATA

No human data on the odor threshold, lethal concentrations, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of bromine chloride were found.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

A single, unpublished study of the acute lethality of bromine chloride was found (Dow Chemical Co. 1977). Groups of six male Sprague-Dawley rats were exposed in a 19-L glass cylinder to bromine chloride at nominal concentrations of 550, 960, 2,110, or 2,925 ppm for 7 h. The vapor was metered from a cylinder containing liquid bromine chloride and mixed with clean air before entering the chamber. Flow rates for the vapor and clean air were used to estimate the nominal concentrations. The investigators reported that the vapor had been analyzed and showed 70% chloride and 30% bromine (molar fraction); it is unclear where the sample was taken or how it was analyzed. Relative humidity in the exposure chamber was not reported, but a diagram of the exposure chamber showed that the air supply passed through a desiccant (Drierite scrubber) before entering the chamber, suggesting that the humidity was probably low.

A separate experiment was conducted to measure the actual chamber concentrations, because the rats appeared to have survived exposure at concentrations far above "working tolerance levels." Six rats were exposed to bromine

chloride at a nominal concentration of 1,100 ppm (estimated on the basis of the mass of bromine chloride liquid lost from the cylinder and air flow rate) for 5 h. Air samples were taken from the gas inlet and from the top, middle, and bottom of the chamber, once per hour; the heights of the three chamber sample inlets were not reported. The air samples were scrubbed through a solution of potassium iodide (1 g/50 mL) and a known amount of 0.025 N sodium thiosulfate (quantity not reported) until the scrubbing solution exhibited a yellow color indicating free iodine; subsequently, the samples were titrated iodometrically to a starch-iodide end point. Total halogen concentration in ppm was reported; the investigators indicated that the halogen concentration was calculated using an assumption of 70% Cl and 30% Br. The halogen concentration estimates presented in Table 1-3 show that the concentration in the bottom of the chamber was roughly twice the concentrations of the middle and top of the chamber.

The investigators estimated the actual exposure concentrations of bromine chloride in the acute lethality study as 4% of the nominal values. That estimate appears to be based on the average concentration in the top and middle chambers (approximately 42-45 ppm) divided by the nominal concentration (1,100 ppm). The actual concentrations were estimated to be 20, 40, 80, and 120 ppm (nominal concentrations of 550, 960, 2,110, and 2,925 ppm, respectively).

In the lethality study, the behavior of the rats was consistent with the observed vapor stratification, as rats tried to breathe the air in the top of the chamber. The report did not indicate the frequency or duration of rearing behavior, nor the dimensions of the inhalation chamber; thus, it is unclear whether the rats were exposed primarily to vapor concentrations corresponding to the bottom, middle, or top of the chamber. However, the estimated concentrations may be conservative, as only the concentrations in the top and middle of the chamber, which were lower than those in the bottom of the chamber, were used in the calculations. Furthermore, because chlorine gas is less dense (vapor density of 1.4 [NRC 2004a]) than bromine (vapor density of 3.5 [NRC 2010]) or bromine chloride (estimated vapor density of approximately 4), the upper portions of the chamber may have contained more chlorine gas than other constituents.

All rats exhibited respiratory problems during and after exposure. At all concentrations, rats lost considerable body weight and recovery to normal was slow. The death of a single rat exposed to bromine chloride at 80 ppm occurred 3 days after exposure; deaths at 120 ppm occurred during the exposure. The primary cause of death was severe upper- and lower-respiratory tract irritation. Mortality and observations over a 14-day period after exposure are presented in Table 1-4.

3.2. Developmental and Reproductive Toxicity

No data on the developmental or reproductive toxicity of bromine chloride were found.

TABLE 1-3 Analytic Measurements of Bromine Chloride in the Test Chamber

	Concentration (ppm) in Chamber Where Sample Was Taken[a]			
Time of Sample (h)	Gas inlet	Top	Middle	Bottom
1	529	78[a]	58	96
2	527	53	44	86
3	544	40	32	98
4	507	37	40	86
5	502	32	40	88
6	530	–	–	–
Average	523	48 (41, excluding sample 1)	43	91

[a]Nominal concentration was 1,100 ppm.
[b]Study authors believed that this sample was potentially contaminated by the initial inlet sample.
Source: Adapted from Dow Chemical Co. 1977.

TABLE 1-4 Mortality Data and Observations from a Study of Rats Exposed to Bromine Chloride

Nominal concentration (ppm)	Estimated actual concentration (ppm)	Exposure Duration	Mortality	Observations
550	20	7 h	0/6	Respiratory distress, bloody eyes and noses, yellow fur, and weight loss with slow recovery.
960	40	5 h	0/6	Extreme respiratory irritation, bloody eyes and noses, and yellow fur.
960	40	7 h	0/6	Respiratory distress, bloody eyes and noses, yellow fur, and weight loss with slow recovery.
2,110	80	7 h	1/6	Death on day 3 after exposure; severe respiratory-tract irritation, yellow fur, and considerable weight loss with slow recovery in remaining rats.
2,925	120	7 h	5/6	Deaths during exposure; severe upper- and lower-respiratory tract irritation and subsequent mouth breathing. Yellow fur and extreme weight loss with slow recovery in surviving rat.

Source: Adapted from Dow Chemical Co. 1977.

3.3. Genotoxicity

No data on the genotoxicity of bromine chloride were found.

3.4. Chronic Toxicity and Carcinogenicity

No data on the chronic toxicity or carcinogenicity of bromine chloride were found.

3.5. Summary

A single study on the lethality of bromine chloride was found. Groups of six male Sprague-Dawley rats were exposed at concentrations of 20, 40, 80, or 120 ppm for 7 h (Dow Chemical Co. 1977). Mortality rates at those concentrations were 0/6, 0/6, 1/6, and 5/6, respectively. All rats experienced respiratory problems during and after the exposure. No data on developmental toxicity, reproductive toxicity, genotoxicity, and chronic toxicity or carcinogenicity of bromine chloride were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information on the metabolism or disposition of bromine chloride in humans or animals is available.

4.2. Mechanism of Toxicity

Halogens are contact irritants. Death in the single study of bromine chloride was due to severe irritation of the upper- and lower-respiratory tract (Dow Chemical Co. 1977), providing evidence for the direct contact mode of action.

4.3. Structure-Activity Relationships

In the atmosphere, bromine chloride is expected to exist in equilibrium with its dissociation and hydrolysis products, including chlorine, bromine, hydrogen chloride, and hydrogen bromide. Although the data on bromine chloride is sparse, information is available on the toxicity of its dissociation and hydrolysis products, all of which exhibit similar direct-contact irritation modes of action. Table 1-5 shows LC_{50} (lethal concentration, 50% lethality) values for the four compounds in the mouse and rat, along with the 7-h rat LC_{50} for bromine chloride. The LC_{50} values suggest that chlorine and bromine are more toxic than the hydrogenated forms, and that chlorine may be somewhat more toxic than

bromine. In addition, time-scaling the 1-h rat LC_{50} values for chlorine using the equation $C^n \times t = k$ (n =2 [NRC 2004a]) results in estimated 7-h LC_{50} values of 110-170 ppm, compared with the LC_{50} of 98 ppm for bromine chloride estimated from the study by Dow Chemical Co. (1977). Thus, on the basis of sparse (and uncertain) data, the lethality of bromine chloride appears to be comparable to that of chlorine.

4.4. Other Relevant Information

4.4.1. Species Variability

No data on species variability in response to bromine chloride were found. For other halogens, the mouse appeared to be slightly more sensitive than the rat (see Table 1-5).

4.4.2. Susceptible Populations

No data on populations susceptible to the effects of bromine chloride were found. Individuals with respiratory diseases or individuals under stress may be more susceptible to the effects of bromine chloride.

TABLE 1-5 Comparison of LC_{50} Values for Bromine Chloride and Its Dissociation and Hydrolysis Products

Chemical	30 min	1 h	2 h	3 h	6 h	7 h
Mouse						
Chlorine[a]	127	137	<170	<10	-	~250
Bromine[b]	174	–	240	>40	<22	>750
Hydrogen chloride[c]	2,600	1,108	–	–	–	–
Hydrogen bromide	–	814[d]	–	–	–	–
Rat						
Bromine chloride	–	–	–	–	–	98[d]
Chlorine[a]	700	293-455	–	–	–	–
Bromine[b]	–	–	–	–	–	–
Hydrogen chloride[c]	4,700	3,124	–	–	–	–
Hydrogen bromide	>1,300[e]	2,858[f]	–	–	–	–

[a]NRC 2004a.
[b]NRC 2010.
[c]NRC 2004b.
[d]Dow Chemical Co. 1977; based on estimated actual exposure concentrations.
[e]Stavert et al. 1991.
[f]MacEwen and Vernot 1972.

4.4.3. Concentration-Exposure Duration Relationship

No data on concentration-exposure duration relationships for bromine chloride were found.

4.4.4. Concurrent Exposure Issues

No data on concurrent exposure issues for bromine chloride were found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No data on human exposure to bromine chloride were found.

5.2. Animal Data Relevant to AEGL-1

No animal data on bromine chloride relevant to developing AEGL-1 values were found.

5.3. Derivation of AEGL-1 Values

No data relevant to deriving AEGL-1 values for bromine chloride were available. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No data on human exposure to bromine chloride were found.

6.2. Animal Data Relevant to AEGL-2

Seven-hour exposures of rats to analytically-determined concentrations of bromine chloride at 20, 40, 80, or 120 ppm resulted in mortality rates of 0/6, 0/6, 1/6, and 5/6, respectively (Dow Chemical Co. 1977). Severe clinical signs and respiratory problems were observed at all concentrations. Those effects are more severe than those defined by AEGL-2 values.

6.3. Derivation of AEGL-2 Values

No data relevant to deriving AEGL-2 values for bromine chloride were available. The dose-response curve for bromine chloride is steep, with 0, 17, and

83% mortality at 40, 80, and 120 ppm, respectively (Dow Chemical Company 1977). In accordance with NRC (2001) guidelines for chemicals with steep dose-response curves, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 (see Section 7.3). AEGL-2 values for bromine chloride are presented in Table 1-6; the calculations are presented in Appendix A and a category graph of AEGL values and toxicity data is presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data on human exposure to bromine chloride were found.

7.2. Animal Data Relevant to AEGL-3

Seven-hour exposures of rats to estimated concentrations of bromine chloride at 20, 40, 80, or 120 ppm resulted in mortality rates of 0/6, 0/6, 1/6, and 5/6, respectively (Dow Chemical Co. 1977). Severe clinical signs and respiratory problems were observed at all concentrations. The death at 80 ppm occurred 3 days after exposure.

7.3. Derivation of AEGL-3 Values

Benchmark concentration analysis was applied to the Dow Chemical Co. (1977) data to estimate the NOAEL for lethality (NRC 2001). The data yielded a 7-h $BMCL_{05}$ of 39.4 ppm and BMC_{01} of 60.2 ppm (see Appendix C). The $BMCL_{05}$ of 39.4 ppm was selected as the point-of-departure. A total uncertainty factor of 10 was applied; a factor of 3 for interspecies differences and a factor of 3 for intraspecies variability. The effects of direct-acting irritants like bromine chloride are not expected to differ significantly between species or among individuals (NRC 2001). A modifying factor of 3 was applied to account for the sparse data on bromine chloride and the uncertainty in the exposure concentrations in the Dow Chemical study. Time scaling was performed using the equation $C^n \times t = k$. Data on bromine chloride were inadequate to derive an empirical value for n, so default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). Because of the uncertainty associated with time scaling a 7-h point-of-departure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min value. AEGL-3 values for bromine chloride are presented in Table 1-7; the calculations are presented in Appendix A and a category graph of AEGL values and toxicity data is presented in Appendix B.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for bromine chloride are presented in Table 1-8, and a summary of the derivations is provided in Appendix D.

8.2. Other Standards and Guidelines

There are no other standards or guidelines for bromine chloride. AEGL values for the dissociation and hydrolysis products of bromine chloride (including chlorine, bromine, hydrogen chloride, and hydrogen bromide) are presented in Table 1-9 for comparison with the values derived for bromine chloride. The comparison suggests that the AEGLs for bromine chloride, which are lower than those of chlorine, should be protective. Although bromine appears to be somewhat less toxic than chlorine (see Table 1-5), the AEGL-3 values for bromine are lower than those for chlorine as a consequence of the less robust database on bromine.

8.3. Data Adequacy and Research

The database on bromine chloride is sparse. Only a single, unpublished acute lethality study is available (Dow Chemical Co. 1977). The exposure concentrations in the study are uncertain as a result of vapor stratification in the chamber and lack of concentration measurements during the study. The AEGL values derived for bromine chloride are supported by comparison to AEGL values for its dissociation and hydrolysis products. However, additional studies of the acute toxicity of bromine chloride, with analysis of actual exposure concentrations and speciation of the compounds in the exposure chamber, should be conducted to refine the AEGL-3 values and provide data relevant to AEGL-2 and AEGL-1 end points. Additional studies comparing the acute toxicity of bromine chloride with that of its dissociation and hydrolysis products would also be beneficial.

TABLE 1-6 AEGL-2 Values for Bromine Chloride

10 min	30 min	1 h	4 h	8 h
1.1 ppm (5.2 mg/m^3)	1.1 ppm (5.2 mg/m^3)	0.83 ppm (3.9 mg/m^3)	0.53 ppm (2.5 mg/m^3)	0.37 ppm (1.7 mg/m^3)

TABLE 1-7 AEGL-3 Values for Bromine Chloride

10 min	30 min	1 h	4 h	8 h
3.2 ppm (15 mg/m^3)	3.2 ppm (15 mg/m^3)	2.5 ppm (12 mg/m^3)	1.6 ppm (7.6 mg/m^3)	1.1 ppm (5.2 mg/m^3)

TABLE 1-8 AEGL Values for Bromine Chloride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	1.1 ppm (5.2 mg/m^3)	1.1 ppm (5.2 mg/m^3)	0.83 ppm (3.9 mg/m^3)	0.53 ppm (2.5 mg/m^3)	0.37 ppm (1.7 mg/m^3)
AEGL-3 (lethal)	3.2 ppm (15 mg/m^3)	3.2 ppm (15 mg/m^3)	2.5 ppm (12 mg/m^3)	1.6 ppm (7.6 mg/m^3)	1.1 ppm (5.2 mg/m^3)

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

TABLE 1-9 AEGL Values for Bromine Chloride and Its Dissociation and Hydrolysis Products

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
Bromine Chloride					
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	1.1 ppm	1.1 ppm	0.83 ppm	0.53 ppm	0.37 ppm
AEGL-3	3.2 ppm	3.2 ppm	2.5 ppm	1.6 ppm	1.1 ppm
Chlorine (NRC 2004a)					
AEGL-1	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm
AEGL-2	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.70 ppm
AEGL-3	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm
Bromine (NRC 2010)					
AEGL-1	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm
AEGL-2	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm
AEGL-3	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.3 ppm
Hydrogen Chloride (NRC 2004b)					
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
Hydrogen Bromide (NRC 2014)					
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	15 ppm

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

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APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values

Data on bromine chloride were insufficient to derive AEGL-1 values; therefore, AEGL-1 values are not recommended.

Derivation of AEGL-2 Values

The AEGL-2 values for bromine chloride were derived by dividing the AEGL-3 values by 3.

10-min AEGL-2: 3.2 ppm ÷ 3 = 1.1 ppm

30-min AEGL-2: 3.2 ppm ÷ 3 = 1.1 ppm

1-h AEGL-2: 2.5 ppm ÷ 3 = 0.83 ppm

4-h AEGL-2: 1.6 ppm ÷ 3 = 0.53 ppm

8-h AEGL-2: 1.1 ppm ÷ 3 = 0.37 ppm

Derivation of AEGL-3 Values

Key study: Dow Chemical Co. 1977. Evaluation of Acute Inhalation Toxicity of Bromine Chloride in Rats. Dow Report No. 77 2993. Submitted to EPA by Dow Chemical Company, Midland, MI, with Cover Letter Dated 05/28/92. EPA Document No. 88-920002267.

Toxicity end point: Lethality threshold, $BMCL_{05}$ of 39.4 ppm for a 7-h exposure (see Appendix C)

Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001)
$(39.4 \text{ ppm} \div 30)^3 \times 7 \text{ h} = 15.85707 \text{ ppm-h}$
$(39.4 \text{ ppm}/30)^1 \times 7 \text{ h} = 9.19333 \text{ ppm-h}$

Uncertainty factors: Total uncertainty factor: 10
Interspecies: 3, because the mechanism of action of direct-acting irritants is not expected to differ greatly among species.

	Intraspecies: 3, because the mechanism of action of direct-acting irritants is not expected to differ greatly among individuals.
Modifying factor:	3, to account for sparse database and uncertainty associated with the exposure concentrations in the key study.
Calculations:	
10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 3.2 ppm, because of the uncertainty associate with time-scaling a 7-h point-of-departure to a 10-min value.
30-min AEGL-3:	$(15.85707 \text{ ppm-h} \div 0.5 \text{ h})^{1/3}$ C = 3.2 ppm
1-h AEGL-3:	$(15.85707 \text{ ppm-h} \div 1 \text{ h})^{1/3}$ C = 2.5 ppm
4-h AEGL-3:	$(15.85707 \text{ ppm-h} \div 4 \text{ h})^{1/3}$ C = 1.6 ppm
8-h AEGL-3:	$(9.19333 \text{ ppm-h} \div 8 \text{ h})$ C = 1.1 ppm

APPENDIX B

CATEGORY PLOT FOR BROMINE CHLORIDE

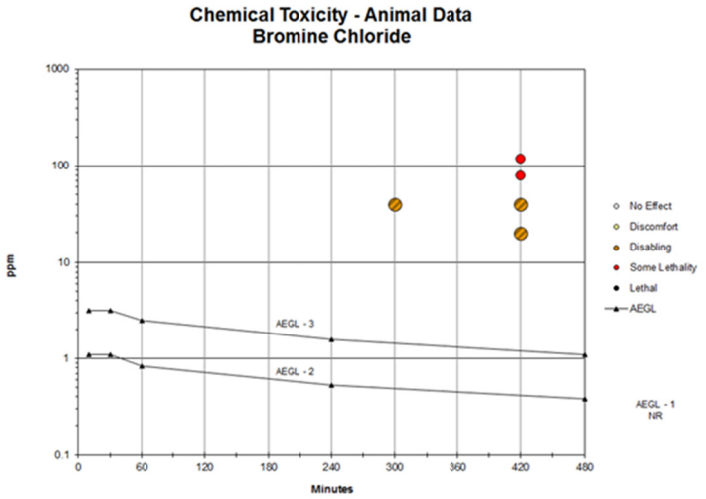

FIGURE B-1 Category plot of toxicity data and AEGL values for bromine chloride.

TABLE B-1 Data Used in Category Plot for Bromine Chloride

Source	Species	ppm	Minutes	Category
AEGL-2		1.1	10	AEGL
AEGL-2		1.1	30	AEGL
AEGL-2		0.83	60	AEGL
AEGL-2		0.53	240	AEGL
AEGL-2		0.37	480	AEGL
AEGL-3		3.2	10	AEGL
AEGL-3		3.2	30	AEGL
AEGL-3		2.5	60	AEGL
AEGL-3		1.6	240	AEGL
AEGL-3		1.1	480	AEGL
Dow Chemical Co. 1977	Rat	20	420	2, respiratory distress
	Rat	40	420	2, respiratory distress
	Rat	40	300	2, extreme respiratory irritation
	Rat	80	420	SL (1/6)
	Rat	120	420	SL (5/6)

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

APPENDIX C

DERIVATION OF BENCHMARK CONCENTRATION FOR BROMINE CHLORIDE

Probit Model. (Version: 3.2; Date: 10/28/2009)
Input Data File: C:/Users/hclynch.ESC1/Documents/BMDS 220/Data/lnp_Dax_Setting.(d)
Gnuplot Plotting File: C:/Users/hclynch.ESC1/Documents/BMDS 220/Data/lnp_Dax_Setting.plt
Wed Sep 11 12:38:40 2013

BMDS_Model_Run

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

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -9.28868
Slope = 2.05319

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-21.8829	9.72809	-40.9496	-2.81617
slope	4.77295	2.11983	0.61815	8.92775

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

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance	Test d.f.	P-value
Full model	-5.40673	3			
Fitted model	-5.40679	2	0.000114402	1	0.9915
Reduced model	-11.4573	1	12.101	2	0.002357

AIC: 14.8136

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
40.0000	0.0000	0.000	0.000	6	-0.008
80.0000	0.1666	1.000	1.000	6	0.000
120.0000	0.8334	5.000	5.000	6	-0.000

Chi-square = 0.00 d.f. = 1 P-value = 0.9940

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

BMD = 69.4182
BMDL = 39.372

Probit Model. (Version: 3.2; Date: 10/28/2009)
Input Data File: C:/Users/hclynch.ESC1/Documents/BMDS 220/Data/lnp_Dax_Setting.(d)
Gnuplot Plotting File: C:/Users/hclynch.ESC1/Documents/BMDS 220/Data/lnp_Dax_Setting.plt
Wed Sep 11 12:39:15 2013

BMDS_Model_Run

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

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -9.28868
slope = 2.05319

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-21.8829	9.72809	-40.9496	-2.81617
slope	4.77295	2.11983	0.61815	8.92775

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

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance	Test d.f.	P-value
Full model	-5.40673	3			
Fitted model	-5.40679	2	0.000114402	1	0.9915
Reduced model	-11.4573	1	12.101	2	0.002357

AIC: 14.8136

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
40.0000	0.0000	0.000	0.000	6	-0.008
80.0000	0.1666	1.000	1.000	6	0.000
120.0000	0.8334	5.000	5.000	6	-0.000

Chi-square = 0.00 d.f. = 1 P-value = 0.9940

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 60.1816
BMDL = 27.4878

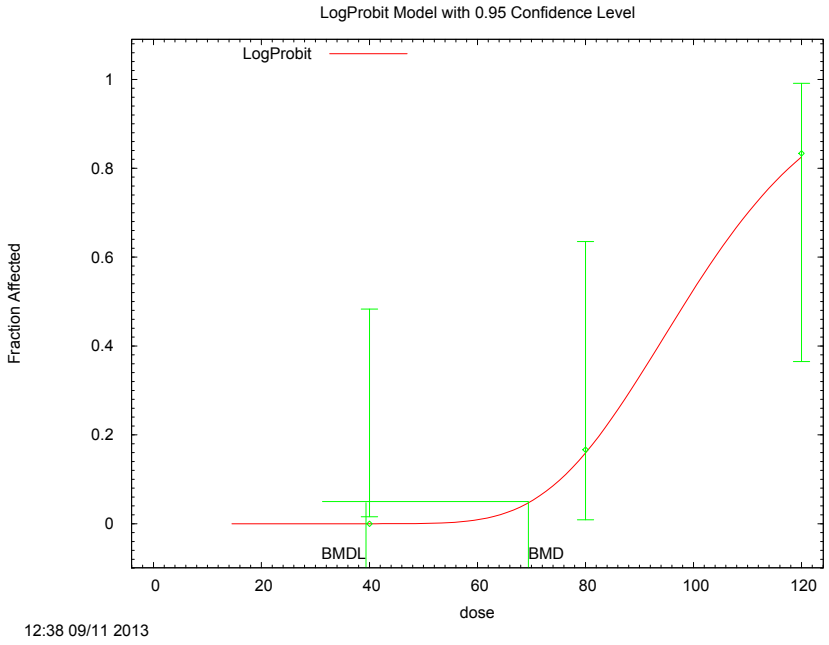

FIGURE C-1 LogProbit model with 0.95 confidence level.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR BROMINE CHLORIDE

Derivation Summary

AEGL-1 VALUES

Data on bromine chloride were insufficient to derive AEGL-1 values; therefore, AEGL-1 values are not recommended.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.1 ppm	1.1 ppm	0.83 ppm	0.53 ppm	0.37 ppm

Data adequacy: The database on bromine chloride was inadequate for deriving AEGL-2 values. However, because bromine chloride has a steep dose-response curve (0% mortality at 40 ppm and almost 100% mortality at 120 ppm), the AEGL-2 values were derived by dividing the AEGL-3 values by 3 (NRC 2001).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.2 ppm	3.2 ppm	2.5 ppm	1.6 ppm	1.1 ppm

Key reference: Dow Chemical Co. 1977. Evaluation of Acute Inhalation Toxicity of Bromine Chloride in Rats. Dow Report No. 77 2993 EPA Document No.: 88-920002267.

Test species/Strain/Number: Rat; Sprague-Dawley; 6 males/group

Exposure route/Concentrations/Durations: Inhalation; 0, 40, 80, or 120 ppm for 7 h

Effects: Mortality
20 ppm: 0/6
40 ppm: 0/6
80 ppm: 1/6 (death 3 days after exposure)
120 ppm: 5/6 (deaths during exposure)

End point/Concentration/Rationale: Approximate threshold for death, $BMCL_{05}$ of 39.4 ppm for a 7-h exposure

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of action of direct-acting irritants is not expected to differ greatly among species.
Intraspecies: 3, because the mechanism of action of direct-acting irritants in not expected to differ greatly among individuals.

Modifying factor: 3, to account for the sparse database and uncertainty in the exposure concentrations in the key study.

Animal-to-human dosimetric adjustment: Not applied

(Continued)

AEGL-3 VALUES Continued

Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001). The 30-min value was adopted as the 10-min value.
Data adequacy: The database on lethality from exposure to bromine chloride was considered adequate. The values are supported by the rich database on lethality for the related chemical chlorine.

2

Carbonyl Fluoride[1]

Acute Exposure Guideline Levels

PREFACE

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

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

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

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

SUMMARY

Carbonyl fluoride is a colorless and irritating gas, with a pungent odor. It is hygroscopic, and is hydrolyzed into carbon dioxide and hydrogen fluoride by water. It is used as an intermediate in the synthesis of organic compounds. The thermal decomposition of fluoropolymers, such as polytetrafluoroethylene and polyfluoroethylenepropylene, is a major source of exposure because carbonyl fluoride is the major reaction product from the rapid destruction of plastic materials at temperatures above 500°C. Pyrolysis products are composed of a large number of compounds, can be of variable composition, and pose significant analytic challenges. Pyrolysis products of polytetrafluoroethylene include a number of highly toxic compounds in addition to carbonyl fluoride, including perfluoroisobutylene, which is approximately 10-fold more toxic than phosgene (Patocka and Bajgar 1998; IPCS 2004).

Carbonyl fluoride is a strong irritant of the eyes and respiratory tract. Its irritancy is hypothesized to be due to hydrogen fluoride, a known sensory irritant. However, the toxicity of carbonyl fluoride is greater than that of hydrogen fluoride, and may be the result of the chemical's deep penetration into the lungs as well as the production of hydrogen fluoride. No data on exposure of humans to carbonyl fluoride were found.

No AEGL-1 values for carbonyl fluoride were derived because of insufficient data. Data were also inadequate to derive AEGL-2 values. According to the standing operating procedures for deriving AEGL values (NRC 2001), AEGL-3 values may be divided by 3 to estimate AEGL-2 values. That approach is justified because carbonyl fluoride appears to have a steep concentration-

response curve. Rats exposed to carbonyl fluoride at 5 or 10 ppm for 4 h experienced dyspnea and rapid, shallow respiration (DuPont 1956, 1959). At concentrations of 26.7 ppm or higher for 4 h death occurred (DuPont 1976).

The AEGL-3 values for carbonyl fluoride were derived by using the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 5.2 ppm from a study in rats (DuPont 1976) as the point-of-departure. Rapid to convulsive respiration and pulmonary edema were observed in rats exposed to carbonyl fluoride for 4 h. Death occurred at all concentrations tested. An interspecies uncertainty factor of 3 was applied, because the toxicity of a direct-acting irritant in not expected to differ greatly among species. A study by Scheel et al. (1968a) provides some support for a factor of 3. However, carbonyl fluoride was generated via polytetrafluoroethylene pyrolysis in that study; therefore, exposure included other pyrolysis products. Exposure of rats to carbonyl fluoride at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The investigators stated that those effects were produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lungs were not provided for those species. As noted earlier, carbonyl fluoride also has a steep concentration-response curve. An intraspecies uncertainty factor of 3 was applied because effects from a direct-acting irritant of the lungs and respiratory tract are not expected to differ greatly among individuals. Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on carbonyl fluoride were inadequate to derive an empirical value for n, so default values of n = 3 for extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min value in accordance with the standing operating procedures for developing AEGL values (NRC 2001).

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

TABLE 2-1 AEGL Values for Carbonyl Fluoride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	0.35 ppm (0.95 mg/m^3)	0.35 ppm (0.95 mg/m^3)	0.28 ppm (0.76 mg/m^3)	0.17 ppm (0.46 mg/m^3)	0.087 ppm (0.23 mg/m^3)	One-third of the AEGL-3 values (NRC 2001)
AEGL-3 (lethal)	1.0 ppm (2.7 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.83 ppm (2.2 mg/m^3)	0.52 ppm (1.4 mg/m^3)	0.26 ppm (0.70 mg/m^3)	4-h rat $BMCL_{05}$ (DuPont 1976)

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

1. INTRODUCTION

Carbonyl fluoride is a colorless, pungent, and irritating gas. It is hygroscopic, and is hydrolyzed by water (HSDB 2009). Chemical and physical properties of carbonyl fluoride are presented in Table 2-2. Carbonyl fluoride can be prepared from fluorine or bromine trifluoride and carbon monoxide. Alternately, it can be prepared by the action of silver fluoride on carbon monoxide or through the reaction of phosgene with sodium fluoride and hydrogen cyanide. It is a thermal decomposition product of fluoropolymers, such as polytetrafluoroethylene and polyfluoroethylenepropylene, heated at temperatures above 500°C. Pyrolysis products are composed of a large number of compounds, can be of variable composition, and pose significant analytic challenges. For polytetrafluoroethylene, pyrolysis products include a number of highly toxic compounds in addition to carbonyl fluoride, including perfluoroisobutylene, which is approximately 10-fold more toxic than phosgene (Patocka and Bajgar 1998; IPCS 2004). Carbonyl fluoride is used as a chemical intermediate in the synthesis of organic compounds, such as fluorinated alkyl isocyanates (HSDB 2009). Recent production data were not found. Carbonyl fluoride is shipped as a liquefied compressed gas (NIOSH 2011a).

TABLE 2-2 Chemical and Physical Properties of Carbonyl Fluoride

Parameter	Value	References
Synonyms	Carbon difluoride oxide; carbon fluoride oxide; carbonic difluoride; carbon oxyfluoride; carbonyl fluoride, difluoroformaldehyde; fluophosgene; fluoroformyl fluoride; fluorophosgene	HSDB 2009
CAS registry no.	353-50-4	HSDB 2009
Chemical formula	COF_2	NIOSH 2011a
Molecular weight	66.007	HSDB 2009
Physical state	Colorless gas	HSDB 2009
Melting point	-111.26°C	HSDB 2009
Boiling point	-84.57°C	HSDB 2009
Solubility in water	Unstable in presence of water, very hygroscopic	HSDB 2009
Vapor density (air = 1)	2.29	NIOSH 2011a
Vapor pressure	4.45×10^4 mm Hg at 25°C	HSDB 2009
Flammability limits	Nonflammable	NIOSH 2011a
Conversion factors	1 ppm = 2.7 mg/m^3 1 mg/m^3 = 0.37 ppm	NIOSH 2011a

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human lethality following exposure to carbonyl fluoride were found.

2.2. Nonlethal Toxicity

The odor of carbonyl fluoride is described as pungent and irritating (NIOSH 2011a), but no information on the odor threshold was available. No case reports or epidemiologic studies of exposure to carbonyl fluoride were found.

2.3. Developmental and Reproductive Toxicity

No data regarding the developmental or reproductive toxicity of carbonyl fluoride in humans were found.

2.4. Genotoxicity

No data regarding the genotoxicity of carbonyl fluoride in humans were found.

2.5. Carcinogenicity

No data regarding the carcinogenicity of carbonyl fluoride in humans were found.

2.6. Summary

No information on human exposure to carbonyl fluoride was available. Carbonyl fluoride is a strong irritant to the skin, eyes, mucous membranes, and respiratory tract; direct contact with the skin may cause frostbite (HSDB 2009).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of two male ChR-CD rats were exposed to carbonyl fluoride by inhalation at nominal concentrations of 5 or 10 ppm and a group of six rats was exposed at 100 ppm for 4 h. Three rats exposed at 100 ppm died, and pathologic examination showed they had acute tracheobronchitis and pulmonary congestion. The surviving rats exhibited no pathologic changes. The 4-h LC_{50} (lethal

concentration, 50% lethality) was approximately 100 ppm. No deaths occurred in the groups exposed at lower concentrations. The data were presented in a table of a one-page preliminary report (DuPont 1959).

Scheel et al. (1968a) evaluated the acute inhalation toxicity of carbonyl fluoride in groups of five male and five female Greenacres Controlled Flora rats (8 and 24 weeks old). Carbonyl fluoride was generated by polytetrafluoroethylene pyrolysis at 550ºC. The authors referenced work by Coleman et al. (1968), which identified carbonyl fluoride as a principal toxic component of the pyrolysis gases, as their rationale for using polytetrafluoroethylene pyrolysis to produce carbonyl fluoride. Atmospheres were generated with a metered air stream into the exposure chamber, and concentrations were measured by the hydrolysable fluoride method. Rats were exposed at various concentrations with the lowest being 310 ppm for 1 h, followed by a 14-day observation period. (With the exception of the 310-ppm value, actual concentrations were not provided). Deaths usually occurred within 24 h with few latent deaths. The LC_{50} values for the 8- and 24-week-old rats were 360 and 460 ppm, respectively. Although an age difference in mortality was apparent, no difference between the sexes was found. Exposure at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The authors stated that those effects were produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lungs were not provided for those species. The lungs showed rapid cellular reorganization and clearing of edema 48 h after exposure, but alveolar damage was still present. Extravasation of red cells from damaged capillaries continued for up to 7 days; the effect was accompanied by mild interstitial fibrosis. Although data were not provided, Scheel et al. (1968a) reported that a 4-h exposure at 90 ppm also resulted in approximately 50% mortality.

DuPont (1976) exposed male ChR-CD rats (10/group) to carbonyl fluoride (>97% pure) at 26.7, 30.8, 32.7, 41.3, 44.7, 47.2 (48.8 by infra-red analysis), or 47.6 ppm for 4 h. Test atmospheres were analyzed with a fluoride-specific electrode and confirmed by infra-red analysis. Deaths occurred at every concentration. Mortalities in the respective groups were 5/10, 3/10, 3/10, 6/10, 8/10, 9/10, and 6/10. The calculated LC_{50} was 34.3 ppm. The calculated BMC_{01} was 10.4 ppm and the $BMCL_{05}$ was 5.2 ppm. Respiration in the rats varied directly with exposure concentration and ranged from rapid shallow breathing to convulsive respiration. Pathologic examination revealed white plaques, red focal spots, and consolidation and edema of the lungs. Liver congestion and bright red spleens were also found.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of four male albino rats were exposed to carbonyl fluoride at nominal concentrations of 2.5 or 5 ppm for 2 and 2.5 h in a preliminary investigation

of toxicity (DuPont 1956). The rats were then observed for 24 h or 8 days. The low concentration of 2.5 ppm was not lethal to the rats and no clinical signs developed. At 5 ppm, the rats developed slight dyspnea and cyanosis. No other information was reported.

In other studies conducted by DuPont (1959), groups of two male ChR-CD rats were exposed to carbonyl fluoride at nominal concentrations of 5 or 10 ppm and a group of six rats was exposed at 100 ppm for 4 h. Clinical signs included rapid, shallow respiration and loss of weight in the 5- and 10-ppm groups, but no pathologic changes were found. The data were presented in a table of a one-page preliminary report.

TABLE 2-3 Summary of Acute Inhalation Data in Laboratory Animals

Species (age)	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	2.5[a]	2, 2.5 h	None0	DuPont 1956
	5.0[a]	2, 2.5 h	Slight dyspnea and cyanosis	
Rat	5[a]	4 h	Rapid, shallow respiration	DuPont 1959
	10[a]	4 h	Rapid, shallow respiration	
	100[a]	4 h	LC_{50}, pulmonary congestion	
Rat (8 wk)	360	1 h	LC_{50}	Scheel et al. 1968a[b]
Rat (24 wk)	460	1 h	LC_{50}	
Rat (8 wk)	90	4 h	LC_{50}	
Rat	26.7	4 h	50% mortality	DuPont 1976
	30.8	4 h	30% mortality	
	32.7	4 h	30% mortality	
	34.3	4 h	LC_{50} (calculated)	
	41.3	4 h	60% mortality	
	44.7	4 h	80% mortality	
	47.2 (48.8 IR[c])	4 h	90% mortality	
	47.6	4 h	60% mortality	

[a]Nominal concentrations.
[b]Exposed rats to polytetrafluoroethylene pyrolysis products (550ºC) and reported concentrations of measured fluoride.
[c]Measurement by infrared analysis.

3.3. Repeated Dose Toxicity

Scheel et al. (1968b) examined whether the toxic action of carbonyl fluoride is due to the toxicity of hydrogen fluoride. Twenty male and 20 female rats (Greenacres Controlled Flora) were exposed to polytetrafluoroethylene pyrolysis products (temperature not reported) for 1 h per day for 5 days. Although the authors state that the exposures were to carbonyl fluoride at 50 ppm, the total exposure reported of 158 ppm-h and graphic data presented in the report indicate that successive daily exposures were at concentrations of 52, 43, 29, 25, and 9 ppm. Urine was collected and analyzed for fluoride, tissues were collected and analyzed for inhibition of succinic dehydrogenase, and urine was analyzed for protein, glucose, ketones, and occult blood. After 5 days of exposure (158 ppm-h plus 18 g of particulates), mortality was 22%; rats died during or shortly after exposure, and rats that died exhibited extreme malaise and weakness. No deaths occurred until the third day. Urinary fluoride increased from 3 to 42 mg/L in 5 days. Eighteen days after the last exposure, the urinary fluoride concentration was four times that of controls. Protein, glucose, ketones, and occult blood were detected in the urine. A 30% weight loss occurred subsequent to exposure. The succinic dehydrogenase activity in the kidneys was inhibited to less than 5% of its normal value. Increased levels of succinic dehydrogenase activity were produced in the lungs. The liver showed enlarged nuclei and fatty infiltration. The metabolic inhibition was reversible, as were the pathologic changes in the lungs (with the exception of a small amount of emphysematous change), liver, and kidneys (examined 18 days after exposure). The authors concluded that the toxic syndrome described in this study is compatible with the descriptions of hydrogen fluoride toxicity.

3.4. Developmental and Reproductive Toxicity

No data on the developmental or reproductive toxicity of carbonyl fluoride were found.

3.5. Genotoxicity

No data on the genotoxicity of carbonyl fluoride were found.

3.6. Chronic Toxicity and Carcinogenicity

No data on the chronic toxicity or carcinogenicity of carbonyl fluoride were found.

3.7. Summary

Acute inhalation of carbonyl fluoride causes rapid or labored respiration and respiratory irritation, pulmonary congestion and edema, increases in urinary

fluoride excretion, proteinuria, and can cause death in rats. Varying LC_{50} values for rats have been reported: 4-h LC_{50} of 34.3 ppm (DuPont 1976), 90 ppm (Scheel et al. 1968a), and 100 ppm (DuPont 1959), and 1-h LC_{50}s of 360 ppm and 460 ppm for 8-week-old and 24-week-old rats, respectively. The 1-h LC_{50} for hydrogen fluoride in rats is 1,278 ppm (MacEwen and Vernot 1970). Converting the carbonyl fluoride concentration of 460 ppm to an equivalent concentration of hydrogen fluoride yields a concentration of 867 ppm, which suggests that carbonyl fluoride produces toxicity greater than that caused by hydrogen fluoride released by hydrolysis. Converting the LC_{50} for hydrogen fluoride to an equivalent concentration of carbonyl fluoride gives a predicted value of 680 ppm, nearly 50% greater than that observed. No data on the developmental toxicity, reproductive toxicity, genotoxicity, chronic toxicity, or carcinogenicity of carbonyl fluoride were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Carbonyl fluoride is hygroscopic and hydrolyzed in the moist respiratory tract to carbon dioxide and two moles of hydrogen fluoride (Arito and Soda 1977). Hydrogen fluoride is soluble in water and is absorbed by the respiratory tract (HSDB 2012). It has a relatively low dissociation constant (3.5×10^{-4}), which allows the non-ionized compound to penetrate the skin, respiratory system, or gastrointestinal tract. The fluoride ion is readily absorbed into the bloodstream and is distributed to all organs. Equilibrium is rapidly reached (Perry et al. 1994). Elimination is primarily through the kidneys.

4.2. Mechanism of Toxicity

Carbonyl fluoride is a contact irritant that hydrolyzes in the presence of water to hydrogen fluoride. Hydrogen fluoride is irritating to the skin, eyes, and respiratory tract. Exposure via inhalation produces pulmonary hemorrhage, congestion, and death in laboratory animals (HSDB 2012). Carbon dioxide is also produced when carbonyl fluoride is hydrolyzed. However, carbon dioxide toxicity occurs at very high concentrations, and the 10-h time-weighted average is currently set at 5,000 ppm (NIOSH 2011b).

4.3. Structure-Activity Relationships

Carbonyl fluoride is the fluorine analogue of phosgene (carbonyl chloride). However, only a small amount of phosgene hydrolyzes when it comes into contact with moisture (NRC 2002), whereas carbonyl fluoride is “instantly hydrolyzed by water” (HSDB 2009). The primary mechanism of action of phosgene is acylation resulting in lipid and protein denaturation, irreversible membrane changes, and disruption of enzymatic function. Death is caused by

pulmonary edema following a latency period of 24 h or longer (NRC 2002). The mechanism of action for carbonyl fluoride is unknown. A latency period was not reported by DuPont (1976), but Scheel et al. (1968a) reported that deaths usually occurred within 24 h of exposure with few latent deaths. In the DuPont (1976) study, a 4-h exposure to carbonyl fluoride in rats led to pulmonary consolidation and edema. Scheel et al. (1968a) reported deep lung focal hemorrhage and edema in rats exposed for 1 h to carbonyl fluoride produced from polytetrafluoroethylene pyrolysis.

4.4. Other Relevant Information

No additional relevant information on carbonyl fluoride was found.

4.4.1. Species Variability

According to Scheel et al. (1968a), pathologic changes in the respiratory tract and liver following exposure to carbonyl fluoride at 310 ppm for 1 h were similar in the dog, rat, mouse, rabbit, and guinea pig.

4.4.2. Susceptible Populations

No information was available on populations especially sensitive to carbonyl fluoride toxicity.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data from which to derive an empirical value for the exponent n, default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used (NRC 2001).

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues for carbonyl fluoride were identified.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to developing AEGL-1 values for carbonyl fluoride were found.

5.2. Animal Data Relevant to AEGL-1

Male albino rats were exposed to carbonyl fluoride at nominal concentrations of 2.5 or 5 ppm for 2 and 2.5 h (DuPont 1956). The low concentration of 2.5 ppm was not lethal to the rats and no clinical signs developed.

5.3. Derivation of AEGL-1 Values

Details of the animal study of carbonyl fluoride (DuPont 1956) were insufficient to consider using it as a basis to derive AEGL-1 values. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to developing AEGL-2 values for carbonyl fluoride were found.

6.2. Animal Data Relevant to AEGL-2

In a study of rats exposed to carbonyl fluoride at nominal concentrations of 2.5 or 5 ppm for 2 or 2.5 h, the no-effect level was 2.5 ppm for both durations. Rats exposed at 5 ppm exhibited dyspnea and cyanosis (DuPont 1956). Rats exposed to carbonyl fluoride at nominal concentrations of 5 or 10 ppm for 4 h (DuPont 1956, 1959) also experienced dyspnea and rapid shallow respiration; a no-effect level was not identified in the study. However, almost no information on the experimental details or assessments of the animals was reported. Thus, the DuPont (1956, 1959) studies do not provide adequate information to accurately define a no-effect level for AEGL-2 effects.

6.3. Derivation of AEGL-2 Values

The available studies on carbonyl fluoride are inadequate for deriving AEGL-2 values. Results of the DuPont (1956, 1959, 1976) studies indicate a steep exposure-response curve. The highest no-effect level for lethality was 10 ppm for 4 h (DuPont 1959) and the lowest lethal concentration was 26.7 ppm for 4 h, with 50% lethality (DuPont 1976). Thus, AEGL-2 values for carbonyl fluoride were set at one-third of the AEGL-3 values, in accordance with the standing operating procedures for developing AEGL values (NRC 2001).

TABLE 2-4 AEGL-2 Values for Carbonyl Fluoride

10 min	30 min	1 h	4 h	8 h
0.35 ppm (0.95 mg/m^3)	0.35 ppm (0.95 mg/m^3)	0.28 ppm (0.76 mg/m^3)	0.17 ppm (0.46 mg/m^3)	0.087 ppm (0.23 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to developing AEGL-3 values for carbonyl fluoride were found.

7.2. Animal Data Relevant to AEGL-3

DuPont (1976) exposed male ChR-CD rats to carbonyl fluoride at 26.7, 30.8, 32.7, 41.3, 44.7, 47.2, or 47.6 ppm for 4 h. Deaths occurred at every concentration. The calculated LC_{50} was 34.3 ppm. The calculated BMC_{01} was 10.4 ppm and the $BMCL_{05}$ was 5.2 ppm (DuPont 1976). The study by Scheel et al. (1968a) was not considered relevant because animals were exposed to a mixture of pyrolysis products of polytetrafluoroethylene, including carbonyl fluoride (Arito and Soda 1977).

7.3. Derivation of AEGL-3 Values

The AEGL-3 values for carbonyl fluoride were determined by using the $BMCL_{05}$ of 5.2 ppm derived from the study by DuPont (1976) as the point-of-departure. The $BMCL_{05}$ was more conservative than the BMC_{01} calculated from the same study. Rapid to convulsive respiration and pulmonary edema were observed in rats exposed for 4 h. Death occurred at all concentrations. An interspecies uncertainty factor of 3 was applied because the toxicity of a direct-acting irritant is not expected to differ substantially among species. The Scheel et al. (1968a) study provides some support for the interspecies uncertainty factor of 3. However exposure to carbonyl fluoride was generated via polytetrafluoroethylene pyrolysis; therefore, exposure included other pyrolysis products. Exposure of rats to carbonyl fluoride at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The investigators stated that the same effects were produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse, but individual data and photomicrographs of the lungs were not provided for those species. An intraspecies uncertainty factor of 3 was applied because carbonyl fluoride is a direct-acting irritant of the lungs and its effects are not expected to differ greatly among individuals.

The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases can be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data from which to derive an empirical value for the exponent n, default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The AEGL-3 values for carbonyl fluoride are presented in Table 2-5.

8. SUMMARY OF AEGLS

8.1. AEGLS Values and Toxicity End Points

AEGL-1 values for carbonyl fluoride are not recommended because of insufficient data. AEGL-2 values are based on a three-fold reduction of the AEGL-3 values because experimental data were not available to empirically derive AEGL-2 values. AEGL-3 values for carbonyl fluoride are based on a $BMCL_{05}$ derived from lethality data in rats. AEGL values for carbonyl fluoride are presented in Table 2-6. For comparison, Table 2-7 provides the AEGL values for phosgene and hydrogen fluoride, because those chemicals are also pyrolysis products of polytetrafluorethylene (see Sections 3.7, 4.1, and 4.2).

8.2. Other Standards and Guidelines

Standards and guidelines for carbonyl fluoride are presented in Table 2-8. No other emergency standards such as emergency response planning guidelines or immediately dangerous to life and health values are available for carbonyl fluoride. The threshold limit value–time-weighted average for carbonyl fluoride was established by the American Conference of Governmental Industrial Hygienists (ACGIH) on the basis of data from Scheel et al. (1968a). The 8-h AEGL values are much lower than the industrial standards and guidelines for carbonyl fluoride. The values of ACGIH and the National Institute for Occupational Safety and Health were determined by analogy with fluorides and hydrogen fluoride and are intended to minimize the potential for pulmonary irritation and disabling bone changes.

TABLE 2-5 AEGL-3 Values for Carbonyl Fluoride

10 min	30 min	1 h	4 h	8 h
1.0 ppm (2.7 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.83 ppm (2.2 mg/m^3)	0.52 ppm (1.4 mg/m^3)	0.26 ppm (0.70 mg/m^3)

TABLE 2-6 AEGL Values for Carbonyl Fluoride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]
AEGL-2 (disabling)	0.35 ppm (0.95 mg/m^3)	0.35 ppm (0.95 mg/m^3)	0.28 ppm (0.76 mg/m^3)	0.17 ppm (0.46 mg/m^3)	0.087 ppm (0.23 mg/m^3)
AEGL-3 (lethal)	1.0 ppm (2.7 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.83 ppm (2.2 mg/m^3)	0.52 ppm (1.4 mg/m^3)	0.26 ppm (0.70 mg/m^3)

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

TABLE 2-7 AEGL Values for Phosgene and Hydrogen Fluoride

Classification	10 min	30 min	1 h	4 h	8 h
Phosgene (NRC 2002)					
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm
AEGL-3 (lethal)	3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm
Hydrogen fluoride (NRC 2004)					
AEGL-1 (nondisabling)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 (disabling)	95 ppm	34 ppm	24 ppm	12 ppm	12 ppm
AEGL-3 (lethal)	170 ppm	62 ppm	44 ppm	22 ppm	22 ppm

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

TABLE 2-8 Standards and Guidelines for Carbonyl Fluoride

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	NR	–	NR	NR	NR	NR
AEGL-2	0.35 ppm (0.95 mg/m^3)	–	0.35 ppm (0.95 mg/m^3)	0.28 ppm (0.76 mg/m^3)	0.17 ppm (0.46 mg/m^3)	0.087 ppm (0.23 mg/m^3)
AEGL-3	1.0 ppm (2.7 mg/m^3)	–	1.0 ppm (2.7 mg/m^3)	0.83 ppm (2.2 mg/m^3)	0.52 ppm (1.4 mg/m^3)	0.26 ppm (0.70 mg/m^3)
TLV-TWA (ACGIH)[a]	–	–	–	–	–	2 ppm (5.4 mg/m^3)
REL-TWA (NIOSH)[b]	–	–	–	–	–	2 ppm (5.4 mg/m^3)
TLV-STEL (ACGIH)[c]	–	5 ppm (13 mg/m^3)	–	–	–	–
REL-STEL (NIOSH)[d]	–	5 ppm (15 mg/m^3)	–	–	–	–
MAC (The Netherlands)[e]	–	0.38 ppm (1 mg/m^3)	–	–	–	–

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

[b]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011a) is defined as the time-weighted average concentration for up to a 10-h workday during a 40-h workweek.
[c]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is defined as a 15-min time-weighted average exposure which should not be exceeded at any time during the workday even if the 8-h time-weighted average is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in that range.
[d]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011a) is defined as a 15-min time-weighted average exposure that should not be exceeded at any time during the workday.
[e]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

There are no human data available on carbonyl fluoride. DuPont (1956, 1959, and 1976) conducted studies of rats exposed to carbonyl fluoride for 2-4 h, but two of the studies reported only nominal concentrations, used relatively few animals, and reported few study details. Scheel et al. (1968a, 1968b) exposed rats to carbonyl fluoride produced by burning polytetrafluoroethylene. While carbonyl fluoride is a major pyrolysis product, it is not the only pyrolysis product produced (Arito and Soda 1977) and the rats were probably exposed to other compounds that contain fluoride. The animals were also exposed to the particulate matter produced from polytetrafluoroethylene pyrolysis, which may have increased observed effects. Additional acute animal studies in other species and with a greater range of concentrations would be helpful in deriving AEGL values. No studies on genotoxicity or reproductive and developmental toxicity were found; additional studies evaluating those outcomes would also help to strengthen the basis of the AEGL values for carbonyl fluoride.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CARBONYL FLUORIDE

Derivation of AEGL-1 Values

AEGL-1 values are not recommended because of insufficient data on carbonyl fluoride. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

In the absence of empirical data on carbonyl fluoride, the AEGL-2 values for carbonyl fluoride were set at one-third of the AEGL-3 values. That approach is in in accordance with the standing operating procedures for developing AEGL values for chemicals with steep concentration-response curves (NRC 2001). Rats exposed to carbonyl fluoride at 5 or 10 ppm for 4 h experienced dyspnea and rapid shallow respiration (DuPont 1956, 1959). At higher concentrations (26.7 ppm or higher for 4 h), death occurred, indicating a steep exposure-response curve (DuPont 1976).

Calculations:

10-min AEGL-2:	1.04 ppm ÷ 3 = 0.35 ppm
30-min AEGL-2:	1.04 ppm ÷ 3 = 0.35 ppm
1-h AEGL-2:	0.83 ppm ÷ 3 = 0.28 ppm
4-h AEGL-2:	0.52 ppm ÷ 3 = 0.17 ppm
8-h AEGL-2:	0.26 ppm ÷ 3 = 0.087 ppm

Derivation of AEGL-3 Values

Key study:	DuPont (E.I. DuPont de Nemours and Company, Inc.). 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont, Haskell Laboratory, Newark, DE
Toxicity end point:	Threshold for lethality; $BMCL_{05}$ of 5.2 ppm
Time scaling:	The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases may be described by

	the relationship $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data to derive an empirical value for n, default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min value in accordance with the standing operating procedures for developing AEGL values (NRC 2001). 5.2 ppm ÷ 10 = 0.52 ppm $(0.52 \text{ ppm})^3 \times 240 \text{ min} = 33.74592 \text{ ppm-min}$ $(0.52 \text{ ppm})^1 \times 240 \text{ min} = 124.8 \text{ ppm-min}$
Uncertainty factors:	Interspecies: 3, effects of a direct-acting irritant of the lungs and respiratory tract are not expected to differ greatly among species. The study by Scheel et al. (1968a) provides some support for a factor of 3. However, exposure to carbonyl fluoride was generated via polytetrafluoroethylene pyrolysis; therefore, exposure included other pyrolysis products. Exposure of rats to carbonyl fluoride at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The investigators stated that those effects were produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse. However, individual data and photomicrographs of the lungs were not provided for those species. Intraspecies: 3, effects of a direct-acting irritant of the lungs and respiratory tract are not expected to differ greatly among individuals.
Modifying factor:	None applied
Calculations:	
10-min AEGL-3:	$C^3 \times 30 \text{ min} = 33.74592 \text{ ppm-min}$ C = 1.0 ppm
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 33.74592 \text{ ppm-min}$ C = 1.0 ppm

1-h AEGL-3:	$C^3 \times 60$ min = 33.74592 ppm-min C = 0.83 ppm
4-h AEGL-3:	C × 240 min = 124.8 ppm-min C = 0.52 ppm
8-h AEGL-3:	C × 480 min = 124.8 ppm-min C = 0.26 ppm

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR CARBONYL FLUORIDE

Derivation Summary

AEGL-1 VALUES

No AEGL-1 values were derived for carbonyl fluoride because of insufficient data.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.35 ppm	0.35 ppm	0.28 ppm	0.17 ppm	0.087 ppm

Data adequacy: Data on carbonyl fluoride were inadequate for deriving AEGL-2 values, so values were estimated by dividing the AEGL-3 values by 3. That procedure, based on guidance in NRC (2001), is applicable for chemicals with steep concentration-response curves. Rats exposed to carbonyl fluoride at 5 or 10 ppm for 4 h experienced dyspnea and rapid shallow respiration (DuPont 1956, 1959). At higher concentrations (26.7 ppm and higher for 4 h), death occurred indicating a steep exposure-response curve (DuPont 1976).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.0 ppm	1.0 ppm	0.83 ppm	0.52 ppm	0.26 ppm

Key reference: DuPont (E.I. DuPont de Nemours and Company, Inc.) 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont, Haskell Laboratory, Newark, DE.

Test species/Strain/Number: Rat; ChR-CD; 10/group

Exposure route/Concentrations/Durations: Inhalation; 26.7, 30.8, 32.7, 41.3, 44.7, 47.2, 47.6 ppm for 4 h

Effects: Rapid shallow respiration and pulmonary edema.
26.7 ppm: 50% mortality
30.8 ppm: 30% mortality
32.7 ppm: 30% mortality
41.3 ppm: 60% mortality
44.7 ppm: 80% mortality
47.2 ppm: 90% mortality
47.6 ppm: 60% mortality

End point/Concentration/Rationale: Threshold for lethality ($BMCL_{05}$ of 5.2 ppm)

Uncertainty factors/Rationale:
Interspecies: 3, effects of a direct-acting irritant of the lungs and respiratory tract are not expected to differ greatly among species. The study by Scheel et al. (1968a) provides some support for a factor of 3. However exposure to carbonyl fluoride was generated

(Continued)

AEGL-3 VALUES Continued

via polytetrafluoroethylene pyrolysis; therefore, exposure included other pyrolysis products. Exposure of rats to carbonyl fluoride at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The investigators stated that this effect was produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse. However, individual data and photomicrographs of the lungs were not provided for those species. Intraspecies: 3, effects of a direct-acting irritant of the lungs and respiratory tract are not expected to differ greatly among individuals.
Modifying factor: None
Animal-to-human dosimetric adjustment: Not applied
Time scaling: The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases has been described by the relationship $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific to derive an empirical value for n, default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min value in accordance with the standing operating procedures for developing AEGL values (NRC 2001).
Data adequacy: The study was well done with an appropriate number of animals. Analytic concentrations were measured and an end point consistent with the AEGL-3 definition was observed.

APPENDIX D

BENCHMARK DOSE CALCULATIONS

BMDS MODEL RUN $BMCL_{05}$

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

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 8
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -7.52665
Slope = 2.13336

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-6.88857	2.62927	-12.0418	-1.7353
Slope	1.94933	0.724479	0.529374	3.36928

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

Analysis of Deviance Table

Model	Log (likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.8638	8			
Fitted model	-44.0906	2	6.45349	6	0.3744
Reduced model	-55.4518	1	29.1759	7	0.0001344

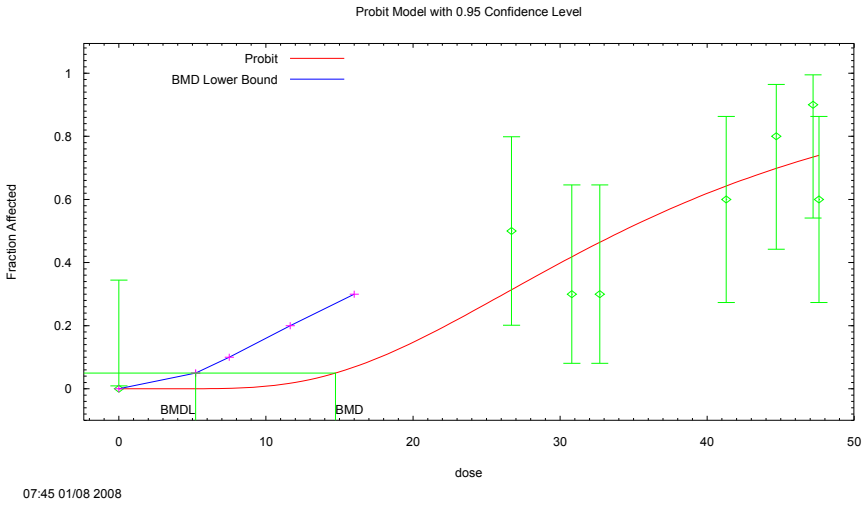
AIC: 92.1812

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0.000
26.7000	0.3136	3.136	5	10	1.271
30.8000	0.4179	4.179	3	10	-0.756
32.7000	0.4639	4.639	3	10	-1.039
41.3000	0.6423	6.423	6	10	-0.279
44.7000	0.6981	6.981	8	10	0.702
47.2000	0.7340	7.340	9	10	1.188
47.6000	0.7394	7.394	6	10	-1.004

Chi-square = 6.26 d.f. = 6 P-value = 0.3951

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 14.7319
BMDL = 5.21965



BMDS MODEL RUN BMC_{01}

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

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 8
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -7.52665
Slope = 2.13336

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-6.88857	2.62918	-12.0417	-1.73548
Slope	1.94933	0.724454	0.529424	3.36923

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

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance	Test d.f.	P-value
Full model	-40.8638	8			
Fitted model	-44.0906	2	6.45349	6	0.3744
Reduced model	-55.4518	1	29.1759	7	0.0001344

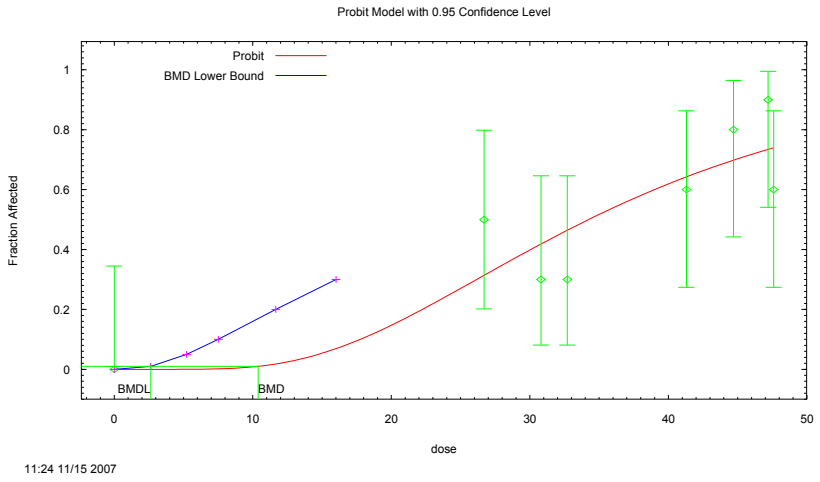
AIC: 92.1812

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
26.7000	0.3136	3.136	5	10	1.271
30.8000	0.4179	4.179	3	10	-0.756
32.7000	0.4639	4.639	3	10	-1.039
41.3000	0.6423	6.423	6	10	-0.279
44.7000	0.6981	6.981	8	10	0.702
47.2000	0.7340	7.340	9	10	1.188
47.6000	0.7394	7.394	6	10	-1.004
0.0000	0.0000	0.000	0	10	0.000

Chi-square = 6.2 d.f. = 6 P-value = 0.3951

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 10.3855
BMDL = 2.64042



APPENDIX E

CATEGORY PLOT FOR CARBONYL FLUORIDE

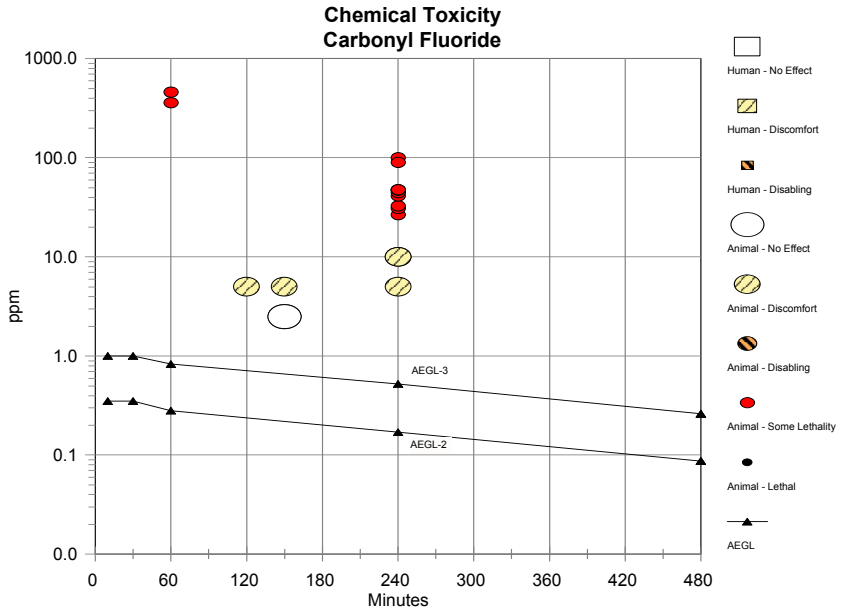


FIGURE E-1 Category plot of toxicity data and AEGL values for carbonyl fluoride.

TABLE E-1 Data Used in the Category Plot for Carbonyl Fluoride

Source	Species	Sex	No. of Exposures	ppm	Time (min)	Category	Comments
AEGL-2				0.35	10	AEGL	
AEGL-2				0.35	30	AEGL	
AEGL-2				0.28	60	AEGL	
AEGL-2				0.17	240	AEGL	
AEGL-2				0.087	480	AEGL	
AEGL-3				1	10	AEGL	
AEGL-3				1	30	AEGL	
AEGL-3				0.83	60	AEGL	
AEGL-3				0.52	240	AEGL	
AEGL-3				0.26	480	AEGL	
DuPont 1956	Rat	M	1	2.5	120	0	No effect
DuPont 1956	Rat	M	1	2.5	150	0	No effect
DuPont 1956	Rat	M	1	5	120	1	Slight dyspnea; cyanosis
DuPont 1956	Rat	M	1	5	150	1	Slight dyspnea; cyanosis
DuPont 1959	Rat	M	1	5	240	1	Rapid, shallow respiration
DuPont 1959	Rat	M	1	10	240	1	Rapid, shallow respiration
DuPont 1959	Rat	M	1	100	240	SL	Pulmonary congestion
Scheel et al. 1968a	Rat	B	1	360	60	SL	50% mortality
Scheel et al. 1968a	Rat	B	1	460	60	SL	50% mortality

Scheel et al. 1968a	Rat	B	1	90	240	SL	50% mortality
DuPont 1976	Rat	M	1	26.7	240	SL	50% mortality
DuPont 1976	Rat	M	1	30.8	240	SL	30% mortality
DuPont 1976	Rat	M	1	32.7	240	SL	30% mortality
DuPont 1976	Rat	M	1	41.3	240	SL	60% mortality
DuPont 1976	Rat	M	1	44.7	240	SL	80% mortality
DuPont 1976	Rat	M	1	47.2	240	SL	90% mortality
DuPont 1976	Rat	M	1	47.6	240	SL	60% mortality

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

3

Selected Halogen Fluorides[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

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

1. GENERAL INFORMATION ON SELECTED HALOGEN FLUORIDES

In this chapter, the bases of the AEGL values for the following three halogen fluorides are described: chlorine pentafluoride (ClF_5), bromine pentafluoride (BrF_5), and bromine trifluoride (BrF_3). Information relevant to all three compounds is presented first, and is followed by separate sections on the individual chemicals.

1.1. Physical and Chemical Properties

The physical and chemical properties for ClF_5, BrF_5, and BrF_3 are presented in Table 3-1. ClF_5 is an extremely reactive gas. The gas does not burn, but may ignite combustibles. It explodes on contact with organic materials, is violently hydrolyzed by water, and reacts vigorously or explosively with metals and fuels. Explosions may result from reaction with other chemicals, including ammonia, carbon monoxide, hydrogen sulfide, sulfur dioxide, and hydrogen gas (Teitelbaum 2001).

TABLE 3-1 Chemical and Physical Properties of Selected Halogen Fluorides[a]

Parameter	Chlorine pentafluoride	Bromine pentafluoride	Bromine trifluoride
Synonyms	None	Bromine fluoride	None
CAS registry no.	13637-63-3	7789-30-2	7787-71-5
Chemical formula	ClF_5	BrF_5	BrF_3
Molecular weight	130.45	174.89	136.91
Physical state	Colorless gas[b]	Liquid	Colorless to pale yellow liquid
Melting point	-103ºC[b]	-60.5ºC	8.77°C
Boiling point	-13.1ºC[b]	40.76ºC	125.75ºC
Solubility in water	Violently hydrolyzed by water[c]	Explodes on contact with water	Reacts with water
Density/specific gravity (water = 1)	1.79 mg/L at 20ºC[d]	2.4604 g/mL at 25ºC	2.803 g/mL at 25ºC
Vapor density (air = 1)	5.3 g/L[b]	6.05	4.7[e]
Vapor pressure	3.4 bar at 20ºC[f]	328 mm Hg at 20ºC[g]	2.8030 g/cm^3
Flammability limits	Nonflammable[c]	Nonflammable	Nonflammable
Conversion factors (calculated)	1 ppm = 5.34 mg/m^3 1 mg/m^3 = 0.19 ppm	1 ppm = 7.15 mg/m^3 1 mg/m^3 = 0.14 ppm	1 ppm = 5.6 mg/m^3 1 mg/m^3 = 0.18 ppm

[a]HSDB (2007a,b) except where noted.
[b]Lide (1999).
[c]Teitelbaum (2001).
[d]Bailey and Woytek (2004).
[e]Weiss (1980).
[f]Air Liquide (2005).
[g]NIOSH/OSHA (1992).

ClF_5 is proposed to react with water according to the following reaction (Darmer 1971):

$$ClF_5 + 2H_2O \rightarrow ClO_2F + 4HF$$

The reaction of ClF_5 and other halogen fluorides with water is violent (Aigueperse et al. 2000; Bailey and Woytek 2004; Atwood 2006). Following hydrolysis of ClF_5, the reaction of the breakdown product hydrogen fluoride (HF) with OH is endothermic and, therefore, not a viable source of F atoms (Syage 1994).

BrF_5 is a colorless or light yellow liquid when below its boiling point of 40.8ºC. Above its boiling point, BrF_5 is a colorless, pungent, and corrosive gas. It is stable to heat, shock, and electric sparks (ACGIH 2001). Although nonflammable, fire may result from contact of BrF_5 with combustibles at room temperature. Reaction with water is violent, with potential release of bromine, fluorine, hydrogen bromide, and hydrogen fluoride (Dost et al. 1968; NIOSH/OSHA 1992; Teitelbaum 2001).

BrF_3 is a highly toxic, colorless to yellow or red liquid. The commercial grade is yellow to red in color due to contamination with bromine. BrF_3 has the highest boiling point of any of the halogen fluorides. It is extremely reactive; reaction with water releases bromine, oxygen, and bromic and hydrofluoric acids. BrF_3 etches glass, sets fire to paper and wood, and reacts violently with most organic compounds (Braker and Mossman 1980; Bailey and Woytek 2004; HSDB 2007a). Reaction of BrF_3 with water is likewise violent, producing a complex mixture of products including bromine and bromic and hydrofluoric acids (Braker and Mossman 1980; Owen 2005). According to Weiss (1980), the primary product is HF.

Information on the hydrolysis of ClF_3 provides additional information on the hydrolysis of the halogen fluorides, as similar products are formed. ClF_3 decomposes by hydrolysis to a variety of substances including ClOF (the initial product), ClF, ClO_2F, ClO_3F, ClO_2, Cl_2, and HF; higher humidity increases the rate of decomposition (reviewed by NRC 2007a).

1.2. Use and Production

ClF_5 was once considered for use as an oxidizing propellant for missile propulsion, along with hydrazine and monomethyl hydrazine (Darmer et al. 1972; Syage 1994). A typical missile-launch-propellant payload would involve 2,000 kg of ClF_5 (Syage 1994). At present, ClF_5 has no significant industrial use other than as a fluorinating and oxidizing agent (Teitelbaum 2001). The halogen fluorides are manufactured by the reaction of fluorine with the corresponding halogen (Bailey and Woytek 2004). No information on storage and transportation of ClF_5 was available.

BrF_5 is manufactured by the fluorination of bromine at 200ºC in a metal apparatus (O'Neil et al. 2001). It can also be prepared by heating a mixture of BrF_3 and fluorine to 200ºC. It is shipped in compressed gas containers under its own vapor pressure (Braker and Mossman 1980; NIOSH/OSHA 1992). BrF_5 is predominantly used as a fluorinating agent to produce fluorocarbons and as an oxidizer in rocket propellant systems (ACGIH 2001). Metal chlorides, bromides, and iodides are converted to fluorides by treatment with BrF_5 (Braker and Mossman 1980). Uranium is converted to uranium hexafluoride by strong oxidizing agents, including BrF_5 (Bailey and Woytek 2004).

BrF_3 is prepared by direct combination of one part bromine with three parts fluorine in a water-cooled copper reactor at temperatures between 15 and 50°C, or by the reaction of bromine fluoride with fluorine (Braker and Mossman 1980). No production data on BrF_3 were available. BrF_3 is used as a solvent for other fluorides and as a fluorinating agent. It is used as an oxidizing agent in cutting tools used in deep oil-well drilling. Uranium is converted by BrF_3 to uranium hexafluoride. It has also been of interest as a propellant for rockets and missiles (Braker and Mossman 1980; Bailey and Woytek 2004).

1.3. Structure-Activity Relationships

ClF_5, ClF_3, BrF_5, BrF_3, HF, and ClO_2 are toxicologically related, and all produce the toxic effect at the point of absorption, which is primarily related to the agent's physical form (vapor, mist, and aerosol). 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. Hydrolysis of ClF_5 is predicted to follow a similar path. If a similar path exists for bromine to form BrO_2, it is expected to be less toxic than ClO_2, as BrO_2 is less reactive than ClO_2.

Lethality data provide a means of comparing the relative toxicities of these compounds; 1-h lethality data for ClO_2, CLF_5, CLF_3, BrF_5, and HF are presented in Table 3-2 (no data were available for BrF_3). On the basis of LC_{50} (lethal concentration, 50% lethality) values, the relative toxicities of these agents are:

$$ClO_2 > ClF_5 > ClF_3 \approx BrF_5 > HF$$

The toxicities could be expressed in terms of HF equivalents. ClF_3 is approximately seven times more toxic than HF, and ClF_5 is approximately 10 times more toxic than HF. The relative toxicities indicate that ClO_2, an intermediate in the dissociation of ClF_x, plays a role in the toxicity of these agents. Inhalation studies with rats indicate that the toxicity of ClF_3 is comparable to that of chlorine dioxide (ClO_2) on the basis of chlorine equivalents and is comparable to that of HF on the basis of fluorine equivalents (Dost et al. 1974).

The hydrolysis of ClF_5 is exothermic. Therefore, the enhanced toxicity of ClF_5 relative to HF on a fluorine atom equivalent basis may be due to the effect of heat from the reaction (Syage 1994).

Few data are available for bromine fluorides. For BrF_5, Dost et al. (1970) reported a 1-h 95% lethal concentration of 500 ppm in male Sprague-Dawley rats. When the exposure duration was reduced to 30 min, none of the rats died; however, the observation period after exposure was for only 20 h before the rats were killed. The 1-h LC_{50}s for ClF_5 and ClF_3 in rats were 122 and 299 ppm, respectively. The data suggests that BrF_5 is less toxic than ClF_5, which is in accordance with their chemical reactivity. By extension, BrF_3 is predicted to be less toxic than ClF_3.

The order of relative toxicities closely follows the chemical reactivity of the halogenated fluorine compounds. According to Bailey and Woytek (2004), the chemical reactivity of these compounds is, in order of decreasing reactivity: ClF_5 > ClF_3 > BrF_5 > iodine heptafluoride (IF_7) > chlorine monofluoride (ClF) > BrF_3 > iodine pentafluoride (IF_5) > bromine monofluoride (BrF).

TABLE 3-2 One-hour LC_{50} Values for Halogen Fluorides and Related Compounds or Decomposition Products[a]

Species	ClO_2 (ppm)	ClF_5 (ppm)	ClF_3 (ppm)	BrF_5 (ppm)	HF (ppm)
Monkey	–	173	230	–	1,774
Dog	–	122	–	–	–
Rat	$10 < LC_{50} < 54$[b]	122	299	<500 (LC_{95})[c]	1,276
Mouse	–	57	178	–	501

[a]Darmer et al. (1972) except where noted.
[b]NRC (2004).
[c]Dost et al. (1968, 1970).

1.4. Absorption, Distribution, Metabolism, and Excretion

As discussed above, the halogen fluorides are expected to hydrolyze rapidly in the moist respiratory tract. No information on the absorption, metabolism, or excretion of these compounds was found in the scientific literature.

Few data are available to evaluate systemic fluoride deposition after exposure to the halogen fluorides. Bone fluoride concentrations in monkeys exposed by inhalation to ClF_5 at 10 ppm for 60 min, 20 ppm for 30 min, or 30 ppm for 10 min were not substantially different from those of untreated controls; measurements were made 28 days after exposure (MacEwen and Vernot 1972). Dost et al. (1970) measured fluoride in rat tissues following exposure to BrF_5 at 500 ppm for 30 min or ClF_3 at 400 ppm for 15 min; selected results are presented in Table 3-3. The data show increased fluoride content in the blood and lungs immediately after exposure, which declined over time. Mean fluoride in bone increased from 300 µg/g immediately after exposure to BrF_5 to 353 µg/g 20 h later. After exposure to ClF_3, mean fluoride in bone increased from 118 to 172 µg/g over a 24-h period. Although a small number of animals (four to six) are represented by the mean values and fluoride concentrations in untreated rats (see Table 3-3) varied widely, the data suggest that, at higher concentrations of halogen fluorides, fluoride may be absorbed into the bloodstream and distributed to bone and other tissues.

Systemic distribution of fluoride is not believed to be a significant factor in the acute inhalation toxicity and lethality of the halogen fluorides, as the primary symptoms and cause of death (see Section 1.5) are associated with corrosion of the tissues at the site of contact. In contrast, acute systemic fluoride poisoning leads to hypocalcemia and symptoms of convulsions, coma, hypotension, and acidosis (HSDB 2007a,b).

1.5. Mechanism of Toxicity

The mechanism by which halogen fluorides exert their acute toxicity is by direct irritation and corrosion. In experimental animals, these strong oxidizing

chemicals produce lacrimation, sneezing, and salivation, which progresses to nausea, difficult respiration, and unconsciousness with cyanosis. Lacrimation and rhinorrhea are responses to stimulation of the trigeminal nerve. The eyes and exposed skin suffer burns. At the high concentrations that cause lethality, the capacity of the upper respiratory tract to scrub the halogen fluorides from the inhaled air is exceeded, and the chemicals penetrate to the lungs, causing edema and destruction of the pulmonary tissue (Horn and Weir 1955; Dost et al. 1968, 1974; MacEwen and Vernot 1970, 1973; Darmer et al. 1972). These signs were observed in monkeys, dogs, rats, and mice exposed to ClF_5 (Darmer et al. 1972) and in rats exposed to BrF_5.

The hydrolysis of ClF_5 is exothermic. Acute intraperitoneal, intravenous, or intragastric administration of ClF_5 (10, 25, or 50 µL) to rats, rabbits, guinea pigs, and cats resulted in rupture of the surrounding areas and destruction of the blood vessels leading to hemorrhage, and was followed by respiratory depression, cardiac failure, and death (Weinberg and Goldhamer 1967). Hydrolysis of other halogenated fluorides may be similarly exothermic. Thus, at sufficiently high concentrations, the heat of hydrolysis may play a fundamental role in tissue destruction.

1.6. Species Variability

As evidenced by the 15-, 30-, and 60-min LC_{50} values (see Table 3-4), the mouse is more sensitive to the lethal effects of ClF_5 than the other species tested. The dog and rat are equally sensitive, and the monkey is the least sensitive to the toxic effects of ClF_5. The 1- h LC_{50} values for ClF_5 differ by a factor of 3 between the most sensitive species, the mouse (57 ppm), and the least sensitive species, the monkey (173 ppm).

TABLE 3-3 Fluoride Content in Bone, Blood Plasma, and Lungs of Rats Exposed to BrF_5 (500 ppm for 30 min) or ClF_3 (400 ppm for 15 min) and in Control Rats

Exposure	Bone (µg/g)	Blood plasma (µg/g)	Lungs (µg/g)
Unexposed rats (group A)	308 (230-403)	No data	2.0 (0.8-2.8)
Unexposed rats (group B)	144 (112-174)	0.4 (0-0.6)	0.2 (0-0.6)
Unexposed rats (group C)	145 (125-184)	1.6 (1.5-1.7)	1.2 (0.9-1.7)
BrF_5 (immediately after exposure)	300 (235-378)	7.8 (6.5-9.0)	5.9 (3.0-8.5)
BrF_5 (20 h after exposure)	353 (278-415)	3.7 (3.0-4.5)	2.0 (1.5-3.0)
ClF_3 (immediately after exposure)	118 (97-135)	No data	2.6 (1.4-4.2)
ClF_3 (24 h after exposure)	172 (128-232)	No data	1.3 (0.2-3.2)

Source: Data from Dost et al. 1970.

TABLE 3-4 Species Variability in LC_{50} Values for ClF_5

Species	15 min	30 min	1 h
Monkey	249 ppm	-	173 ppm
Dog	298 ppm	156 ppm	122 ppm
Rat	257 ppm	194 ppm	122 ppm
Mouse	144 ppm	105 ppm	57 ppm

Source: Adapted from Darmer et al. 1972.

No information was found on species variability in the lethal effects of BrF_5 or BrF_3. There is very little variation in species sensitivity to lethal concentrations of the related compound ClF_3. As Table 3-2 shows, the 1-h LC_{50} values for three species, the monkey, rat, and mouse, were remarkably similar, exhibiting a less than 2-fold difference. For HF, the order of relative sensitivity is generally mouse > rat > monkey (Table 3-2).

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 air-flow 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 for irritants to humans than is the rodent. Furthermore, 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. Lethality data (Table 3-4) demonstrate this difference; the monkey is the least sensitive of the four species exposed to ClF_5. On the basis of relative body size, the respiratory rate of humans is lower than that of monkeys, resulting in a lower dose to the target tissues in the respiratory tract in humans.

1.7. Susceptible Populations

No information on subpopulations that are especially sensitive to the effects of the halogen fluorides was found. Individuals with asthma may respond to exposure to respiratory irritants with increased bronchial responsiveness. The elderly and those who are ill may also have increased susceptibility to the effects of irritants.

Individuals under stress, such as those involved in emergency situations and individuals engaged in physical activity, will experience greater deposition and pulmonary irritation than individuals at rest. Furthermore, individuals who breathe through their mouths would be at greater risk.

1.8. Concentration-Exposure Duration Relationship

For ClF_5, the dose-response curve for lethality is steep. Data on four species exposed to ClF_5 (see Section 2.2.1.) show that less than a doubling of a con-

centration is necessary to go from no deaths to the LC_{50} value. Dost et al. (1970) noted that the dose-response curve for fluoride oxidizing agents is generally steep. Using the mortality data for four species in the study of Darmer et al. (1972), ten Berge et al. (1986) calculated regression coefficients for the concentration-time-mortality response relationships of ClF_5. The n value in the equation $C^n \times t = k$ for the monkey, dog, rat, and mouse were 4.1, 1.4, 1.9, and 1.5, respectively. On the basis of lethality data, the n value for HF is 2 (NRC 2004) and for ClF_3 is 1.3. A graph showing the regression analyses of 15-, 30-, and 60-min LC_{50} values for the rat is shown in Appendix A. The regression analysis confirmed the ten Berge et al. (1986) time-scaling value for n of 1.9 in the rat.

The data from the MacEwen and Vernot (1971, 1972, 1973) studies of ClF_5 indicate that, at least for the direct irritant responses to ClF_5, concentration may be more important than exposure duration. However, for the other effects observed (e.g., lung pathology, pale liver and kidneys), the role of exposure duration versus concentration is difficult to interpret because the studies provided few qualitative and quantitative details of the pathology findings. Discordant findings could be due to the dissociation to other agents or to a metabolic pathway.

The lethality data from the sparse data set on BrF_5 (see Section 3.2.1.) indicate that the dose-response curve is steep. Using the two nonlethal data points, 500 ppm for 40 min and 1,000 ppm for 20 min, the value for the exponent n value in the relationship $C^n \times t = k$ might be approximated at 1. However, because lethality data for BrF_5 is sparse, the more conservative default time-scaling values of $n = 3$ when extrapolating to shorter durations and $n = 1$ when extrapolating to longer durations were used when time-scaling the AEGL-3 values.

No information on a concentration-exposure duration relationship for BrF_3 was found.

For comparison, an n value of 1.3 was used to time scale AEGL values for ClF_3 (NRC 2007a) and an n value of 2.0 was used for hydrogen fluoride (NRC 2004).

1.9. Concurrent Exposure Issues

The available data suggest that the halogen fluorides operate via direct contact irritation, and are highly reactive in a moist environment. As noted in Section 1.1, higher humidity is expected to increase the rate of decomposition of these compounds and, thus, may enhance their toxicity.

Coexposure to more than one of the halogen fluorides may result in greater exposure to the common decomposition products such as ClO_2 and HF. In addition, use of BrF_5 and BrF_3 in the synthesis of uranium hexafluoride suggests the possibility of coexposure to bromine and uranium fluorides in the context of accidental releases. As HF is a hydrolysis product of both the bromine fluorides and uranium hexafluoride (NRC 2004), coexposure to these compounds might lead to greater toxicity due to higher levels of the reaction product HF.

1.10. Summary of AEGLs for Selected Halogen Fluorides

AEGL-1 values are not recommended for ClF_5, as the available data for AEGL-1 effects resulted in values that were very similar to the AEGL-2 values, indicating inadequate warning properties for this compound. AEGL-2 values were based on no-effect levels for irritation symptoms that might impair escape in four animal species exposed to ClF_5 for 10 min or 1 h. AEGL-3 values were derived from the highest nonlethal concentration in rats. An uncertainty factor of 3 was used to account for interspecies differences and another factor of 3 was used to account for intraspecies variability. The factors are supported by data on ClF_5 and related compounds that indicate limited interspecies variability and because the mechanism of action of ClF_5 is direct irritation or corrosion, so metabolic and physiologic differences are unlikely to play a major role. Time scaling was performed using the equation $C^n \times t = k$. An empirical value for n of 1.9 was derived from lethality data on ClF_5.

No data pertinent to the AEGL-1 values for BrF_5 were found, so AEGL-1 values are not recommended. Similarly, no data were available for AEGL-2 end points. In the absence of suitable data, the AEGL-2 values were set equal to those for the related compound ClF_5. AEGL-3 values for BrF_5 were based on the highest nonlethal concentration in rats. As with ClF_5, uncertainty factor of 3 each were used to account for interspecies differences and intraspecies variability. Time scaling was performed using the equation $C^n \times t = k$; default values of n = 1 when extrapolating to longer durations and n = 3 when extrapolating to shorter durations were used.

No human or animal data on the toxicity of BrF_3 were available. AEGL values for this compound were set equal to the AEGLs for the related compound ClF_3 (NRC 2007a). Because BrF_3 is expected to be less toxic than ClF_3, a modifying factor to account for lack of data was not used.

A summary of the AEGL values for the three halogen fluorides is presented in Table 3-5. For comparison, AEGL values for ClF_3, HF, and ClO_2 are presented in Table 3-6.

1.11. Data Adequacy and Research Need

Other than a brief case report on ClF_5 exposure, there are no human data on the toxicity of ClF_5, BrF_5, or BrF_3. Likewise, human data on the related compound ClF_3 include a single case report of a brief (1-2 min) exposure (NRC 2007a).

The acute toxicity of ClF_5 in animals has been well-studied for durations up to 1 h, although some of the studies lack histopathology data. There are no data on the toxicity of ClF_5 for exposures longer than 1 h. Data on the acute toxicity of BrF_5 include a single study (Dost et al. 1968) conducted in male rats exposed to one of two concentrations for durations of 20-60 min. The study provided inadequate information on methods (in particular, duration of follow-up was not specified) and did not include microscopic examination of tissues.

TABLE 3-5 AEGL Values for Selected Halogen Fluorides

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
Chlorine pentafluoride						
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient warning properties.
AEGL-2 (disabling)	0.70 ppm (3.7 mg/m^3)	0.39 ppm (2.1 mg/m^3)	0.17 ppm (0.91 mg/m^3)	0.082 ppm (0.44 mg/m^3)	0.057 ppm (0.30 mg/m^3)	No-effect level for impaired ability to escape (MacEwen and Vernot 1972, 1973).
AEGL-3 (lethal)	21 ppm (110 mg/m^3)	12 ppm (64 mg/m^3)	8.0 ppm (43 mg/m^3)	3.9 ppm (21 mg/m^3)	2.7 ppm (14 mg/m^3)	Highest 1-h nonlethal concentration in rats (Darmer et al. 1972).
Bromine pentafluoride						
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	0.70 ppm (5.0 mg/m^3)	0.39 ppm (2.8 mg/m^3)	0.17 ppm (1.2 mg/m^3)	0.082 ppm (0.57 mg/m^3)	0.057 ppm (0.41 mg/m^3)	Set equal to AEGL-2 values for chlorine pentafluoride.
AEGL-3 (lethal)	79 ppm (570 mg/m^3)	55 ppm (390 mg/m^3)	33 ppm (240 mg/m^3)	8.3 ppm (59 mg/m^3)	4.2 ppm (30 mg/m^3)	Highest nonlethal concentration in rats (Dost et al. 1970).
Bromine trifluoride						
AEGL-1 (nondisabling)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	Set equal to AEGL-1 values for chlorine trifluoride (NRC 2007a).
AEGL-2 (disabling)	8.1 ppm (45 mg/m^3)	3.5 ppm (20 mg/m^3)	2.0 ppm (11 mg/m^3)	0.70 ppm (3.9 mg/m^3)	0.41 ppm (2.3 mg/m^3)	Set equal to AEGL-2 values for chlorine trifluoride (NRC 2007a).
AEGL-3 (lethal)	84 ppm (470 mg/m^3)	36 ppm (200 mg/m^3)	21 ppm (120 mg/m^3)	7.3 ppm (41 mg/m^3)	7.3 ppm (41 mg/m^3)	Set equal to AEGL-3 values for chlorine trifluoride (NRC 2007a).

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

TABLE 3-6 AEGL Values for Hydrogen Fluoride, Chlorine Trifluoride, and Chlorine Dioxide

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1						
Hydrogen fluoride (NRC 2004)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	Threshold, pulmonary inflammation in humans (Lund et al. 1997, 1999).
Chlorine trifluoride (NRC 2007a)	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	Slight irritation – dog (Horn and Weir 1956).
Chlorine dioxide (NRC 2007b)	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	Slight salivation, slight lacrimation, and slight chromodacryorrhea in rats exposed at 3 ppm for 6 h (DuPont 1955).
AEGL-2						
Hydrogen fluoride (NRC 2004)	95 ppm	34 ppm	24 ppm	12 ppm	12 ppm	NOAEL for pulmonary effects in cannulated rats (Dalbey 1996, Dalbey et al. 1998)[a], sensory irritation in dogs (Rosenholtz et al. 1963)[b].
Chlorine trifluoride (NRC 2007a)	8.1 ppm	3.5 ppm	2.0 ppm	0.70 ppm	0.41 ppm	Threshold, impaired ability to escape – dog (Horn and Weir 1956).
Chlorine dioxide (NRC 2007b)	1.4 ppm	1.4 ppm	1.1 ppm	0.69 ppm	0.45 ppm	Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed at 12 ppm for 6 h (DuPont 1955).
AEGL-3						
Hydrogen fluoride (NRC 2004)	170 ppm	62 ppm	44 ppm	22 ppm	22 ppm	Lethality threshold in cannulated rats (Dalbey 1996; Dalbey et al. 1998)[c]; lethality threshold in mice (Wohlslagel et al. 1976)[d].
Chlorine trifluoride (NRC 2007a)	84 ppm	36 ppm	21 ppm	7.3 ppm	7.3 ppm	Threshold for lethality – monkey (MacEwen and Vernot 1970).
Chlorine dioxide (NRC 2007b)	3.0 ppm	3.0 ppm	2.4 ppm	1.5 ppm	0.98 ppm	No lethality in rats exposed at 26 ppm for 6 h (DuPont 1955).

[a]10-min AEGL-2 value.
[b]30-min and 1-, 4-, and 8-h AEGL-2 values.
[c]10-min AEGL-3 value.
[d]30-min and 1-, 4-, and 8-h AEGL-3 values.

No human or animal data on the toxicity of BrF3 were available. Taken collectively with the toxicity data on the related halogenated compounds ClF3, HF, and ClO2, the available data provide a reasonable basis for deriving AEGL values for the selected halogen fluorides; however, additional studies would serve to refine the AEGL values. In particular, the following studies would be beneficial: studies of the acute lethality of BrF3 in laboratory animals, studies of ClF5 and BrF5 for exposure durations of 1-8 h, studies of the acute toxicity of BrF5 in species other than rats, and additional data on the concentration-time relationship for BrF5.

2. CHLORINE PENTAFLUORIDE

2.1. Human Toxicity Data

ClF_3 is a colorless gas with a pungent or suffocating odor (Teitelbaum 2001; Air Liquide 2005). No information on the odor threshold was found, nor was information available on lethal or sublethal concentrations, neurotoxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of ClF_3 in humans.

In the performance of animal studies of ClF_5 at the Aerospace Medical Research Facility, Wright-Patterson AFB, Ohio, a research staff member had occasion to take a single breath of ClF_3 at 30 ppm in the exposure chamber (MacEwen and Vernot 1973). The staff member experienced a mild "burning" of the lungs, mild nausea, an unpleasant taste in the mouth, and headache. The duration of these symptoms persisted was not reported.

2.2. Animal Toxicity Data

2.2.1. Acute Lethality

Acute lethality data for ClF_5 are summarized in Table 3-7 and discussed further below.

2.2.1.1. Nonhuman Primates

Darmer et al. (1972; see also Darmer 1971; MacEwen and Vernot 1971) exposed groups of four male and female rhesus monkeys to various measured concentrations of ClF_5 for 15, 30, or 60 min to determine LC_{50} values. The observation period was 14 days. Chamber concentrations were measured with a fluoride ion specific electrode. Concentrations and mortality for the 15-, 30-, and 60-min exposures are presented in 3-8. Except for the death of one animal on the third day after exposure to ClF_5 at 225 ppm for 15 min, all deaths occurred during or immediately following exposure. The investigators calculated 15-, 30-,

TABLE 3-7 Acute Lethality in Laboratory Animals Exposed to Chlorine Pentafluoride

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Monkey	249	15 min	LC_{50}	Darmer et al. 1972
	165	15 min	No deaths	
	218	30 min	LC_{50}	
	198	30 min	No deaths	
	173	60 min	LC_{50}	
	116	60 min	No deaths	
Dog	298	15 min	LC_{50}	Darmer et al. 1972
	168	15 min	No deaths	
	156	30 min	LC_{50}	
	102	30 min	25% mortality	
	122	60 min	LC_{50}	
	63	60 min	No deaths	
Rat	400	10 min	100% mortality	Weinberg and
	200	10 min	10% mortality	Goldhamer 1967
	100	15 min/d for 6 d	"Survival of most"	
Rat	257	15 min	LC_{50}	Darmer et al. 1972
	175	15 min	10% mortality	
	194	30 min	LC_{50}	
	163	30 min	No deaths	
	122	60 min	LC_{50}	
	80	60 min	No deaths	
Mouse	144	15 min	LC_{50}	Darmer et al. 1972
	100	15 min	25% mortality	
	105	30 min	LC_{50}	
	102	30 min	25% mortality	
	57	60 min	LC_{50}	
	35	60 min	10% mortality	

[a]The LC_{50} values are calculated values; the other mortality values are the empirical data.

and 60-min LC_{50} values of 249 ppm (95% confidence limits [95% CI]: 191-326 ppm), approximately 218 ppm, and 173 ppm (95% CI: 148-204 ppm), respectively (see Table 3-8). Examination of the data indicates that the 30- and 60-min lethality data reported in this study exhibited a clear linear concentration-response relationship when plotted on a semi-log plot, lending confidence to the calculated LC_{50} values for these durations. In contrast, the 15-min data in monkeys did not; thus, there is uncertainty associated with the 15-min LC_{50} value for monkeys.

Almost immediately upon onset of exposure, monkeys had signs of irritation that included salivation, lacrimation, sneezing, nausea, and labored breathing. Cyanosis was usually evident by the end of exposure. The signs disappeared in surviving animals within 30 min after exposure. Monkeys, dogs, rats, and mice (see following sections) that died during exposure exhibited similar pathology in the respiratory tract, the primary target of ClF_5. Alveolar destruction

TABLE 3-8 Acute Lethality in Monkeys Exposed to Chlorine Pentafluoride

Concentration (ppm)	Exposure Duration	Mortality
165	15 min	0/4
193	15 min	1/4
225	15 min	3/4
335	15 min	3/4
395	15 min	3/4
198	30 min	0/4
218	30 min	2/4
236	30 min	4/4
116	60 min	0/4
122	60 min	1/4
140	60 min	1/4
189	60 min	2/4
215	60 min	2/4
223	60 min	4/4

Source: Adapted from Darmer et al. 1972.

was indicated by fluid and blood in the lungs. Nasal passages generally contained large amounts of mucus and fluids; blood was also found in some cases. There were no apparent systemic effects. The authors suggested that chemical pneumonitis was the cause of death that occurred during or immediately after exposure. Animals that survived the 14-day observation exposure period had incomplete recovery of the pulmonary tissue. Residual damage involved scarring and consolidation of pulmonary tissue. Corneal opacity was observed in most species but was less pronounced in monkeys, possibly because they tended to keep their eyes closed during exposure.

2.2.1.2. Dogs

Darmer et al. (1972) exposed groups of four male and female beagles to various measured concentrations of ClF_5 for 15, 30, and 60 min to determine LC_{50} values. The observation period was 14 days. Most deaths occurred during the first 2 days after exposure. Concentrations and mortalities for the 15-, 30-, and 60-min exposures are presented in Table 3-9. Dogs exposed at 143 ppm for 60 min died 8-14 days after exposure, whereas all dogs exposed at 170 ppm for 60 min died during the first day after exposure. The 15-, 30-, and 60-min LC_{50} values were 298 ppm (95% CI: 238-374 ppm), 156 ppm (95% CI: 113-256 ppm), and 173 ppm (95% CI: 148-204 ppm), respectively (Table 3-7). Corneal opacity was a common occurrence.

2.2.1.3. Rats

In preliminary experiments, Weinberg and Goldhamer (1967) exposed groups of rats (strain not specified) to ClF_5 at 200 (10 rats) or 400 ppm (three groups of six rats) for various durations. In the first two groups of rats exposed

at 400 ppm for 10 or 60 min, all died either during the exposure or within 15 min of the start of exposure. Of another group of six rats exposed to ClF_5 at 400 ppm for 10 min, three survived but were sacrificed immediately after exposure. Gross findings in the three survivors included marked pulmonary edema and hemorrhage, myocardial infarction, and congestion in the liver and brain. Among 10 rats exposed to ClF_5 at 200 ppm for 10 min, nine survived the exposure and three survived for 24 h, when the animals were killed. Examination of the animals revealed protein leakage into the lungs in all animals and regeneration of the enzymes aspartate aminotransferase and alanine aminotransferase 16 h after exposure. No systemic effects were noted in these rats.

In the same study (Weinberg and Goldhamer 1967), 40 rats were exposed to ClF_5 at 100 ppm for 15 min/day for up to 5 consecutive days. Groups of three rats were killed either immediately after or 16 h after each daily exposure (six rats/day). The authors stated that, "almost all rats survived exposure to 100 ppm for 15 min daily up to 5 days." The days on which deaths occurred were not clearly documented, but one death may have occurred on the first day of exposure. Six rats survived to day 5. Surviving rats began to lose weight by the third exposure day.

Groups of 10 male Sprague-Dawley rats were exposed to ClF_5 at various concentrations and durations to determine LC_{50} values (Darmer et al. 1972). LC_{50} values were 257 ppm for 15 min (95% CI: 210-314 ppm), 194 ppm for 30 min (95% CI: 135-278 ppm), and 122 ppm for 60 min (95% CI: 108-139 ppm) (Table 3-7). Concentrations and mortalities for this study are presented in Table 3-10. The rats were observed for 14 days following exposure. Most deaths occurred either on the day of exposure or the day after. A few delayed deaths occurred 8-14 days after exposure. Corneal opacity was a common occurrence.

TABLE 3-9 Acute Lethality in Dogs Exposed to Chlorine Pentafluoride

Concentration (ppm)	Exposure Duration	Mortality
168	15 min	0/4
202	15 min	1/4
300	15 min	2/4
360	15 min	2/4
443	15 min	4/4
102	30 min	1/4
150	30 min	2/4
190	30 min	2/4
223	30 min	3/4
252	30 min	3/4
274	30 min	4/4
63	60 min	0/4
110	60 min	1/4
128	60 min	2/4
143	60 min	4/4
170	60 min	4/4

Source: Adapted from Darmer et al. 1972.

TABLE 3-10 Acute Lethality Data in Rats Exposed to Chlorine Pentafluoride

Concentration (ppm)	Exposure Duration	Mortality
175	15 min	1/10
235	15 min	4/10
258	15 min	6/10
300	15 min	7/10
325	15 min	9/10
373	15 min	6/10
432	15 min	9/10
120	30 min	0/10
163	30 min	0/10
185	30 min	3/10
190	30 min	6/10
233	30 min	9/10
250	30 min	10/10
80	60 min	0/10
100	60 min	1/10
120	60 min	4/10
136	60 min	8/10

Source: Adapted from Darmer et al. 1972.

2.2.1.4. Mice

Groups of 10 male ICR mice were exposed to ClF_5 at various concentrations and durations to determine LC_{50} values (Darmer et al. 1972). LC_{50} values were 144 ppm for 15 min (95% CI: 112-186 ppm), 105 ppm for 30 min (95% CI: 93-119 ppm), and 57 ppm for 60 min (95% CI: 47-70 ppm) (Table 3-7). Concentrations and mortalities from the study are presented in Table 3-11. The mice were observed for 14 days. Most deaths occurred immediately after exposure or the next day. Delayed deaths occurred 8-14 days after exposure. Corneal opacity was a common occurrence.

2.2.2. Nonlethal Toxicity

Nonlethal toxicity studies of ClF_5 in the monkey, dog, rat, and mouse are summarized in Table 3-12.

2.2.2.1. Nonhuman Primates

Groups of four male and two female rhesus monkeys were exposed to ClF_5 at 10 ppm for 60 min, 20 ppm for 30 min, or 30 ppm for 10 min (MacEwen and Vernot 1972). The monkeys were killed after a 28-day observation period. Concentrations were measured with a fluoride ion specific electrode. Lacrimation and nausea were observed almost immediately after onset of exposure and

disappeared within 30 min after exposure. Signs were similar in the three treatment groups. One monkey in the group exposed at 20 ppm for 30 min was found dead six days after exposure. Necropsy of the animal revealed purulent material in the upper respiratory tract and focal bronchopneumonia in the lungs. Because no monkeys exposed to ClF_5 at 198 ppm for 30 min died in an earlier experiment at the same facility (Darmer et al. 1972), the cause of death for this animal is uncertain. No gross lesions were observed in monkeys exposed at 30 ppm for 10 min. One monkey in the 30-ppm group had some multifocal, white caseous material in the lungs. Monkeys exposed at 10 ppm for 60 min exhibited congested lungs. However, in summarizing this study in a report the following year, MacEwen and Vernot (1973) reported that "gross and histopathological examination at 28 days postexposure failed to produce any evidence of permanent effects of exposure" in monkeys or any other species; thus, it is difficult to interpret the pathology findings in the various exposure groups. Although mean body weights were not significantly affected following a 28-day observation period, weight gains during this period were depressed. At necropsy, the bone fluoride content of the treated monkeys did not differ from that of the control group.

TABLE 3-11 Acute Lethality in Mice Exposed to Chlorine Pentafluoride

Concentration (ppm)	Exposure Duration	Mortality
100	15 min	2/10
130	15 min	4/10
166	15 min	7/10
174	15 min	7/10
195	15 min	6/10
212	15 min	9/10
231	15 min	8/10
305	15 min	9/10
360	15 min	15/15
70	30 min	2/10
90	30 min	3/10
117	30 min	6/10
120	30 min	5/10
140	30 min	8/10
145	30 min	8/10
166	30 min	9/10
175	30 min	10/10
35	60 min	1/10
47	60 min	2/10
62	60 min	5/10
75	60 min	9/10

Source: Adapted from Darmer et al. 1972.

TABLE 3-12 Nonlethal Data from Studies of Laboratory Animals Exposed to Chlorine Pentafluoride

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
Monkey	10	60 min	Lacrimation, nausea, transient weight gain depression, and congested lungs.	MacEwen and Vernot 1972
	20	30 min	One death with bronchopneumonia, lacrimation, nausea, transient weight gain depression, multifocal caseous material in lungs of one monkey, and no grossly observed pathology in the others.	
	30	10 min	Lacrimation, nausea, transient weight gain depression, and no grossly observed pathology.	
Monkey	5	60 min	Salivation, ocular irritation, lacrimation, and rhinorrhea in all groups. No grossly observed pathology in any group.	MacEwen and Vernot 1973
	10	30 min		
	30	10 min		
Dog	5	60 min	Salivation, ocular irritation, lacrimation, and rhinorrhea in all groups; no grossly observed pathology in any group.	MacEwen and Vernot 1973
	10	30 min		
	30	10 min		
Rat	10	60 min	Lacrimation, salivation, and pale livers and kidneys.	MacEwen and Vernot 1972
	20	30 min	Lacrimation, salivation, and no grossly observed pathology.	
	30	10 min	Lacrimation, salivation, and no grossly observed pathology	
Rat	5	60 min	Salivation, ocular irritation, lacrimation, and rhinorrhea in all groups. No grossly observed pathology.	MacEwen and Vernot 1973
	10	30 min		
	30	10 min		
Rat	30	10 min	Irritation and increase in lung wet weight when killed immediately after exposure. (Gross pathology not assessed.)	MacEwen and Vernot 1973
Rat	3	10 min	No irritation and no effect on body weight gain or lung wet weight.	MacEwen and Vernot 1973
	7	10 min	Slight ocular irritation, and no effect on body weight gain or lung wet weight.	
Mouse	10	60 min	Lacrimation and transient effect on body weight.	MacEwen and Vernot 1972
	20	30 min	One death (cause not specified), lacrimation, and transient effect on body weight.	
	30	10 min	Lacrimation, no effects on body weight, and no grossly observed pathology.	

Mouse	5 10 30	60 min 30 min 10 min	Salivation, ocular irritation, lacrimation, and rhinorrhea in all groups. No grossly observed pathology.	MacEwen and Vernot 1973
Mouse	30	10 min	Irritation, mild pulmonary congestion observed when killed immediately after exposure.	MacEwen and Vernot 1973

In a follow-up study, groups of five rhesus monkeys were exposed to ClF_5 at 30 ppm for 10 min, 10 ppm for 30 min, or 5 ppm for 60 min (MacEwen and Vernot 1973). A single concurrent control group was maintained. The protocol was the same as in the previously described study by MacEwen and Vernot (1972), with the exception that monkeys were observed for 6 weeks after exposure. Blood chemistry and body weight were monitored. Salivation, ocular irritation, lacrimation, and rhinorrhea, described by the study authors as "typical ClF_5 irritation and discomfort symptoms," were seen during the exposures, with the most severe signs observed in the group exposed at 30 ppm for 10 min. All groups (including the control group) exhibited a slight weight loss 2 weeks after exposure due to a change in living quarters. All groups except the one exposed at 5 ppm for 60 min exhibited a weight gain 4 weeks after exposure. Both the 5-ppm (60 min) and the 30-ppm (10 min) groups exhibited slight weight loss 6 weeks after exposure. Clinical chemistry parameters failed to show a pattern consistent with exposure. Gross pathologic examinations revealed no lesions consistent with exposure.

2.2.2.2. Dogs

Groups of eight beagles (gender not specified) were exposed to ClF_5 at 30 ppm for 10 min, 10 ppm for 30 min, or 5 ppm for 60 min (MacEwen and Vernot 1973). A single concurrent control group was maintained. The protocol was the same as in the study by MacEwen and Vernot (1972) described earlier. Blood chemistry and body weight were monitored. Salivation, ocular irritation, lacrimation, and rhinorrhea, described by the study authors as "typical ClF_5 irritation and discomfort symptoms," were seen during the exposures, with the most severe signs observed in the group exposed for 10 min at 30 ppm. Exposed groups exhibited weight gains similar to that of the control group. Clinical chemistry parameters failed to show a pattern consistent with exposure. Gross pathologic examinations revealed no lesions consistent with exposure.

2.2.2.3. Rats

Groups of 30 male Sprague-Dawley rats were exposed to ClF_5 at 30 ppm for 10 min, 20 ppm for 30 min, or 10 ppm for 60 min (MacEwen and Vernot 1972). Concentrations were measured with a fluoride ion specific electrode. Lacrimation and salivation were observed almost immediately after onset of exposure and disappeared within 30 min after exposure. Signs were similar in the three treatment groups. Mean body weights and body weight gains were unaffected during the 28-day observation period. Gross examination at necropsy revealed no effects in any of the control rats or rats exposed for 10 min. Rats exposed for 60 min had pale livers and kidneys.

In a follow-up experiment, groups of 30 Sprague-Dawley rats were exposed to ClF_5 at 30 ppm for 10 min, 10 ppm for 30 min, or 5 ppm for 60 min

(MacEwen and Vernot 1973). A single concurrent control group was maintained. The protocol was the same the one used in the previously described study by MacEwen and Vernot (1972). Blood chemistry and body weight were monitored over a 4-week period. Salivation, ocular irritation, lacrimation, and rhinorrhea, described by the study authors as "typical ClF_5 irritation and discomfort symptoms," were seen during the exposures, with the most severe signs observed in the group exposed for 10 min at 30 ppm. Exposed groups exhibited body weight gains similar to that of the control group. Gross pathologic examinations revealed no lesions consistent with exposure.

An additional experiment was conducted to study the effects of ClF_5 on the lungs of 10 Sprague-Dawley rats exposed at 30 ppm for 10 min (MacEwen and Vernot 1973). Rats were killed immediately after exposure and the lungs were weighed. The mean wet weight of the lungs was significantly increased over that of the controls (by 0.1 g), indicating the presence of edema (dry lung weights were identical for the two groups). The severity of the irritation was not described, but the study authors concluded that "the degree of discomfort experienced by the experimental animals during exposure, and the fact that significant edema resulted in the lungs of rats exposed to this dose" indicated that 30 ppm would not be an acceptable emergency exposure limit.

A fourth experiment was performed at lower concentrations (MacEwen and Vernot 1973). Groups of 20 male Sprague-Dawley rats were exposed to ClF_5 at 3 ppm or 7 ppm for 10 min. Half of the rats in each group was killed immediately after exposure to determine lung weight and the remaining animals were followed for 28 days to evaluated weight gain patterns and pulmonary lesions. Two groups of 10 rats each comprised the concurrent control groups. No signs of irritation were observed during the 10 min exposure at 3 ppm. Slight moistening of the eyes was observed following the 10-min exposure at 7 ppm. There was no effect on body weight gain or lung wet weight following the exposures.

2.2.2.4. Mice

Groups of 30 male ICR mice were exposed to ClF_5 at 30 ppm for 10 min, 20 ppm for 30 min, or 10 ppm for 60 min (MacEwen and Vernot 1972). Concentrations were measured with a fluoride ion specific electrode. Lacrimation was observed almost immediately after onset of exposure and disappeared within 30 min after exposure. Signs were similar in the three treatment groups. One mouse exposed at 20 ppm for 30 min was found dead 4 days after exposure; the cause of death could not be ascertained. Mean body weight and body weight gain of all treatment groups were lower during the first week after exposure, but were unaffected during the remainder of the 28-day observation period. Gross examination at necropsy revealed no effects in any of the control mice or mice exposed for 10 min. "Significant pathology" in the group exposed for 60 min was reported, but no details were described other than pale liver and kidneys.

In a follow-up experiment, groups of 30 ICR mice were exposed to ClF_5 at 30 ppm for 10 min, 10 ppm for 30 min, or 5 ppm for 60 min (MacEwen and Vernot 1973). A single concurrent control group was maintained. The protocol was the same as that described for the study by MacEwen and Vernot (1972). Blood chemistry and body weight were monitored over a 4-week period. Salivation, ocular irritation, lacrimation, and rhinorrhea, described by the study authors as "typical ClF_5 irritation and discomfort symptoms," were seen during the exposures, with the most severe signs observed in the group exposed for 10 min at 30 ppm. Exposed groups exhibited body weight gains during the first week after exposure. The group exposed for 30 min at 10 ppm exhibited slight weight loss 2-4 weeks after exposure. Gross pathologic examinations revealed no lesions consistent with exposure.

A third experiment was conducted in which 10 mice were exposed to ClF_5 at 30 ppm for 10 min, (MacEwen and Vernot 1973). The animals were killed immediately after exposure and their lungs were examined. "Typical" irritation symptoms were reported. Gross examination revealed mild pulmonary congestion in the exposed group but not in the control group. The severity of the irritation was not described, but the study authors cited the "degree of discomfort experienced by the experimental animals during exposure" as a contributing rationale for concluding that 30 ppm would not be an acceptable emergency exposure limit.

2.2.3. Neurotoxicity

No information on the neurotoxicity of ClF_5 in animals was found.

2.2.4. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of ClF_5 in animals was found.

2.2.5. Genotoxicity

No information on the genotoxicity of ClF_5 was found.

2.2.6. Chronic Toxicity and Carcinogenicity

No information on the chronic toxicity or carcinogenicity of ClF_5 was found.

2.2.7. Summary

A series of studies with four species (monkey, dog, rat, and mouse) provided information on the irritation and lethality of ClF_5. One-hour LC_{50} values were 173 ppm for monkeys, 122 ppm for dogs, 122 ppm for rats, and 57 ppm for

mice (Darmer et al. 1972). The highest nonlethal concentrations for 1-h exposures for the monkey, dog, and rat were 116, 63, and 80 ppm, respectively. The four species were also exposed to ClF_5 at 5 or 10 ppm for 60 min, 10 or 20 ppm for 30 min, and 30 ppm for 10 min. The animals had distinct signs of irritation, including lacrimation, salivation, nausea (monkey), and for some species, reversible pulmonary congestion (MacEwen and Vernot 1972, 1973). Rats exposed at 3 ppm for 10 min had no signs of irritation, and rats exposed at 7 ppm for 10 min had slight ocular irritation (MacEwen and Vernot 1973).

2.3. Data Analysis for AEGL-1

2.3.1. Human Data Relevant to AEGL-1

No human data on ClF_5 relevant to developing AEGL-1 values were found.

2.3.2. Animal Data Relevant to AEGL-1

Animal data relevant to developing AEGL-1 values for ClF_5 are sparse. No signs of irritation were observed during a 10-min exposure of 20 Sprague-Dawley rats to ClF_5 at 3 ppm (MacEwen and Vernot 1973). Ocular moisture was observed following a 10-min exposure at 7 ppm. Animals of both groups killed immediately after exposure had wet lung weights similar to those of the control groups. The absence of fluid in the lungs (edema) indicates that toxicologically significant quantities of ClF_5 did not reach the lungs at those concentrations. Animals of both groups killed after a 28-day observation period had no alternations in body weight gain or gross pathologic findings in the lungs.

2.3.3. Derivation of AEGL-1 Values

An AEGL-1 value for chlorine pentafluoride could have been derived on the basis of a no-effect level for irritation in the rat of 3 ppm for 10 min (MacEwen and Vernot 1973). A total uncertainty factor of 10 would have been applied; a factor of 3 for interspecies differences and a factor of 3 for intraspecies variability. However, the resulting 10-min AEGL-1 value (0.30 ppm) exceeds the 4- and 8-h AEGL-2 values (0.24 and 0.17 ppm, respectively) and is close to the 1-h AEGL-2 value (0.50 ppm). Thus, AEGL-1 values are not recommended for ClF_5 because of inadequate sensory warning properties.

2.4. Data Analysis for AEGL-2

2.4.1. Human Data Relevant to AEGL-2

There are no human data relevant to developing AEGL-2 values. An individual suffered mild “burning” of the lungs, unpleasant taste, nausea and head-

ache following a single breath of ClF_5 at 30 ppm (MacEwen and Vernot 1973). However, no meaningful understanding of the toxicity of ClF_5 can be obtained from this report.

2.4.2. Animal Data Relevant to AEGL-2

Data relevant to deriving AEGL-2 values for ClF_5 are available from a series of experiments in monkeys, dogs, rats, and mice by MacEwen and Vernot (1972, 1973). In the first experiment, exposure of groups of six rhesus monkeys, 30 rats, and 30 mice to ClF_5 at 10 ppm for 60 min, 20 ppm for 30 min, or 30 ppm for 10 min or groups of eight beagles at 30 ppm for 10 min resulted in irritation, as exhibited by salivation and lacrimation (MacEwen and Vernot 1972). All animals were monitored for several weeks. At gross necropsy, pulmonary congestion was observed in monkeys exposed at 10 ppm for 60 min, and rats had pale livers and kidneys. A second experiment at lower concentrations reported salivation, ocular irritation, lacrimation, and rhinorrhea, but no gross pathologic findings in groups of five rhesus monkeys, eight beagles, 30 rats, and 30 mice exposed to ClF_5 at 5 ppm for 60 min, 10 ppm for 30 min, or 30 ppm for 10 min (MacEwen and Vernot 1973). Irritation was reportedly more severe in the groups exposed at 30 ppm for 10 min; however, no detail about the severity of the irritant symptoms was provided. No gross pathologic findings related to exposure were observed (MacEwen and Vernot 1973). In a third experiment, wet weights of the lungs were increased in a group of 10 rats killed immediately after exposure to ClF_5 at 30 ppm for 10 min (the only concentration-exposure duration group examined in that experiment) (MacEwen and Vernot, 1973). As part of the same experiment, gross examination of 10 mice following exposure at 30 ppm for 10 min revealed mild pulmonary congestion; this finding was not observed in the control group (MacEwen and Vernot 1973). In the fourth experiment, 20 rats exposed at 7 ppm for 10 min exhibited only slight moistening of the eyes, but 20 rats exposed at 3 ppm for 10 min had no signs of irritation (MacEwen and Vernot 1973). Table 3-13 summarizes the data relevant to deriving AEGL-2 values for ClF_5.

2.4.3. Derivation of AEGL-2 Values

The studies by MacEwen and Vernot (1972, 1973) provide little or no information on the severity of irritant symptoms in the animals; as a consequence, it is difficult to identify no-effect levels for AEGL-2 end points. The data indicate that exposure to ClF_5 at concentrations 30 ppm or higher for 10 min, 10 ppm or higher for 30 min, and 5 ppm or higher for 60 min results in irritant effects, including salivation, ocular irritation, lacrimation, and rhinorrhea in all species tested. Additionally, pathologic effects in the lungs were found in monkeys exposed at 10 ppm for 60 min, in one monkey exposed at 20 ppm for 30 min, and in rats and

TABLE 3-13 Data Relevant to AEGL-2 Values for Chlorine Pentafluoride

Duration (min)	Concentration (ppm)	Symptoms	Gross pathology	Other effects	Species
10	3	None	None	No effect on body weight	Rats
	7	Slight moistening of eyes	None	No effect on body weight	Rats
	30	Salivation, ocular irritation, lacrimation, and rhinorrhea (all species); nausea (monkeys).	Reversible pulmonary congestion and edema (rat and mice).	Slight transient weight loss (monkeys).	Monkeys, dogs, rats, and mice
30	10	Salivation, ocular irritation, lacrimation, and rhinorrhea.	None	Transient weight gain loss (monkey and mouse).	Monkeys, dogs, rats, and mice
	20	Lacrimation (all species); salivation (rats); nausea (monkeys).	White caseous material in lung (one monkey).	Transient weight gain depression (monkeys and mice); one monkey died with bronchopneumonia; one mouse died of undetermined cause.	Monkeys, rats, and mice
60	5	Salivation, ocular irritation, lacrimation, and rhinorrhea (all species).	None	Slight transient weight gain depression (monkeys).	Monkeys, dogs, rats, and mice
	10	Lacrimation (all species); salivation (rats); nausea (monkeys).	Congested lungs (monkeys); pale livers and kidneys (rats).	Transient weight gain depression (monkeys and mice)	Monkeys, rats, and mice

Source: Data from MacEwen and Vernot 1972, 1973.

mice exposed at 30 ppm for 10 min. Among the experiments conducted, minimal or no irritation was found only in the studies of rats exposed for 10 min at 3 or 7 ppm; no irritation occurred at 3 ppm and only slight moistening of the eyes was observed at 7 ppm. Without additional information on the severity and prevalence of the irritant symptoms, it is difficult to determine the concentration and exposure duration at which escape might be impaired. However, a conservative assumption is that the lacrimation and ocular irritation exhibited by all species exposed at 10 ppm for 30 min or at 5 ppm for 60 min were of sufficient severity to impair escape. Thus, those concentrations were considered effect levels for AEGL-2 end points. Under that assumption, the highest no-effect level is 7 ppm, which was associated with slight moistening of the eyes in rats exposed for 10 min.

The 10-min no-effect level of 7 ppm was selected as the point-of-departure for the 10-min and 30-min AEGL-2 values. Because of the uncertainty associated with extrapolating a 10-min point-of-departure to exposure durations of 1 h and longer, the point-of-departure for the 1-, 4-, and 8-h AEGL-2 values was based on the effect level of 5 ppm for a 60-min exposure; that concentration was reduced by a modifying factor of 3 to account for extrapolation from an effect level to a no-effect level for AEGL-2 end points. Thus, the point-of-departure was 1.7 ppm. A total uncertainty factor of 10 was applied; a factor of 3 for interspecies difference and a factor of 3 for intraspecies variability. A factor of 3 was selected for interspecies difference because LC_{50} values for ClF_5 and related compounds were within a factor of 3 among different species (see Sections 1.3 and 1.6). Further, an interspecies uncertainty factor of 3 is appropriate when the point-of-departure is obtained from data in the most appropriate species (NRC 2001); monkeys were included in the animals tested in the critical study, and monkeys are considered a more appropriate species to predict human toxicity than rodents. An intraspecies uncertainty factor of 3 was also applied; this uncertainty factor is appropriate when the mode of action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). The values of the two uncertainty factors are also consistent with those used to derive AEGL values for the related compounds ClF_3, HF, and ClO_2 (NRC 2004, 2007a,b).

Time scaling was performed using the equation $C^n \times t = k$. The 30-min AEGL-2 value was extrapolated from the 10-min point-of-departure of 7 ppm, and the 4- and 8-h AEGL-2 values were extrapolated from the 1-h point of departure of 1.7 ppm. An empirical value for the exponent n of 1.9 was deriving from lethality data in the rat (see Section 1.8). The irritation observed in the study used as the basis for the AEGL-2 values are believed to exist on a continuum that leads to lung pathology and death at higher concentrations, supporting the use of a time scaling value (n) based on lethality. AEGL-2 values for ClF_5 are presented in Table 3-14, the calculations are provided in Appendix B, and a category plot of toxicity data and AEGL values is presented in Appendix C.

TABLE 3-14 AEGL-2 Values for Chlorine Pentafluoride

10 min	30 min	1 h	4 h	8 h
0.70 ppm (3.7 mg/m^3)	0.39 ppm (2.1 mg/m^3)	0.17 ppm (0.91 mg/m^3)	0.082 ppm (0.44 mg/m^3)	0.057 ppm (0.30 mg/m^3)

2.5. Data Analysis for AEGL-3

2.5.1. Human Data Relevant to AEGL-3

No human data relevant to developing AEGL-3 values for ClF_5 were found.

2.5.2. Animal Data Relevant to AEGL-3

Lethality data on ClF_5 were available for the monkey, dog, rat, and mouse (Darmer et al. 1972). The 15-, 30-, and 60-min LC_{50} values and the highest concentrations that did not result in deaths are presented in Table 3-7. The highest 1-h nonlethal values were 116 ppm in the monkey, 63 ppm in the dog, and 80 ppm in the rat.

2.5.3. Derivation of AEGL-3 Values

Analysis of the ClF_5 data using benchmark-concentration analysis proved to be inappropriate for developing AEGL-3 values. Using the log-probit model, the 15-, 30-, and 60-min benchmark concentration-derived data failed to follow a concentration-response relationship for any of the four species. For example, the 15-, 30-, and 60-min $BMCL_{05}$ values for the rat were 72, 146, and 81 ppm, respectively. The failure to follow a concentration-response relationship is most likely due to experimental error encountered with short exposure durations (15 min) as well as from the small data sets (groups of four monkeys and dogs or groups of 10 rats and mice). The LC_{50} values and the highest exposures to ClF_5 resulting in no lethality for all four species follow a more realistic concentration-response relationship (see Table 3-2).

The highest 60-min nonlethal concentration in rats of 80 ppm (Darmer et al. 1972) was used as the point-of-departure for the AEGL-3 values for ClF_5. Although the rat is not the most sensitive species (mice exhibited the lowest LC_{50} values of the four species tested; see Table 3-2), the rat data were selected over the mouse data because they were more consistent with the lethality benchmarks observed in monkeys and, thus, would be expected to be a more appropriate species than the mouse to predict human response. The LC_{50} values in monkeys and rats were 249 and 257 ppm (15 min), 218 and 194 ppm (30 min), and 173 and 122 ppm (60 min), respectively. In contrast, the mouse LC_{50} values were one-half to one-third of the rat and monkey LC_{50} values. The rat data were selected over the monkey and dog data because they provided a better dose-response relationship over the 15- to 60-min periods and because a larger

number of animals were tested. The longest exposure duration of 60 min was considered the most reliable value.

An interspecies uncertainty factor of 3 was selected because differences in LC_{50} values for ClF_5 and related compounds in various test species were within a factor of 3 of each other (see Sections 1.3 and 1.6). Further, an interspecies uncertainty factor of 3 is appropriate when the point-of-departure is obtained from data in the most appropriate species (NRC 2001). The monkey shares greater physiologic similarity with humans than rodents (see Section 1.6), and the monkey data for ClF_5 were well-approximated by the rat data used for the point-of-departure. An intraspecies uncertainty factor of 3 was also applied, because the mode of action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). As discussed in Section 1.5, ClF_5 and related compounds exert toxicity via direct irritation and corrosive action on the respiratory tissues. The values for the two uncertainty factors are also consistent with those used to derive AEGL values for the related compounds ClF_3, HF, and ClO_2 (NRC 2004; 2007a,b). In summary, the 80 ppm point-of-departure was adjusted by a total uncertainty factor of 10.

Time scaling was performed using the equation $C^n \times t = k$. An empirical value for the exponent n of 1.9 was deriving from lethality data in the rat (see Section 1.8). AEGL-3 values for ClF_5 are presented in Table 3-15.

2.6. Summary of AEGLs

2.6.1. AEGL Values and Toxicity End Points

AEGL values for ClF_5 are presented in Table 3-16.

TABLE 3-15 AEGL-3 Values for Chlorine Pentafluoride

10 min	30 min	1 h	4 h	8 h
21 ppm (110 mg/m^3)	12 ppm (64 mg/m^3)	8.0 ppm (43 mg/m^3)	3.9 ppm (21mg/m^3)	2.7 ppm (14 mg/m^3)

TABLE 3-16 AEGL Values for Chlorine Pentafluoride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	0.70 ppm (3.7 mg/m^3)	0.39 ppm (2.1 mg/m^3)	0.17 ppm (0.91 mg/m^3)	0.082 ppm (0.44 mg/m^3)	0.057 ppm (0.30 mg/m^3)
AEGL-3 (lethal)	21 ppm (110 mg/m^3)	12 ppm (64 mg/m^3)	8.0 ppm (43 mg/m^3)	3.9 ppm (21 mg/m^3)	2.7 ppm (14 mg/m^3)

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

2.6.2. Other Standards and Guidelines

There are no other exposure standards or guidelines for ClF_5.

3. BROMINE PENTAFLUORIDE

3.1. Human Toxicity Data

No information on lethality, sublethal effects, neurotoxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of BrF_5 in humans was found. The odor threshold is unknown. According to Braker and Mossman (1980), BrF_5 provides adequate warning of its presence by its sharp, penetrating odor.

3.2. Animal Toxicity Data

3.2.1. Acute Lethality

Dost et al. (1968) exposed groups of 10-14 male Sprague-Dawley rats to BrF_5 at 500 or 1,000 ppm for various durations (see Table 3-17). All 10 rats survived a 40-min exposure at 500 ppm, but 11 of 14 rats exposed at 500 ppm for 50 min died. All 10 rats survived a 20-min exposure at 1,000 ppm, but all 12 rats exposed at 25 min died. Rats were observed for several days following exposure. All rats survived additional exposures to BrF_5 at 500 ppm for durations shorter than 40 min, and all rats survived additional exposures to 1,000 ppm for durations shorter than 20 min (data not provided). Exposed rats exhibited corrosive damage to the lungs, corneal and conjunctival damage, yellow and sticky fur, and necrotic damage to unprotected areas of the skin; however, the concentrations and exposure durations associated with those effects were not reported.

In citing their earlier, unpublished experiments on BrF_5, Dost et al. (1970) reported a 1-h 95% lethal concentration of 500 ppm in rats. No deaths were reported when groups of 4-6 male Sprague-Dawley rats were exposed to BrF_5 at 500 ppm for 30 min (half of the 95% lethal exposure duration) in a study evaluating systemic fluorine distribution.

TABLE 3-17 Lethality Data from Studies of Rats Exposed to Bromine Trifluoride

Concentration (ppm)	Exposure Duration	Effect
1,000	20 min	No deaths (0/10)
	25 min	100% mortality (12/12)
500	30 min	No deaths (0/4-6)
	40 min	No deaths (0/10)
	50 min	79% mortality (11/14)
	60 min	95% mortality

Source: Data from Dost et al. 1968, 1970.

3.2.2. Nonlethal Toxicity

No information on the nonlethal toxicity, neurotoxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of BrF_5 was found.

3.3. Data Analysis for AEGL-1

3.3.1. Human Data Relevant to AEGL-1

No human data relevant to developing AEGL-1 values for BrF_5 were found.

3.3.2. Animal Data Relevant to AEGL-1

No animal data relevant to developing AEGL-1 values for BrF_5 were found.

3.3.3. Derivation of AEGL-1 Values

In the absence of chemical-specific data, no AEGL-1 values were developed for BrF_5.

3.4. Data Analysis for AEGL-2

3.4.1. Human Data Relevant to AEGL-2

No human data relevant to developing AEGL-2 values for BrF_5 were found.

3.4.2. Animal Data Relevant to AEGL-2

No animal data relevant to developing AEGL-2 values for BrF_5 were found.

3.4.3. Derivation of AEGL-2 Values

In the absence of data relevant to deriving AEGL-2 values for BrF_5, data for the structurally-related chemical, ClF_5, were used. The database for ClF_5 is more robust than the database for BrF_5. ClF_5 is considered more toxic than BrF_5, on the basis that the highest 60-min nonlethal concentration of ClF_5 in the rat is 80 ppm whereas the highest 40-min nonlethal concentration for BrF_5 in the rat is 500 ppm. Thus, setting AEGL-2 values for BrF_5 that are equal those for ClF_5 should be protective. The AEGL-2 values for BrF_5 are presented in Table 3-18.

TABLE 3-18 AEGL-2 Values for Bromine Pentafluoride

10 min	30 min	1 h	4 h	8 h
0.70 ppm (5.0 mg/m^3)	0.39 ppm (2.8 mg/m^3)	0.17 ppm (1.2 mg/m^3)	0.082 ppm (0.57 mg/m^3)	0.057 ppm (0.41 mg/m^3)

3.5. Data Analysis for AEGL-3

3.5.1. Human Data Relevant to AEGL-3

No human data relevant to developing AEGL-3 values for BrF_5 were found.

3.5.2. Animal Data Relevant to AEGL-3

A single study provided lethal and nonlethal concentration-exposure durations for the rat. Dost et al. (1968) reported no deaths in rats from exposures to BrF_5 at 500 ppm for 40 min or 1,000 ppm for 20 min (Table 3-17). The observation periods were shorter (maximum of 20 h) than the usual 2-week observation period; however, for most strong oxidizing chemicals, death occurs during or shortly after exposure when concentrations approach lethal levels (MacEwen and Vernot 1970; Darmer et al. 1972; Dost et al. 1974).

3.5.3. Derivation of AEGL-3 Values

Data were unavailable for calculating a benchmark concentration or an LC_{01} for BrF_5. Therefore, the highest concentrations that resulted in no mortality in rats of 500 ppm for 40 min and 1,000 ppm for 20 min (Dost et al. 1968) were considered. The longer exposure duration of 40 min at 500 ppm was considered more a reliable point-of-departure. A total uncertainty factor of 10 was applied; a factor of 3 for interspecies differences and a factor of 3 for intraspecies variability. Although the data on BrF_5 are only from studies of rats, data on related compounds indicate little interspecies differences (within a factor of 3; see Section 1.6), supporting the selection of an interspecies uncertainty factor of 3. An intraspecies uncertainty factor of 3 was also applied; this uncertainty factor is appropriate when the mode of action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). As discussed in Section 1.5, BrF_5 and related compounds exert toxicity via direct irritation and corrosive action on the respiratory tissues. The values of the two uncertainty factors are also consistent with those used to derive the AEGL values for the related compounds ClF_3, HF, and ClO_2 (NRC 2004, 2007a,b). Application of a total uncertainty factor of 10 to the point-of-departure of 500 ppm results in a value of 50 ppm. Time scaling was performed using the equation $C^n \times t = k$. Default values for n = 3 for extrapolating to shorter durations and n = 1 for extrapolating for shorter durations were used. The resulting AEGL-3 values are presented in Table 3-19, and the calculations are in Appendix B.

Because of the sparse data base on BrF_5, application of a modifying factor of 2 was considered when deriving the AEGL-3 values. A modifying factor was not applied because the AEGL-3 values reflect the toxicity of BrF_5 relative to that of ClF_5 and ClF_3. The AEGL-3 values for the slightly more toxic ClF_3 are 84 ppm for 10 min, 36 ppm for 30 min, 21 ppm for 1 h, 7.3 ppm for 4 h, and 7.3 ppm for 8 h (NRC 2007a).

3.6. Summary of AEGLs

3.6.1. AEGL Values and Toxicity End Points

The AEGL values for BrF_5 are presented in Table 3-20.

3.6.2. Other Standards and Guidelines

Bromine pentafluoride has limited uses, and only a few exposure standards and guidelines have been developed (see Table 3-21). The threshold limit value–time-weighted average established by the American Conference of Governmental Industrial Hygienists (ACGIH 2001, 2012) of 0.1 ppm was based on toxicologic analogy with ClF_3, which at the time of the recommendation (1969) had a TLV-ceiling of 0.1 ppm. The recommended exposure limit–time-weighted average (REL-TWA) of the National Institute for Occupational Safety and Health (NIOSH 2011) for BrF_5 is also 0.1 ppm. NIOSH has not established a concentration that is immediately dangerous to life or health, and the Occupational Safety and Health Administration has not established a permissible exposure limit for BrF_5.

TABLE 3-19 AEGL-3 Values for Bromine Pentafluoride

10 min	30 min	1 h	4 h	8 h
79 ppm (570 mg/m^3)	55 ppm (390 mg/m^3)	33 ppm (240 mg/m^3)	8.3 ppm (59 mg/m^3)	4.2 ppm (30 mg/m^3)

TABLE 3-20 AEGL Values for Bromine Pentafluoride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	0.70 ppm (5.0 mg/m^3)	0.39 ppm (2.8 mg/m^3)	0.17 ppm (1.2 mg/m^3)	0.082 ppm (0.57 mg/m^3)	0.057 ppm (0.41 mg/m^3)
AEGL-3 (lethal)	79 ppm (570 mg/m^3)	55 ppm (390 mg/m^3)	33 ppm (240 mg/m^3)	8.3 ppm (59 mg/m^3)	4.2 ppm (30 mg/m^3)

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

TABLE 3-21 Standards and Guidelines for Bromine Pentafluoride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.70 ppm	0.39 ppm	0.17 ppm	0.082 ppm	0.057 ppm
AEGL-3	79 ppm	55 ppm	33 ppm	8.3 ppm	4.2 ppm
TLV-TWA (ACGIH)[a]	–	–	–	–	0.1 ppm
REL-TWA (NIOSH)[b]	–	–	–	–	0.1 ppm
MAC (The Netherlands)[c]	–	–	–	–	0.1 ppm

[a]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[b]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is the time-weighted average concentration for up to a 10-h workday during a 40-h workweek.
[c]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

4. BROMINE TRIFLUORIDE

4.1. Human Toxicity Data

No reliable data on the toxicity of BrF_3 in humans were found. According to Braker and Mossman (1980), concentrations of 50 ppm or more may be fatal in 30 min to 2 h. No reference was provided for this information, so it is of questionable reliability. BrF_3 is irritating and corrosive to the skin, eyes, mucous membranes, and respiratory tract (O'Neil et al. 2001). No information on sublethal effects, neurotoxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of BrF_3 in humans was found. The odor of BrF_3 is considered pungent and choking (Owen 2005), but the odor threshold is unknown.

4.2. Animal Toxicity Data

No data on the toxicity of BrF_3 in animals were found. According to Braker and Mossman (1980), the toxic effects of BrF_3 are comparable to those of ClF_3, which is considered the most toxic of the halogen fluorides. No reference was provided for this information. No information on sublethal effects, neurotoxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of BrF_3 in animals was found.

4.3. Data Analysis for AEGL Values

4.3.1. Human Data Relevant to AEGL Values

No human data relevant to deriving AEGL-1, AEGL-2, or AEGL-3 values for BrF_3 were found.

4.3.2. Animal Data Relevant to AEGL Values

No animal data relevant to deriving AEGL-1, AEGL-2, or AEGL-3 values for BrF_3 were found.

4.3.3. Derivation of AEGL Values

In the absence of chemical-specific data, the AEGL-1, AEGL-2, and AEGL-3 values for BrF_3 were based on its structure-activity relationship with other halogen fluorides and set equal to the AEGL values for the more toxic chemical analogue, ClF_3. A modifying factor was not applied to the ClF_3 AEGL values because BrF_3 is expected to be less toxic than ClF_3 (see Section 1.3). Based on chemical reactivity and relative toxicity, the chlorine fluorides are expected to be more toxic than the bromine fluorides (see Section 1.3). Thus, basing the BrF_3 values on the more toxic ClF_3 values was considered to provide reasonable protection. The AEGL values for BrF_3 are presented in Table 3-22.

4.3.4. Other Standards and Guidelines

There are no other exposure standards or guidelines for BrF_3.

TABLE 3-22 AEGL Values for Bromine Trifluoride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 mg/m^3)
AEGL-2 (disabling)	8.1 ppm (45 mg/m^3)	3.5 ppm (20 mg/m^3)	2.0 ppm (11 mg/m^3)	0.70 ppm (3.9 mg/m^3)	0.41 ppm (2.3 mg/m^3)
AEGL-3 (lethal)	84 ppm (470 mg/m^3)	36 ppm (200 mg/m^3)	21 ppm (120 mg/m^3)	7.3 ppm (41 mg/m^3)	7.3 ppm (41 mg/m^3)

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APPENDIX A

TIME-SCALING CALCULATION FOR CHLORINE PENTAFLUORIDE

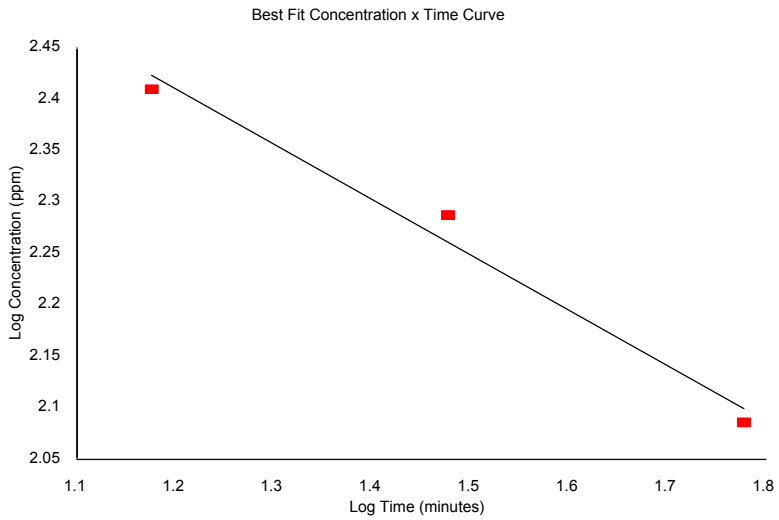

FIGURE A-1 LC_{50} values for chlorine pentafluoride in the rat. Source: Darmer et al. 1972.

TABLE A-1 Oxygen Difluoride Lethality in Rats

Time	Conc.	Log Time	Log Conc.	Regression Output:	
15	257	1.1761	2.4099	Intercept	3.0552
30	194	1.4771	2.2878	Slope	-0.5374
60	122	1.7782	2.0864	R Squared	0.9804
				Correlation	-0.9901
				Degrees of Freedom	1
				Observations	3
n = 1.86	1.27				
k = 483897	245.78				

Source: Lester and Adams 1965; Davis 1970.

APPENDIX B

DERIVATION OF AEGL VALUES FOR SELECTED HALOGEN FLUORIDES

Chlorine Pentafluoride

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for ClF_5 due to inadequate warning properties.

Derivation of AEGL-2 Values

Key study:	MacEwen, J.D., and E.H. Vernot. 1973. Toxic Hazards Research Unit Annual Technical Report. AMRL-TR-73-83. AD-771 025. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.
Toxicity end point:	No-effect levels for escape-impairing irritation (7 ppm for 10 min in rats, and 1.7 ppm for 1 h in monkeys, dogs, rats and mice; latter value was extrapolated from an effect level of 5 ppm by dividing it by a modifying factor of 3).
Time scaling:	$C^n \times t = k$; n = 1.9 (see Appendix A for calculation of n) For 30-min value: $(7 \text{ ppm} \div 10)^{1.9} \times 10 \text{ min} = 5.078$ ppm-min For the 4- and 8-h values: $(1.7 \text{ ppm} \div 10)^{1.9} \times 1 \text{ h} = 0.17$ ppm-h
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Modifying factor:	3 to extrapolate from an effect level to a no-effect level (4-h and 8-h AEGL-2 values)
Calculations:	
10-min AEGL-2:	$7 \text{ ppm} \div 10 = 0.70$ ppm
30-min AEGL-2:	$(5.078 \text{ ppm-min} \div 30 \text{ min})^{1/1.9} = 0.39$ ppm
1-h AEGL-2:	$1.7 \text{ ppm} \div 10 = 0.17$ ppm

4-h AEGL-2:	$(0.17 \text{ ppm-h} \div 4 \text{ h})^{1/1.9} = 0.082$ ppm
8-h AEGL-2:	$(0.17 \text{ ppm-h} \div 8 \text{ h})^{1/1.9} = 0.057$ ppm

Derivation of AEGL-3 Values

Key study:	Darmer, K.I., C.C. Haun, and J.D. MacEwen. 1972. The acute inhalation toxicity of chlorine pentafluoride. Am. Ind. Hygiene Assoc. J. 33(10):661-668.
Toxicity end point:	Highest nonlethal 1-h concentration, 80 ppm in the rat.
Time scaling:	$C^n \times t = k$; n = 1.9 (see Appendix A for calculation of n) $(80 \text{ ppm} \div 10)^{1.9} \times 60 \text{ min} = 3{,}119$ ppm-min
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	
10-min AEGL-3:	$(3{,}119 \text{ ppm-min} \div 10 \text{ min})^{1/1.9} = 21$ ppm
30-min AEGL-3:	$(3{,}119 \text{ ppm-min} \div 30 \text{ min})^{1/1.9} = 12$ ppm
1-h AEGL-3:	$(3{,}119 \text{ ppm-min} \div 60 \text{ min})^{1/1.9} = 8.0$ ppm
4-h AEGL-3:	$(3119 \text{ ppm-min} \div 240 \text{ min})^{1/1.9} = 3.9$ ppm
8-h AEGL-3:	$(3{,}119 \text{ ppm-min} \div 480 \text{ min})^{1/1.9} = 2.7$ ppm

Bromine Pentafluoride

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for BrF_5 because of insufficient data.

Derivation of AEGL-2 Values

No human or animal data relevant to deriving AEGL-2 values for BrF_5 were available. AEGL-2 values were set equal to those for the related compound, ClF_5.

10-min AEGL-2:	0.70 ppm
30-min AEGL-2:	0.39 ppm
1-h AEGL-2:	17 ppm
4-h AEGL-2:	0.082 ppm
8-h AEGL-2:	0.057 ppm

Derivation of AEGL-3 Values

Key study:	Dost, F.N., D.J. Reed, T.D. Cooper, and C.H. Wang. 1970. Fluorine distribution in rats following acute intoxication with nitrogen and halogen fluorides and with sodium fluoride. Toxicol. Appl. Pharmacol. 17(3):573-584.
Toxicity end point:	Highest nonlethal 40-min concentration, 500 ppm in the rat.
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Time scaling:	$C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001). $(500 \text{ ppm} \div 10)^3 \times 40 \text{ min} = 5.0 \times 10^6$ ppm-min $(500 \text{ ppm} \div 10)^1 \times 40 \text{ min} = 2.0 \times 10^3$ ppm-min
Modifying factor:	None applied
Calculations:	
10-min AEGL-3:	$C = ([5.0 \times 10^6 \text{ ppm-min}] \div 10 \text{ min})^{1/3}$ C = 79 ppm
30-min AEGL-3:	$C = ([5.0 \times 10^6 \text{ ppm-min}] \div 30 \text{ min})^{1/3}$ C = 55 ppm
1-h AEGL-3:	$C = (2.0 \times 10^3 \text{ ppm-min}) \div 60 \text{ min}$ C = 33 ppm
4-h AEGL-3:	$C = (2.0 \times 10^3 \text{ ppm-min}) \div 240 \text{ min}$ C = 8.3 ppm
8-h AEGL-3:	$C = (2.0 \times 10^3 \text{ ppm-min}) \div 480 \text{ min}$ C = 4.2 ppm

Bromine Trifluoride

Derivation of AEGL-1 Values

No human or animal data were available on BrF_5. Therefore, AEGL-1 values were set equal to those for the related compound, ClF_3 (see NRC 2007a). Appendix E provides a summary of how the AEGL-1 values for ClF_3 were derived.

10-min AEGL-1: 0.12 ppm

30-min AEGL-1: 0.12 ppm

1-h AEGL-1: 0.12 ppm

4-h AEGL-1: 0.12 ppm

8-h AEGL-1: 0.12 ppm

Derivation of AEGL-2 Values

No human or animal data were available on BrF_3. AEGL-2 values were set equal to those for the related compound, ClF_3 (see NRC 2007a). Appendix E provides a summary of how the AEGL-2 values for ClF_3 were derived.

10-min AEGL-2: 8.1 ppm

30-min AEGL-2: 3.5 ppm

1-h AEGL-2: 2.0 ppm

4-h AEGL-2: 0.70 ppm

8-h AEGL-2: 0.41 ppm

Derivation of AEGL-3 Values

No human or animal data were available on BrF_3. AEGL-3 values were set equal to those for the related compound, ClF_3 (see NRC 2007a). Appendix E provides a summary of how the AEGL-3 values for ClF_3 were derived.

10-min AEGL-3: 84 ppm

30-min AEGL-3: 36 ppm

1-h AEGL-3:	21 ppm
4-h AEGL-3:	7.3 ppm
8-h AEGL-3:	7.3 ppm

APPENDIX C

CATEGORY PLOTS FOR SELECTED HALOGEN FLUORIDES

Chlorine Pentafluoride

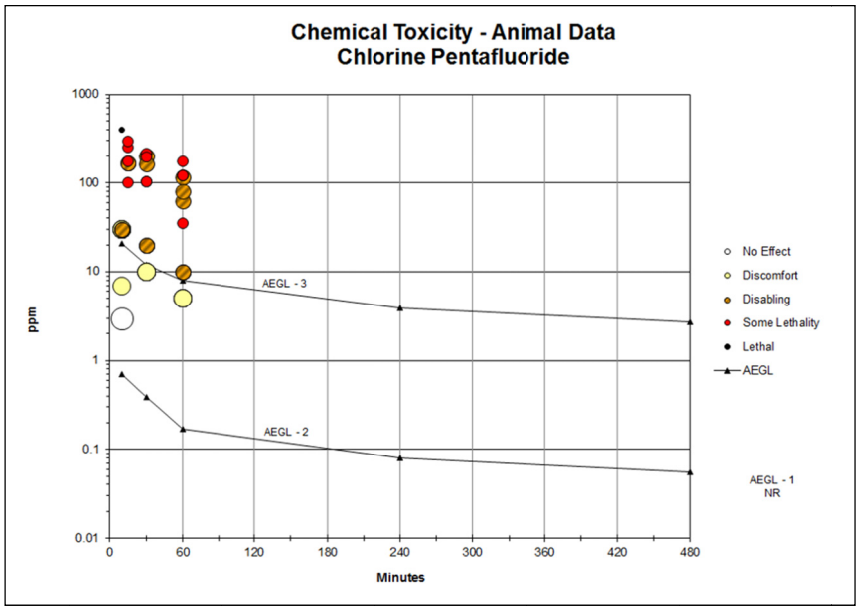

FIGURE C-1 Category plot of toxicity data and AEGL values for chlorine pentafluoride.

TABLE C-1 Data Used in Category Plot for Chlorine Pentafluoride

Source	Species	ppm	Time (min)	Category	Comments
AEGL-2		0.70	10	AEGL	
AEGL-2		0.39	30	AEGL	
AEGL-2		0.17	60	AEGL	
AEGL-2		0.082	240	AEGL	
AEGL-2		0.057	480	AEGL	
AEGL-3		21	10	AEGL	
AEGL-3		12	30	AEGL	
AEGL-3		8.0	60	AEGL	
AEGL-3		3.9	240	AEGL	
AEGL-3		2.7	480	AEGL	
Darmer et al. 1972	Monkey	165	15	2	Severe signs of irritation.
		249	15	SL	LC_{50}
		198	30	2	Severe signs of irritation.
		218	30	SL	LC_{50}
		116	60	2	Severe signs of irritation.
		173	60	SL	LC_{50}
Darmer et al. 1972	Dog	168	15	2	Severe signs of irritation.
		298	15	SL	LC_{50}
		102	30	SL	25% mortality.
		63	60	2	Severe signs of irritation.
		122	60	SL	LC_{50}

(Continued)

TABLE C-1 Continued

Source	Species	ppm	Time (min)	Category	Comments
Darmer et al. 1972	Rat	175	15	SL	10% mortality.
		163	30	2	Severe signs of irritation.
		194	30	SL	LC_{50}
		80	60	2	Severe signs of irritation.
		122	60	SL	LC_{50}
Darmer et al. 1972	Mouse	100	15	SL	25% mortality.
		102	30	SL	25% mortality.
		35	60	SL	10% mortality.
MacEwen and Vernot 1972	Monkey, rat, mouse	10	60	2	Severe irritation, pulmonary pathology.
		20	30	2	Severe irritation, pulmonary pathology.
		30	10	2	Severe irritation, pulmonary pathology.
MacEwen and Vernot 1972	Monkey, dog, rat, mouse	5	60	1	Irritation, discomfort.
		10	30	1	Irritation, discomfort.
		30	10	1	Irritation, discomfort.
MacEwen and Vernot 1972	Rat	3	10	0	No obvious irritation.
		7	10	1	Slight irritation.
Weinberg and Goldhamer 1967	Rat	400	10	3	100% mortality.

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethality.
Severe signs of irritation might include salivation, lacrimation, rhinorrhea, and nausea.

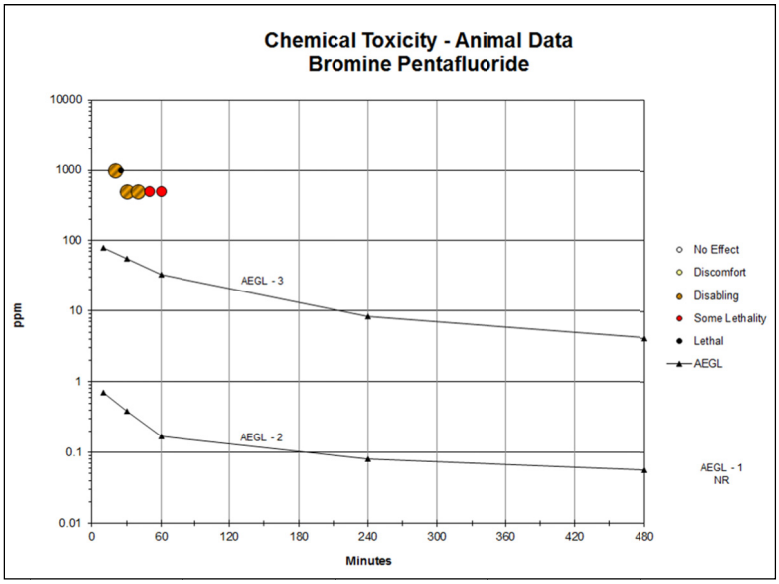

FIGURE C-2 Category plot of toxicity data and AEGL values for bromine pentafluoride.

TABLE C-2 Data Used in Category Plot for Chlorine Pentafluoride

Source	Species	ppm	Time (min)	Category	Comments
AEGL-2		0.70	10	AEGL	
AEGL-2		0.39	30	AEGL	
AEGL-2		0.17	60	AEGL	
AEGL-2		0.082	240	AEGL	
AEGL-2		0.057	480	AEGL	
AEGL-3		79	10	AEGL	
AEGL-3		55	30	AEGL	
AEGL-3		33	60	AEGL	
AEGL-3		8.3	240	AEGL	
AEGL-3		4.2	480	AEGL	
Dost et al. 1970	Rat	500	30	2	No mortality.
		500	40	2	No mortality.
		500	50	SL	79%, mortality.
		500	60	SL	95% mortality.
		1,000	20	2	No mortality.
		1,000	25	3	100% mortality.

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

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR SELECTED HALOGEN FLUORIDES

Derivation Summary for Chlorine Pentafluoride

AEGL-1 Values for Chlorine Pentafluoride

Data relevant to AEGL-1 values for ClF_5 involve only a 10-min exposure. Because the AEGL-1 values that would be derived from those data are similar to the 8-h AEGL-2 values, AEGL-1 values are not recommended.

AEGL-2 Values for Chlorine Pentafluoride

10 min	30 min	1 h	4 h	8 h
0.70 ppm	0.39 ppm	0.17 ppm	0.082 ppm	0.057 ppm

Key reference: MacEwen, J.D. and E.H. Vernot. 1973. Toxic Hazards Research Unit Annual Technical Report: 1973. AD-771 025; AMRL-TR-73-83; Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Test species/Strain/Sex/Number:
Monkey, rhesus, males and females, 6
Dog, beagle, sex not specified, 8
Rat, Sprague-Dawley, male, 30
Mouse, ICR, male, 30

Exposure route/Concentration/Duration: Inhalation; 7 ppm for 10 min and 1.7 ppm for 60 min

Effects: Slight moistening of eyes in rats exposed to ClF_5 at 7 ppm for 10 min. Salivation, lacrimation, ocular irritation, and rhinorrhea (assumed to potentially impair escape) were observed in all species exposed at 30 ppm for 10 min, 10 ppm for 30 min, and 5 ppm for 60 min. The 1-h effect level of 5 ppm was reduced by a modifying factor of 3 (yielding a value of 1.7 ppm) to estimate a no-effect level for escape impairment.

End point/Concentration/Rationale: No-effect level for irritation (7 ppm for 10 min and 1.7 ppm for 60 min)

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because interspecies variability in LC_{50} values ClF_5 and related compounds was within a factor of 3 of each other. Further, an interspecies uncertainty factor of 3 is appropriate when the point-of-departure is obtained from data in the most appropriate species (NRC 2001); monkeys were included in the animals tested in the critical study, and monkeys are considered a more appropriate species to predict human toxicity than rodents. Intraspecies: 3, uncertainty factor is appropriate when the mode of toxic action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). ClF_5 and related compounds exert toxicity via direct irritation and corrosive action on the respiratory tissues.
The values of the two uncertainty factors are consistent with those used to derive AEGL values for the related compounds ClF_3, HF, and ClO_2 (NRC 2004, 2007a,b).

(Continued)

AEGL-2 Values for Chlorine Pentafluoride Continued

Modifying factor: 3, to extrapolate from an effect level of 5 ppm for 60 min to a no-effect level of 1.7 ppm for escape-impairing irritation symptoms.

Animal-to-human dosimetric adjustment: Insufficient data.

Time scaling: $C^n \times t = k$; n = 1.9, determined on the basis of the time-concentration relationship for LC_{50} values reported by Darmer et al. (1972) in rats exposed for 15, 30, and 60 min. Irritation symptoms observed in the study are believed to exist on a continuum that leads to pathologic effects in the lungs and death at higher concentrations, supporting the use lethality data to determine the value for n.

Data adequacy: The acute toxicity of ClF_5 has been well-studied in four species of animal for durations up to 1 h, although some of the studies lacked histopathologic data. There are no data on the toxicity of ClF_5 for exposures longer than 1 h. Considered collectively with the toxicity data on the related halogenated compounds ClF_3, HF, and ClO_2, the data on ClF_5 provide a reasonable basis for deriving AEGL-2 values; however, additional studies of ClF_5 exposure for durations of 1-8 h would enhance the basis of the 4- and 8-h AEGL-2 values.

AEGL-3 Values for Chlorine Pentafluoride

10 min	30 min	1 h	4 h	8 h
21 ppm	12 ppm	8.0 ppm	3.9 ppm	2.7 ppm

Key reference: Darmer, K.I., C.C. Haun, and J.D. MacEwen. 1972. The acute inhalation toxicity of chlorine pentafluoride. Am. Ind. Hyg. Assoc. J. 33(10):661-668.

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

Exposure route/Concentration/Duration: Inhalation; 175, 235, 258, 300, 325, 373, 432 ppm for 15 min; 120, 163, 185, 190, 233, 250 ppm for 30 min; and 80, 100, 120, 136 ppm for 60 min.

Effects: Highest nonlethal concentrations and calculated LC_{50}

Duration	Highest nonlethal concentration	LC_{50}
15 min	Not identified	257 ppm
30 min	163 ppm	194 ppm
60 min	80 ppm	122 ppm

1-h calculated $BMCL_{05}$ = 81 ppm

End point/Concentration/Rationale: Highest nonlethal concentration in the rat was considered the threshold for lethality (80 ppm for 1 h)

Total uncertainty factor: 10
Interspecies: 3, because interspecies variability in LC_{50} values ClF_5 and related compounds was within a factor of 3 of each other. Further, an interspecies uncertainty factor of 3 is appropriate when the point-of-departure is obtained from data in the most appropriate species (NRC 2001); monkeys were included in the animals tested in the critical study, and monkeys are considered a more appropriate species to predict human toxicity than rodents. Intraspecies: 3, uncertainty factor is appropriate when the mode of toxic action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). ClF_5 and related compounds exert toxicity via direct irritation and corrosive action on the respiratory tissues.

(Continued)

AEGL-3 Values for Chlorine Pentafluoride Continued

The values of the two uncertainty factors are consistent with those used to derive AEGL values for the related compounds ClF_3, HF, and ClO_2 (NRC 2004, 2007a,b).
Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data.
Time scaling: $C^n \times t = k$; n = 1.9, determined on the basis of the time-concentration relationship for LC_{50} values reported in the same study. Irritation symptoms observed in the study are believed to exist on a continuum that leads to pathologic effects in the lungs and death at higher concentrations, supporting the use lethality data to determine the value for n.
Data adequacy: The acute toxicity of ClF_5 has been well-studied in four species of animal for durations up to 1 h, although some of the studies lacked histopathologic data. There are no data on the toxicity of ClF_5 for exposures longer than 1 h. Considered collectively with the toxicity data on the related halogenated compounds ClF_3, HF, and ClO_2, the data on ClF_5 provide a reasonable basis for deriving AEGL-3 values; however, additional studies of ClF_5 exposure for durations of 1-8 h would enhance the basis of the 4- and 8-h AEGL-3 values.

Derivation Summary for Bromine Pentafluoride

AEGL-1 Values for Bromine Pentafluoride

Data on BrF_5 are insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Bromine Pentafluoride

10 min	30 min	1 h	4 h	8 h
0.70 ppm	0.39 ppm	0.17 ppm	0.082 ppm	0.057 ppm

Data adequacy: No human or animal data relevant to deriving AEGL-2 values for BrF_5 were available. Therefore, AEGL-2 values were set equal to those for the related compound ClF_5.

AEGL-3 Values for Bromine Pentafluoride

10 min	30 min	1 h	4 h	8 h
79 ppm	55 ppm	33 ppm	8.3 ppm	4.2 ppm

Key reference: Dost, F.N., D.J. Reed, A. Finch, and C.H. Wang. 1968. Metabolism and Pharmacology of Inorganic and Fluorine Containing Compounds. AMRL-TR-67-224, AD 681 161. Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, OH [online]. Available: http://www.dtic.mil/dtic/tr/fulltext/u2/681161.pdf [accessed July 15, 2014].
Test species/Strain/Sex/Number: Rat, Sprague-Dawley, male, 10-12 per group
Exposure route/Concentration/Duration: Inhalation, 500 ppm for 30, 40, 50, or 60 min or 1,000 ppm for 20 or 25 min.

(Continued)

AEGL-3 Values for Bromine Pentafluoride Continued

Effects:

Concentration	Time	Effect
500 ppm	30 min	No deaths
500 ppm	40 min	No deaths
500 ppm	50 min	79% mortality
500 ppm	60 min	95% mortality
1,000 ppm	20 min	No deaths
1,000 ppm	25 min	100% mortality

End point/Concentration/Rationale: The highest non-lethal concentration of 500 ppm for 40 min.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, although only rats have been used to study BrF_5, data on related compounds indicate that there is little interspecies variability (within a factor of 3 of each other), supporting the selection of an interspecies uncertainty factor of 3.
Intraspecies: 3, is appropriate when the mode of toxic action involves a direct-acting mechanism in which metabolic or physiologic differences are unlikely to play a major role (NRC 2001). BrF_5 and related compounds exert toxicity via direct irritation and corrosive action on the respiratory tissues.
The value of the two uncertainty factors is also consistent with those used to derive AEGL values s for the related compounds ClF_3, HF, and ClO_2 (NRC 2004, 2007a,b).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data.

Time scaling: $C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001).

Data adequacy: Data on the acute toxicity of BrF_5 include a single study (Dost et al. 1968) conducted in male rats exposed to one of two concentrations for durations of 20-60 min. The study provided inadequate information on methods (in particular, duration of follow-up was not specified) and did not include microscopic examination of tissues. Considered collectively with the toxicity data on the related halogenated compounds ClF_3, HF, and ClO_2, the data provide a reasonable basis for deriving AEGL values for BrF_5. However, additional studies would serve to refine the AEGL-3 values, including studies of BrF_5 exposure for durations of 1-8 h, studies of the acute toxicity of BrF_5 in species other than the rat, and additional data on the concentration-time relationship for BrF_5.

Derivation Summary for Bromine Trifluoride

AEGL-1 Values for Bromine Trifluoride

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

Data adequacy: No human or animal data relevant for deriving AEGL-1 values for BrF_3 were available. AEGL-1 values were set equal to those for the related compound ClF_3 (see NRC 2007a). That approach is considered reasonable because qualitative and

(Continued)

AEGL-1 Values for Bromine Trifluoride Continued

quantitative data on the halogenated fluorides suggest that the BrF_3 is likely to act via the same mechanism of toxic action as ClF_3, but is expected to be less toxic than ClF_3. Thus, a modifying factor was not applied to account for the lack of data. Additional research on the chemical-specific toxicity of BrF_3 would allow refinement of the AEGL-1 values.

AEGL-2 Values for Bromine Trifluoride

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

Data adequacy: No human or animal data relevant for deriving AEGL-2 values for BrF_3 were available. AEGL-2 values were set equal to those for the related compound ClF_3 (see NRC 2007a). That approach is considered reasonable because qualitative and quantitative data on the halogenated fluorides suggest that the BrF_3 is likely to act via the same mechanism of toxic action as ClF_3, but is expected to be less toxic than ClF_3. Thus, a modifying factor was not applied to account for the lack of data. Additional research on the chemical-specific toxicity of BrF_3 would allow refinement of the AEGL-2 values.

AEGL-3 Values for Bromine Trifluoride

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

Data adequacy: No human or animal data relevant for deriving AEGL-3 values for BrF_3 were available. AEGL-3 values were set equal to those for the related compound ClF_3 (see NRC 2007a). That approach is considered reasonable because qualitative and quantitative data on the halogenated fluorides suggest that the BrF_3 is likely to act via the same mechanism of toxic action as ClF_3, but is expected to be less toxic than ClF_3. Thus, a modifying factor was not applied to account for the lack of data. Additional research on the chemical-specific toxicity of BrF_3 would allow refinement of the AEGL-3 values.

APPENDIX E

DERIVATION SUMMARY FOR CHLORINE TRIFLUORIDE
(Excerpted from NRC 2007a)

AEGL-1 Values for Chlorine Trifluoride

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. Ind. Health 13(4):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 for Chlorine Trifluoride

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. Ind. Health 12(5):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 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 for Chlorine Trifluoride

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 [online]. Available: http://www.dtic.mil/dtic/tr/fulltext/u2/714694.pdf [accessed July 15, 2014].

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

(Continued)

AEGL-3 Values for Chlorine Trifluoride Continued

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.

4

Oxygen Difluoride[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

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

SUMMARY

Oxygen difluoride is an irritating, colorless gas that has been used as an oxidizing propellant for missiles (Darmer et al. 1972). Because of its powerful oxidizing potential, contact with reducing agents should be avoided. Oxygen difluoride reacts slowly with water to form hydrofluoric acid and may be explosive when mixed with hydrocarbons. The odor of oxygen difluoride has been described as “not displeasing”, peculiar, or foul. The concentration at which an odor is detected has been reported to be 0.1 ppm, with an obvious odor at 0.5 ppm. Rapid accommodation to the odor has been reported. No data were available from which to calculate a level of odor awareness.

No information on lethality in humans after exposure to oxygen difluoride was available, but inhalation exposure reportedly produces effects similar to those caused by ozone (respiratory tract irritation and pulmonary edema and hemorrhage). Intractable headaches were associated with oxygen difluoride vapors at concentrations in the parts per billion. Quantitative exposure-response information on oxygen difluoride in humans was not found.

Although acute lethality data are available for monkeys, dogs, rats, and mice, the overall exposure-response relationship for oxygen difluoride is not well defined. Analysis lethality data revealed that 1-h LC_{50} (lethal concentration, 50% lethality) values varied about 17-fold between the least sensitive species (monkeys) and the most sensitive (mice), with larger species appearing to be

less sensitive (1-h LC_{50} values were 1.5, 2.6, 16, and 26.0 ppm, respectively, for mice, rats, dogs, and monkeys). Although pulmonary damage was apparent in exposed animals, the chemical does not appear to damage bronchial mucosal surfaces as do other fluorine compounds. For all species tested, delayed death (hours to days) was a typical response pattern.

Exposure-response data for AEGL-1 severity effects were unavailable. Studies in laboratory species focused on lethality. Where nonlethal responses were reported, the severity of the effects were either not described or likely involved effects that are more severe (e.g., pulmonary damage) than those relevant to AEGL-1 values. Therefore, AEGL-1 values are not recommended for oxygen difluoride because of insufficient data.

Information regarding AEGL-2 severity effects is limited to that obtained from two studies focusing on lethality (Lester and Adams 1965; Davis 1970). Neither study identified a no-effect level for AEGL-2 effects. The lowest concentrations tested (per exposure duration) in monkeys, dogs, and rats were the no-effect levels for lethality. Therefore, the data are not suitable as the basis for AEGL-2 values. Lethality data on oxygen difluoride in monkeys, dogs, rats, and mice indicate that the exposure-response curve is steep. Therefore, in accordance with the standing operating procedures for deriving AEGL values (NRC 2001), AEGL-2 values were determined by dividing the AEGL-3 values by 3.

For AEGL-3 values, a lethality threshold for oxygen difluoride was estimated from the study of rhesus monkeys by Davis (1970). Analysis of the 1-h exposure data resulted in a BMC_{05} (benchmark concentration, 5% response) of 17.2 ppm, a $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 7.48 ppm, and a BMC_{01} (benchmark concentration, 1% response) of 14.4. The $BMCL_{05}$ was used as the point-of-departure because it accounts for the variability due to the small number of animals tested (four per group) and is typically used as the point-of-departure for deriving AEGL-3 values (NRC 2001). It is also lower than the LC_5 determined by the method of Litchfield and Wilcoxon (1949). Time scaling was performed using the equation $C^n \times t = k$. An empirical value of 1.1 for the exponent n was determined using the data of Lester and Adams (1965) and Davis (1970) and the software package of ten Berge.

A total uncertainty factor of 10 was applied. Davis (1970) evaluated acute inhalation toxicity of oxygen difluoride in monkeys, dogs, rats and mice. Results indicate that larger species (dogs and monkeys) are less sensitive to the lethal effects of oxygen difluoride than smaller species (rats and mice). However, the study was conducted using a small number of animals (two males and two females per group), so a factor of 3 was applied to account for species differences. Although asthmatics and individuals with compromised pulmonary function may be considered to be more susceptible to the effects of oxygen difluoride vapor, necropsy findings in multiple animal species indicate that the primary target of oxygen difluoride toxicity is the lungs rather than the airways. For this reason, an intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in the toxic response to inhaled oxygen difluo-

ride. A factor of 3 is also consistent with the uncertainty factor used for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride).

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

1. INTRODUCTION

Oxygen difluoride is an irritating, colorless gas that has been used as an oxidizing propellant for missiles (Darmer et al. 1972). Because of its powerful oxidizing potential, contact with reducing agents should be avoided. It may be explosive when mixed with hydrocarbons (HSDB 2005). The chemical and physical properties of oxygen difluoride are presented in Table 4-2.

TABLE 4-1 AEGL Values for Oxygen Difluoride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	0.43 ppm (0.95 mg/m^3)	0.16 ppm (0.35 mg/m^3)	0.083 ppm (0.18 mg/m^3)	0.024 ppm (0.053 mg/m^3)	0.013 ppm (0.029 mg/m^3)	One-third of AEGL-3 values.
AEGL-3 (lethal)	1.3 ppm (2.9 mg/m^3)	0.47 ppm (1.0 mg/m^3)	0.25 ppm (0.55 mg/m^3)	0.071 ppm (0.16 mg/m^3)	0.038 ppm (0.084 mg/m^3)	1-h $BMCL_{05}$ of 7.48 ppm for rhesus monkeys (Davis 1970)

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

TABLE 4-2 Chemical and Physical Data for Oxygen Difluoride

Parameter	Value	Reference
Synonyms	Difluorine monoxide;fluorine oxide; oxydifluoride; oxygen fluoride	HSDB 2005
CAS registry no.	7783-41-7	HSDB 2005
Chemical formula	OF_2	NIOSH 2013
Molecular weight	54.00	HSDB 2005
Physical state	Colorless gas; yellowish-brown liquid	HSDB 2005
Melting point	-223.8°C	HSDB 2005
Boiling point	-144.75°C	HSDB 2005
Solubility in water	6.8 mL/100 mL at 0°C	HSDB 2005
Density/Specific gravity	1.9 at -223.8°C (liquid)	HSDB 2005
Relative vapor density	1.86	ACGIH 2001
Vapor pressure	>760 mm Hg	ACGIH 2001
Conversion factors in air	1 ppm = 2.2 mg/m^3 1 mg/m^3 = 0.45 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding lethality in humans following inhalation exposure to oxygen difluoride.

2.2. Nonlethal Toxicity

In a review chapter, Deichmann and Gerarde (1969) noted that inhalation of oxygen difluoride produced effects similar to those caused by ozone. Respiratory tract irritation and pulmonary edema and hemorrhage were observed following exposure at 0.5 ppm for a few hours (duration was not further defined). However, no additional information was reported and a primary reference for this information was not provided. Exposure to oxygen difluoride at concentrations in the parts per billion reportedly caused intractable headaches in workers conducting animal exposure studies (LaBelle et al. 1945). Sullivan et al. (1995) included oxygen difluoride among the compounds considered by the Occupational Safety and Health Administration as potentially causing respiratory effects in construction industry workers, but no exposure-response information was provided. Lester and Adams (1965) reported that oxygen difluoride has a "not displeasing" odor that is detectable at 0.1 ppm and obvious at 0. 5 ppm. However, NIOSH (2011) reported that oxygen difluoride has a peculiar foul odor. Rapid accommodation to the odor has been reported. No additional information was available; therefore, a level of odor awareness could not be calculated.

2.3. Developmental and Reproductive Effects

No human developmental or reproductive toxicity data were available for oxygen difluoride.

2.4. Genotoxicity

No human genotoxicity data on oxygen difluoride were available.

2.5. Carcinogenicity

No data regarding the carcinogenic potential of oxygen difluoride in humans were found.

2.6. Summary

No exposure-response data for inhalation exposure of humans to oxygen difluoride were available. The chemical reportedly is very irritating and has caused severe headaches at concentrations in the parts per billion, and severe irritation and pulmonary edema and hemorrhage following a few hours exposure at 0.5 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

In a multispecies acute inhalation toxicity study, Davis (1970) exposed rhesus monkeys (two males and two females) to oxygen difluoride (commercial grade, 98% purity) for 15 min or 1 h. The oxygen difluoride was diluted with dry nitrogen before the animals were placed in the Longley exposure chambers. An MSA BillionAire was used for concentration monitoring (the BillionAire analyzer functions by exposing an air-gas sample with a suitable reagent and passing it through a radioactive source within the chamber. The ions that are formed create a current which is a function of the concentration of vapor present and which is measured by an electrometer). The animals were observed during the exposure and for 14 days after exposure. Monkeys exhibited dyspnea for several days following exposure, gagging, salivation, lacrimation, vomiting, tetany, and muscular weakness. Necropsies revealed massive pulmonary edema and hemorrhage and also congestion of the liver, spleen, and kidneys. No sign of skin irritation was observed even at lethal concentrations. The lethality data are presented in Table 4-3. Time-to-death was not specified. The reported LC_{50} values were 108 ppm and 26.0 ppm, respectively, for the 15-min and 60-min exposures. On the basis of the concentration-time (C × t) product, the investigator noted a near linear response for the time range tested (1,620 ppm-min vs. 1,560 ppm-min for the 15-min and 60-min exposures, respectively).

A 1-h LC_{50} of 16 ppm for rhesus monkeys (assumed to be a combined value from two males and two females per group) was reported by Darmer et al. (1972). That concentration, cited from Davis (1970), is likely a reporting error and should be 26 ppm which is the value reported in the Davis study.

3.1.2. Dogs

Davis (1970) also studied lethality in beagle dogs exposed to oxygen difluoride for 15 or 60 min. Experimental procedures were the same as those described for the experiments with monkeys (see Section 3.1.1). The dogs ex-

hibited responses similar to those of the monkeys. LC_{50} values of 90 ppm and 26.0 ppm were reported for the 15-min and 60-min exposures, respectively. Similar to the findings in monkeys, the response was near-linear; 1,350 ppm-min and 1,560 ppm-min, respectively, for the 15-min and 1-h exposures. Results of the experiment are summarized in Table 4-4.

Darmer et al. (1972) reported a 1-h LC_{50} of 26.0 ppm for groups of four male and female beagle dogs (assumed to be a combined value with two males and two females per group). Experimental details are described in Section 3.1.1.

3.1.3. Rats

The acute inhalation toxicity of oxygen difluoride in rats was studied by Lester and Adams (1965). Groups of 10 Sprague-Dawley rats (150-175 g; assumed to be five males and five females per group) were exposed to oxygen difluoride (>97% purity) at concentrations of 10, 20, 30, or 40 ppm for 5 min, or

TABLE 4-3 Mortality in Rhesus Monkeys Exposed to Oxygen Difluoride Vapor

No. exposed	Concentration (ppm)	Mortality ratio
15-min exposure		
4	60	0/4
4	100	2/4
4	120	2/4
4	140	4/4
60-min exposure		
4	16.0	0/4
4	21.0	1/4
4	32.0	3/4

Source: Adapted from Davis 1970.

TABLE 4-4 Mortality in Dogs Exposed to Oxygen Difluoride

No. exposed	Concentration (ppm)	Mortality ratio
15-min exposure		
4	60	0/4
4	80	1/4
4	100	3/4
60-min exposure		
4	8.2	0/4
4	16.0	2/4
4	21.0	1/4
4	32.0	4/4

Source: Adapted from Davis 1970.

at 5, 10, or 15 ppm for 15 min. The oxygen difluoride was injected in a synchronized manner into a dry airstream prior to delivery into a 10-L glass desiccator containing the rats. The rats were observed for up to 14 days after exposure. In a separate experiment, a group of 14 rats were exposed to oxygen difluoride for 5 min at 20 ppm, and rats were killed (by over-anesthetization with diethyl ether) at intervals for up to 29 h. Rats were examined grossly and the lungs were examined microscopically. For the 5-min exposures, the investigators estimated a 50% lethal response at 17 ppm. A 5-min LC_5 of 17.635 ppm (95% confidence interval: 14.351 to - 21.669 ppm) was determined by the method of Litchfield and Wilcoxon (see Appendix E). Using the benchmark dose method of EPA (2003), a $BMCL_{05}$ of 7.4 ppm and a BMC_{01} of 9.2 ppm were calculated for the 5-min exposure data (see Appendix D). For the 15-min exposure, the investigators estimated 8 ppm as a 50% lethal response. The data were insufficient to be analyzed by the Litchfield and Wilcoxon procedure. On the basis of both the 5- and 15-min data, 100 ppm-min was considered as an estimate of the C × T product associated with a 50% lethal response (only slightly greater than the C × T of 85 ppm product for the 5-min exposure). $BMCL_{05}$ and BMC_{01} values for the 15-min exposure were 2.3 ppm and 3.6 ppm, respectively (see Appendix D). Although the animals exhibited no signs of irritation or distress during the exposures, "widespread pulmonary damage" was considered the cause of death with respiratory difficulties observed only immediately prior to death. The primary target appeared to be at the level of the alveoli as there were no signs of damage to external mucosal surfaces or the bronchial tree. All deaths occurred 9-66 h after exposure (see Table 4-5).

As described for monkeys (Section 3.1.1), Darmer et al, (1972) also reported a 1-h LC_{50} value of 2.6 ppm for male (n = 10) Sprague-Dawley rats. This is likely the same1-h LC_{50} value of 2.6 ppm (2.5-2.7) reported by Vernot et al. (1977) for male rats and originally reported by Davis (1970).

TABLE 4-5 Mortality in Rats Exposed to Oxygen Difluoride

Exposure Duration (min)	Concentration (ppm)[a]	Mortality	Time-to-death (h)[b]
5	10 (9.7)	0/10	–
5	20 (19.5)	7/10	27, 27, 27, 42, 42, 42, 66
5	30 (29.2)	9/10	10, 10, 17, 17, 17, 27, 29, 31, 39
5	40 (39.0)	10/10	10, 10, 10, 10, 19, 19, 19, 19, 25, 25
15	5 (4.9)	0/10	–
15	10 (9.7)	7/10	9, 17, 17, 20, 28, 41, 49
15	15 (14.6)	7/10	15, 24, 30, 30, 30, 41, 55

[a]Values in parentheses are corrected for the reported 97.4% OF_2 assay efficiency.
[b]Number of hours after exposure.
Source: Lester and Adams 1965. Reprinted with permission; copyright 1965, *Journal of Occupational and Environmental Hygiene*.

Groups of 10-15 male Wistar rats were exposed to oxygen difluoride for 15 or 60 min and observed for 14 days (Davis 1970) (see Section 3.1.1. for experimental details). The rats exhibited somewhat different signs during exposure than did the monkeys and dogs, which involved tachypnea and muscular weakness only. The mortality data for rats is summarized in Table 4-6. LC_{50} values of 12.7 ppm and 2.6 ppm for 15- and 60-min exposures, respectively, were reported.

In a study designed to evaluate ultrastructural changes in respiratory tissue, groups of four white rats (sex not specified) were exposed to oxygen difluoride at 4.5 ppm (mean measured concentrations) for 30 or 60 min (Harrison and Mackenzie 1973). All animals exposed for 60 min died within 3 days of exposure. All rats exposed for 30 min survived exposure but showed signs of respiratory distress (details not reported) which resolved after 2 days.

3.1.4. Mice

Both Darmer et al. (1972) and Vernot et .al. (1977) reported a 1-h LC_{50} of 1.5 ppm for groups of 10 male ICR mice, which originates with the work of Davis (1970).

Groups of 15 male ICR mice were exposed to oxygen difluoride for 15 or 60 min and observed for 14 days in the Davis (1970) study (see Section 3.1.1. for experimental details). The mice exhibited somewhat different signs during exposure than did the monkeys and dogs, which involved tachypnea and muscular weakness only. The mortality data for mice is summarized in Table 4-7. LC_{50} values of 7.5 ppm and 1.5 ppm for the 15- and 60-min exposures, respectively, were reported.

TABLE 4-6 Mortality in Rats Exposed to Oxygen Difluoride Vapor

No. exposed	Concentration (ppm)	Mortality ratio
15-min exposure		
10	9.5	0/10
10	10.4	1/10
10	11.0	3/10
10	11.9	1/10
10	13.8	9/10
10	15.2	8/10
10	16.5	9/10
60-min exposure		
10	2.2	0/10
10	2.7	7/10
15	3.0	14/15
10	4.0	10/10

Source: Adapted from Davis 1970.

3.1.5. Summary of Animal Lethality Data

Lethality data for laboratory species exposed to oxygen difluoride are summarized in Table 4-8. Comparing 1-h LC_{50} values reveals about a 17-fold difference between the least sensitive and most sensitive of the four species tested, with larger species appearing to be less sensitive. On the basis of experimental results from monkeys, dogs, rats, and mice, Davis (1970) summarized that the primary target of oxygen difluoride toxicity is the lungs and that there is a considerable difference in susceptibility among the species tested. Specifically, rats and mice were much more susceptible to the effects of oxygen difluoride than were monkeys or dogs. For all species tested, delayed death (hours to days) was a typical response pattern.

TABLE 4-7 Mortality in Mice Exposed to Oxygen Difluoride Vapor

No. exposed	Concentration (ppm)	Mortality ratio
15-min exposure		
15	4.5	8/15
15	5.8	1/15
15	7.5	8/15
15	8.5	4/15
15	9.5	12/15
15	11.0	8/15
15	11.9	15/15
15	15.2	12/15
15	16.5	14/15
60-min exposure		
15	1.0	5/15
15	2.2	8/15
15	4.2	15/15

Source: Adapted from Davis 1970.

TABLE 4-8 Lethality of Oxygen Difluoride in Laboratory Animals

Species	Exposure Duration	Response	Reference
Monkey	1 h	LC_{50} = 26 ppm	Davis 1970
	15 min	LC_{50} = 108 ppm	Davis 1970
Dog	1 h	LC_{50} = 26.0 ppm	Davis 1970
	15 min	LC_{50} = 90 ppm	Davis 1970
Rat	5 min	LC_{50} = 17.6 ppm	Lester and Adams 1965
	15 min	LC_{50} = 8 ppm[a]	Lester and Adams 1965
	15 min	LC_{50} = 12.7 ppm	Davis 1970
	30 min	No lethality.	Harrison and Mackenzie 1973
	1 h	LC_{50} = 2.6 ppm	Davis 1970
	1 h	100% lethality = 4.5 ppm	Harrison and Mackenzie 1973
Mouse	1 h	LC_{50} = 1.5 ppm	Davis 1970
	15 min	LC_{50} = 7.5 ppm	Davis 1970

[a]Estimated.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Exposure of four rhesus monkeys (two males and two females) to oxygen difluoride at 16 ppm for 1 h or at 60 ppm for 15 min was not lethal (Davis 1970). The monkeys exhibited gagging, lacrimation, salivation, muscular weakness, dyspnea, vomiting, and tetany. Neither the severity of the effects nor the number of subjects affected was specified. Dyspnea reportedly persisted for several days after exposure. Hematologic and clinical chemistry evaluations conducted immediately after exposure and at various (unspecified) times during the 14-day observation period revealed no significant findings in measurements of hematologic parameters, uric acid, creatinine, serum alkaline phosphatase, glutamic oxaloacetic transaminase, blood glucose, or extracellular electrolyte composition. Pathologic examination showed slight to moderate pulmonary congestion and edema.

3.2.2. Dogs

Exposure of male and female beagle dogs (two per sex) to oxygen difluoride at concentrations of 60 ppm for 15 min or 8.2 ppm for 60 min was without lethality over a 14-day observation period (Davis 1970). Signs of exposure were similar to those described for monkeys with dyspnea reportedly persisting for several days after the exposure. Clinical findings were similar to those reported for monkeys.

3.2.3. Rats

In the lethality study by Lester and Adams (1965), no deaths occurred in rats exposed to oxygen difluoride at 10 ppm for 5 min or at 5 ppm for 15 min. The severity of pulmonary damage (if any) for these animals was not reported. The investigators reported that pulmonary damage increased with time and that if damage did not attain sufficient severity to cause death within 9 h of exposure, then repair of the pulmonary tissue would ensue after 3 days. This contention was based on examination of rats exposed to oxygen difluoride at 20 ppm for 5 min and then killed 0.09, 0.17, 0.58, 0.75, 1, 2, 3.5, 5, 6, 7, 14, 22.5, and 29 h after exposure. Microscopic findings in pulmonary tissue were characterized as slight congestion, focal atelectasis, hemorrhage, polymorphonuclear leukocyte infiltration, edema, and acute pneumonia. Gross examination of rats surviving for 14 days revealed varying degrees of pulmonary damage (slight to moderate hemorrhage, edema, and consolidation of whole lung lobes), some to the extent of questionable survival.

There was no lethality over a 14-day observation period in groups of 10 male Wistar rats exposed to oxygen difluoride at a concentration of 9.5 ppm for

15 min or 2.2 ppm for 60 min (Davis 1970). During exposure, the rats exhibited tachypnea and muscular weakness although the severity and the number of animals affected were not specified. Dyspnea reportedly persisted for several days after the exposure. No hematologic or clinical chemistry data were reported.

Harrison and Mackenzie (1973) conducted a study designed to evaluate ultrastructural changes in respiratory tissue following 30- or 60-min exposures to oxygen difluoride at 4.5 ppm (mean measured concentrations). Groups of six white rats (sex not reported) were tested. The rats exposed for 30 min were killed immediately after exposure, and the rats exposed for 60 min were killed either immediately after exposure or after 1 or 2 h. Gross pathologic examination of rats exposed for 60 min and killed 1 or 2 h after exposure revealed patchy areas of edema and "possibly" edema; no gross findings were observed in rats killed immediately after exposure. No findings in any group were observed under light microscopy. Electron microscopy revealed several alterations, including blebbing of endothelial cells and epithelial layers for the alveolo-capillary wall and loss of matrix structure and density of lamellar bodies of Type II cells. Effects became more widespread and extensive with the length of the observation-exposure period. Additional groups of four rats were exposed under that same conditions and observed for lethality. All rats exposed for 30 min survived exposure but showed signs of respiratory distress (details not reported), which resolved after 2 days. All animals exposed for 60 min died within 3 days of exposure.

3.2.4. Mice

There were no nonlethal exposures reported by Davis (1970) for groups of 15 male ICR mice exposed to oxygen difluoride. The lowest concentrations tested (4.5 ppm for 15 min or 1.0 ppm for 60 min) resulted in lethality.

3.2.5. Summary of Nonlethal Toxicity in Animals

Exposures of rats to oxygen difluoride at 10 ppm for 5 min, at 5-9.5 ppm for 15 min, or at 2.2 ppm for 60 min were not lethal (assessed after a 14-day observation period). Nonlethal concentrations in rhesus monkeys were 16 ppm for 1 h or 60 ppm for 15 min. As observed with data on lethality, smaller species (rats and mice) appear to be more sensitive than larger species (monkeys and dogs) to the nonlethal effects of oxygen difluoride. Pathologic examinations of animals exposed to oxygen difluoride confirm pulmonary involvement (congestion, edema, focal atelectasis, and hemorrhage).

3.3. Developmental and Reproductive Effects

Data regarding the developmental and reproductive toxicity of oxygen difluoride following inhalation exposure were not available.

3.4. Genotoxicity

No information regarding the genotoxicity of oxygen difluoride was available.

3.5. Carcinogenicity

There were no data with which to evaluate the carcinogenic potential of inhaled oxygen difluoride.

3.6. Summary

On the basis of lethality data in several species, oxygen difluoride appears to be a potent pulmonary toxicant. Gross and microscopic examinations of rats exposed to oxygen difluoride at 20 ppm for 5 min revealed pulmonary damage (swelling, acute pneumonia, consolidation of lung lobes, focal atelectasis, polymorphonuclear leukocyte infiltration, and pulmonary hemorrhage and edema) that progressed with time following cessation of exposure and which did not appear to affect bronchial regions. Larger species (dogs and monkeys) appeared to be notably less sensitive than rodents (mice and rats) to the lethal effects of oxygen difluoride. The overall toxicity data for oxygen difluoride is compromised by an absence of exposure-response data for nonlethal effects.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data regarding the metabolism and disposition of oxygen difluoride were available.

4.2. Mechanism of Toxicity

Data on the mechanism of action of oxygen difluoride are not available. Its oxidizing potential implies an ability to cause direct-contact tissue damage. Necropsy findings in rats (focal atelectasis, hemorrhage, polymorphonuclear leukocyte infiltration, edema, and acute pneumonia) showed that the primary target is the lungs rather than the airways. Necropsy findings in monkeys included massive pulmonary edema and hemorrhage and congestion of the liver, spleen, and kidneys.

4.3. Structure-Activity Relationships

Because chemical-specific data were available, structure-activity relationships were not used for development of AEGL-3 values for oxygen difluoride.

Both fluorine and hydrogen fluoride are present in the reaction mixture producing oxygen difluoride but are less toxic than oxygen difluoride (Lester and Adams 1965). Other fluorinated compounds (hydrogen fluoride, chlorine pentafluoride, and chlorine trifluoride) also act as direct-contact irritants. Relative lethality data from Davis (1970) and Darmer et al. (1972) for a 1-h exposure to several fluorinated compounds are summarized in Table 4-9. Generally, the potency of the compounds is greatest for oxygen difluoride, followed by chlorine pentafluoride, chlorine trifluoride, and then hydrogen fluoride.

4.4. Species Variability

As shown by the data from Davis, (1970), there is considerable variability in the lethal response to inhaled oxygen difluoride among the species tested (monkeys, dogs, rats, and mice). Specifically, comparison of 1-h LC_{50} values reveals about a 17-fold difference between the least sensitive and most sensitive species, with larger species appearing to be less sensitive. Additionally, the monkey appears to exhibit the least variability in lethal response to other fluorinated compounds.

4.5. Concurrent Exposure Issues

Concurrent exposure to other chemicals affecting the respiratory tract will be of concern but cannot be readily quantified.

4.6. Susceptible Populations

No information on the relative susceptibility of individuals with pre-existing pulmonary diseases was identified. Individuals with pre-existing lung disease might be at increased risk from acute exposure to oxygen difluoride. In addition, asthmatics may respond to irritants with increased bronchial responsiveness. The very old and those who are ill may also have increased susceptibility to irritants such as oxygen difluoride.

TABLE 4-9 Relative Lethality of Oxygen Difluoride to Other Fluorinated Compounds[a]

Species	Oxygen Difluoride	Chlorine Pentafluoride	Chlorine Trifluoride	Hydrogen Fluoride
Rat	2.6/2.6 = 1	122/2.6 = 47	299/2.6 = 115	1,276/2.6 = 491
Mouse	1.5/1.5 = 1	57/1.5 = 38	178/1.5 = 119	501/1.5 = 334
Dog	26/26 = 1	122/26 = 5	–	–
Monkey	26/26 = 1	173/26 = 6.7	230/26 = 8.8	1,774/26 = 68

[a]1-h LC_{50} values expressed in ppm (Davis 1970; Darmer et al. 1972).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No quantitative data regarding AEGL-1 type effects in humans exposed to oxygen difluoride are available.

5.2. Animal Data Relevant to AEGL-1

No data regarding AEGL-1 type effects in animals exposed to oxygen difluoride are available.

5.3. Derivation of AEGL-1 Values

Exposure-response data for AEGL-1 severity effects was unavailable for oxygen difluoride. Studies in animals primarily focused on lethality. Where non-lethal responses were reported, the severity of the effects was not described or likely involved effects more severe (e.g., pulmonary damage) than those relevant to AEGL-1 values. Therefore, AEGL-1 values are not recommended for oxygen difluoride because of insufficient data.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In a review chapter, Diechmann and Gerarde (1969) stated that exposure of humans to oxygen difluoride at 0.5 ppm for "a few hours" produced respiratory-tract irritation and pulmonary edema and hemorrhage; however, no additional information was reported and a primary citation for the findings was not reported. Similar respiratory tract effects have been reported in laboratory animals. No additional information regarding AEGL-2 level effects in humans was identified.

6.2. Animal Data Relevant to AEGL-2

Information regarding AEGL-2 severity effects from oxygen difluoride is limited to that obtained from studies focusing on lethality (Lester and Adams 1965; Davis 1970; Harrison and Mackenzie 1973). The lowest concentrations tested (per exposure duration) in monkeys, dogs, and rats were the no-effect levels for lethality (see Tables 4-3 to 4-6). In addition, at the lowest concentrations tested, AEGL-2 level effects were observed, as summarized below. Therefore, the data are not suitable as the basis for deriving AEGL-2 values.

Davis (1970) reported the oxygen difluoride was nonlethal for a 1-h exposure at 16 ppm in monkeys, at 8.2 ppm in dogs 8.2 ppm, and at 2.2 ppm in rats;

for a 15-min exposure it was nonlethal at 60 ppm in monkeys and dogs and at 9.5 ppm in rats. Nonlethal exposures produced effects which could impair escape (AEGL-2 level effects), including gagging (monkeys and dogs), lacrimation (monkeys and dogs), muscular weakness (monkeys, dogs, and rats), dyspnea (monkeys and dogs), vomiting (monkeys and dogs), tetany (rats), and tachypnea (rats). In addition, slight-to-moderate pulmonary congestion and edema were observed at sublethal exposures; however, the study report did not report provide any additional details of these findings.

No lethality was observed in rats exposed to oxygen difluoride at 10 ppm for 5 min or at 5 ppm for 15 min (Lester and Adams 1965). In rats exposed at 20 ppm for 5 min, gross and microscopic examinations showed significant pulmonary damage, including swelling, acute pneumonia, consolidation of lung lobes, focal atelectasis, polymorphonuclear leukocyte infiltration, and pulmonary hemorrhage and edema; however, the study report did not provide adequate information to determine the severity of pulmonary damage.

At a nonlethal exposure to oxygen difluoride at 4.5 ppm for 30 min, respiratory distress was observed (Harrison and McKenzie, 1973). However, only one concentration was evaluated and, therefore, a no-effect level for AEGL-2 level effects was not identified in this study.

6.3. Derivation of AEGL-2 Values

Available studies on oxygen difluoride did not identify a no-effect level for AEGL-2 effects. Lethality data for oxygen difluoride in monkeys, dogs, rats, and mice indicate that the exposure-response curve for lethality is steep (data reported in Tables 4-3 to 4-7). Therefore, AEGL-2 values were derived by dividing the AEGL-3 values by 3, in accordance with the standing operating procedures for deriving AEGL values (NRC 2001).

The AEGL-2 values for oxygen difluoride are presented in Table 4-10. As noted in Section 6.1, Diechmann and Gerarde (1969) stated that humans exposed to oxygen difluoride at 0.5 ppm for "a few hours" developed respiratory-tract irritation and pulmonary edema and hemorrhage. However, that information cannot be verified or reviewed, as a primary reference to support the statement was not provided. Davis (1970) reported that sublethal exposures of monkeys (16 ppm for 1 h), dogs (8.2 ppm for 1 h), and rats (2.2 ppm for 1 h) produced slight to moderate pulmonary congestion and edema. AEGL-2 values for durations of 30 min or longer are below the effect-level report by Diechmann and Gerarde (1969), with the 4- and 8-h AEGL-2 values more than 10-fold lower. Thus, the AEGL-2 values are protective for AEGL-2 level effects.

TABLE 4-10 AEGL-2 Values for Oxygen Difluoride

10 min	30 min	1 h	4 h	8 h
0.43 ppm (0.95 mg/m^3)	0.16 ppm (0.35 mg/m^3)	0.083 ppm (0.18 mg/m^3)	0.024 ppm (0.053 mg/m^3)	0.013 ppm (0.029 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data on lethality in humans from inhalation exposure to oxygen difluoride were available.

7.2. Animal Data Relevant to AEGL-3

Acute lethality data for several animal species are available (Lester and Adams 1965; Davis, 1970). One-hour LC_{50} values ranged from 1.5 to 26.0 ppm, with larger species (dogs and monkeys) being less sensitive than smaller species (rats and mice) (see Table 4-8). Gross and microscopic examinations of the lungs of rats serially killed over 29 h after a single 5-min exposure to oxygen difluoride at 20 ppm (Lester and Adams 1965) indicated that lethality was contingent on the relationship between pulmonary damage (the primary target of oxygen difluoride) and tissue repair. Three days appeared to define a critical period for determining a lethal versus nonlethal response. Necropsy of rats, mice, dogs, and monkeys exposed at sublethal concentrations of oxygen difluoride revealed minor or moderate pulmonary edema and congestion for up to 14 days after exposure (Davis 1970).

7.3. Derivation of AEGL-3 Values

Lethality data from studies of rhesus monkeys exposed to oxygen difluoride (Davis 1970) were used as the basis for AEGL-3 values, because monkeys are a more relevant test species for humans than rodents and because hematology, clinical chemistry, and gross pathology data were available for 14 days after exposure. Benchmark dose analysis of the 1-h exposure data for monkeys resulted in a BMC_{05} of 17.2 ppm, a $BMCL_{05}$ of 7.48 ppm, and a BMC_{01} of 14.4 ppm (EPA 2003; see Appendix D). Analysis of the same data by the method of Litchfield and Wilcoxon (1949) resulted in an LC_1 value of about 13 ppm and an LC_5 value of about 17 ppm (see Appendix D). The $BMCL_{05}$ (7.48 ppm) accounts for the variability due to the small number of animals tested (four per group); although it is lower than the LC_5 determined by the method of Litchfield and Wilcoxon (1949), the $BMCL_{05}$ is typically used as the point-of-departure for deriving AEGL-3 values (NRC 2001). Time scaling was performed using the equation $C^n \times t = k$. An empirical value of 1.1 for the exponent n was determined using the data of Lester and Adams (1965) and Davis (1970) and the software package of ten Berge. Regression analysis of the 5-, 15- and 60-min LC_{50} values of Lester and Adams (1965) and Davis (1970) resulted in a similar n value of 1.27.

A total uncertainty factor of 10 was applied. Davis (1970) evaluated the acute inhalation toxicity of oxygen difluoride in monkeys, dogs, rats, and mice.

Larger species (dogs and monkeys) appeared to be less sensitive to the lethal effects of inhaled oxygen difluoride than smaller species (rats and mice), with up to a 17-fold difference between the rhesus monkey and the mouse. However, the study was conducted using a small number of animals (two males and two females per group). Therefore, an interspecies uncertainty factor of 3 was applied. Although asthmatics and individuals with compromised pulmonary function may be considered more susceptible to the effects of oxygen difluoride than healthy individuals, necropsy findings in multiple animal species indicate that the primary target of oxygen difluoride toxicity is the lungs rather than airways. For this reason an intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in the toxic response to inhaled oxygen difluoride. A factor of 3 is also consistent with the uncertainty factor used to derive AEGL values for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride). A modifying factor of 3 was also applied to account the sparse data set on oxygen difluoride.

The AEGL-3 values for oxygen difluoride are presented in Table 4-11, and the calculations are shown in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Table 4-12 presents the AEGL values for oxygen difluoride. Data on oxygen difluoride were insufficient for deriving AEGL-1 values. Lethality tests in several laboratory species suggest that inhalation exposure to oxygen difluoride results in latent pulmonary damage. Data with which to derive AEGL-2 value were unavailable. Because lethality data indicate that oxygen difluoride has a steep concentration-response curve, AEGL-2 values were derived by dividing AEGL-3 values by 3. AEGL-3 values for oxygen difluoride were derived from an estimated lethality threshold (1-h $BMCL_{05}$ of 7.48 ppm in rhesus monkeys).

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels established for oxygen difluoride for workplace and community exposures are presented in Table 4-13. The primary distinction that explains the differences between the values established by the American Conference of Governmental Industrial Hygienists, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration is that those values apply to working populations and are intended to prevent adverse health effects from exposures over a working lifetime whereas AEGL values apply to the general population, including susceptible subpopulations, and are intended to protect against adverse health effects from a single exposure occurring only once in a lifetime.

TABLE 4-11 AEGL-3 Values for Oxygen Difluoride

10 min	30 min	1 h	4 h	8 h
1.3 ppm (2.9 mg/m^3)	0.47 ppm (1.0 mg/m^3)	0.25 ppm (0.55 mg/m^3)	0.071 ppm (0.16 mg/m^3)	0.038 ppm (0.084 mg/m^3)

TABLE 4-12 AEGL Values for Oxygen Difluoride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	0.43 ppm (0.95 mg/m^3)	0.16 ppm (0.35 mg/m^3)	0.083 ppm (0.18 mg/m^3)	0.024 ppm (0.053 mg/m^3)	0.013 ppm (0.029 mg/m^3)
AEGL-3 (lethal)	1.3 ppm (2.9 mg/m^3)	0.47 ppm (1.0 mg/m^3)	0.25 ppm (0.55 mg/m^3)	0.071 ppm (0.16 mg/m^3)	0.038 ppm (0.084 mg/m^3)

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

TABLE 4-13 Other Standards and Guidelines for Oxygen Difluoride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.43 ppm	0.16 ppm	0.083 ppm	0.024 ppm	0.013 ppm
AEGL-3	1.3 ppm	0.47 ppm	0.25 ppm	0.071 ppm	0.038 ppm
IDLH (NIOSH)[a]	–	0.5 ppm	–	–	-
TLV-C (ACGIH)[b]	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm
REL-C (NIOSH)[c]	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm
PEL-TWA (OSHA)[d]	–	–	–	–	0.05 ppm

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[b]TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is a concentration that must not be exceeded during any part of the workday.
[c]REL-C (recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-C.
[d]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Safety and Health Administration) (29CFR 1910[2013]) is the average airborne concentration that should not be exceeded in any 8-h work shift of a 40-h work week.

8.3. Data Adequacy and Research Needs

Data on human exposure to oxygen difluoride were not available. Results of animal studies in several species were sufficient for identifying lethal concen-

trations of oxygen difluoride vapor, demonstrating latency in the lethal response, deep pulmonary damage as the probable cause of death, and that smaller species exhibited greater sensitivity to the lethal effects of oxygen difluoride than larger species. The AEGL-2 and AEGL-3 values are based on data from a study in rhesus monkeys. Lethal response data 14-days after exposure, hematologic and clinical chemistry measurements, and gross pathology findings were used to define critical effects. Although lethality data are available to derive AEGL-3 effects, a modifying factor was applied to account for a sparse database. Data from which to definitively assess the exposure response-exposure duration relationship for nonlethal effects of oxygen difluoride were lacking.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR OXYGEN DIFLUORIDE

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

No data were available on oxygen difluoride from which to define a point-of-departure for deriving AEGL-2 values. Lethality data from studies in monkeys, dogs, rats, and mice show that the exposure-response curve for oxygen difluoride is steep (Lester and Adams 1965; Davis 1970). Therefore, in accordance with the standing operating procedures for deriving AEGL values (NRC 2001), the AEGL-2 values were estimated by dividing the AEGL-3 values by 3.

Calculations:

10-min AEGL-2	1.3 ppm ÷ 3 = 0.43 ppm
30-min AEGL-2	0.47 ppm ÷ 3 = 0.16 ppm
1-h AEGL-2	0.25 ppm ÷ 3 = 0.083 ppm
4-h AEGL-2	0.071 ppm ÷ 3 = 0.024 ppm
8-h AEGL-2	0.038 ppm ÷ 3 = 0.013 ppm

Derivation of AEGL-3 Values

Key study:	Davis, H.V. 1970. Acute Toxicity of Oxygen Difluoride. AMRL-TR-70-102 Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base , OH.
Critical effect:	Lethality in rhesus monkeys, 1-h $BMCL_{05}$ of 7.48 ppm. The $BMCL_{05}$ accounts for the variability due to the small number of test animals (four per group) and is typically used as the point-of-departure for deriving AEGL-3 values. The $BMCL_{05}$ is below the 1-h nonlethal concentration of 16 ppm reported by Davis (1970) for rhesus monkeys and beagle dogs. It is also about one-third of the 1-h LC_{50} of 26 ppm determined by the

method of Litchfield and Wilcoxon (1949), but is more conservative than the 1-h LC_5 of 17 ppm calculated by that method.

Time scaling: $C^n \times t = k$; an empirical value for the exponent n of 1.1 was determined using the software of ten Berge and data from the studies by Lester and Adams (1965) and Davis (1979) (see Appendix B). Regression analysis of the 1-h LC_{50} data from those studies resulted in a similar value for n of 1.27.
$(7.48 \text{ ppm})^{1.1} \times 1 \text{ h} = 9.15 \text{ ppm-h}$

Uncertainty factors: Total uncertainty factor: 10

3 for interspecies differences. Davis (1970) evaluated the acute inhalation toxicity of oxygen difluoride in monkeys, dogs, rats and mice. Larger species (dogs and monkeys) appeared to be less sensitive to the lethal effects of oxygen difluoride than smaller species (rats and mice). However, the study was conducted using a small number of animals (two males and two females per group).

3 for intraspecies variability; to account for greater sensitivity of individuals with compromised respiratory function. That value is also consistent with the uncertainty factor used for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride, which all appear to cause tissue irritation by direct-contact mechanisms). Data in animals indicate that the primary target is the deep lung rather than the airways. Therefore, an intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in the toxic response to oxygen difluoride.

Modifying factor: 3, for sparse data set

Calculations:

10-min AEGL-3:
$C^{1.1} \times 0.1667 \text{ h} = 9.15 \text{ ppm-h}$
$C = 38.13 \text{ ppm}$
$38.13 \text{ ppm} \div 30 = 1.27 \text{ ppm (1.3 ppm)}$

30-min AEGL-3:
$C^{1.1} \times 0.5 \text{ h} = 9.15 \text{ ppm-h}$
$C = 14.05 \text{ ppm}$
$14.05 \text{ ppm} \div 30 = 0.468 \text{ ppm (0.47 ppm)}$

1-h AEGL-3:	$C^{1.1} \times 1\ h = 9.15$ ppm-h C = 7.48 ppm 7.48 ppm ÷ 30 = 0.249 ppm (0.25 ppm)
4-h AEGL-3:	$C^{1.1} \times 4\ h = 9.15$ ppm-h C = 2.12 ppm 2.12 ppm ÷ 30 = 0.071 ppm
8-h AEGL-3:	$C^{1.1} \times 8\ h = 9.15$ ppm-h C = 1.13 ppm 1.13 ppm ÷ 30 = 0.038 ppm

APPENDIX B

TIME SCALING CALCULATIONS FOR OXYGEN DIFLUORIDE

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

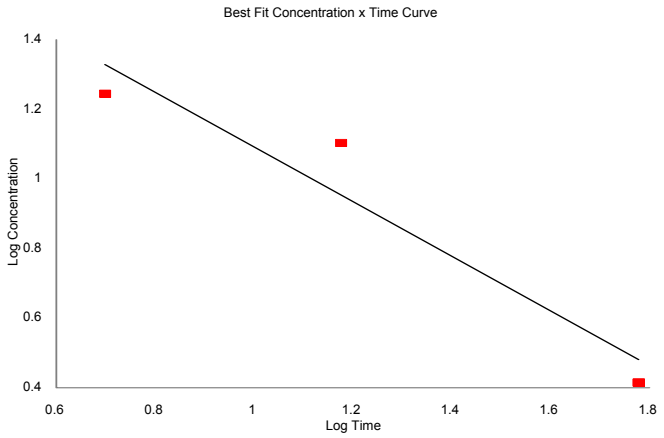
TABLE B-1 Oxygen Difluoride Lethality in Rats

Time	Conc.	Log Time	Log Conc.	Regression Output:	
5	17.6	0.6990	1.2455	Intercept	1.8782
15	12.7	1.1761	1.1038	Slope	-0.7857
60	2.6	1.7782	0.4150	R Squared	0.9145
				Correlation	-0.9563
				Degrees of Freedom	1
				Observations	3
n =	1.27				
k =	245.78				

Source: Lester and Adams 1965; Davis 1970.

Analysis of data from Davis (1970) and Lester and Adams (1965) using the software of ten Berge resulted in a value for n of 1.1. Regression analysis of lethality data for rats (LC_{50} values for 5 min, 15 min, and 1 h) also showed a near linear relationship (n = 1.27), similar to that of the ten Berge software. The n value of 1.1 was used for deriving the AEGL values for oxygen difluoride.

LogProbit_Oxygen difluoride_rat AEGL



LogProbit_Oxygen difluoride_rat AEGL

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:15:08

Seq. Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:18:17

Seq. Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Observations 1 through 18 considered!

Seq. Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Used Probit Equation Y = B0 + B1*×1 + B2*×2
X1 = Conc ppm, ln-transformed
X2 = Minutes, ln-transformed

Chi Square = 74.27
Degrees of freedom = 15
Probability model = 7.66E-10

Ln (likelihood) = -56.25

B 0 = -6.6734E+00 Student t = -1.5079
B 1 = 2.4596E+00 Student t = 2.7662
B 2 = 2.2229E+00 Student t = 2.5684

variance B 00 = 1.9587E+01
covariance B 01 = -3.8663E+00
covariance B 02 = -3.7876E+00
variance B 11 = 7.9059E-01
covariance B12 = 7.3043E-01
variance B 22 = 7.4905E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 1.106
Lower limit (95% CL) = 0.817
Upper limit (95% CI) = 1.396

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:41:36

Seq. Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR OXYGEN DIFLUORIDE

Derivation Summary

AEGL-1 VALUES

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

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.43 ppm (0.95 mg/m^3)	0.16 ppm (0.35 mg/m^3)	0.083 ppm (0.18 mg/m^3)	0.024 ppm (0.053 mg/m^3)	0.013 ppm (0.029 mg/m^3)

Data adequacy: Data were not available from which to define a point-of-departure for AEGL-2 values for oxygen difluoride. Lethality data from studies in monkeys, dogs, rats, and mice show that the exposure-response curve for oxygen difluoride is steep (Lester and Adams 1965; Davis 1970). Therefore, in accordance with the standing operating procedures for deriving AEGL values (NRC 2001), the AEGL-2 values were estimated by dividing the AEGL-3 values by 3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.3 ppm (2.9 mg/m^3)	0.47 ppm (1.0 mg/m^3)	0.25 ppm (0.55 mg/m^3)	0.071 ppm (0.16 mg/m^3)	0.038 ppm (0.084 mg/m^3)

Reference: Davis, H.V. 1970. Acute Toxicity of Oxygen Difluoride. AMRL-TR-70-102. Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH.

Test species/Strain/Sex/Number: Monkey; rhesus; 2/sex/group

Exposure route/Concentrations/Durations: Inhalation; 60, 100, 120, or 140 ppm for 15 min or 16, 21, or 32 ppm for 1 h.

Effects:

15 min		*1 h*	
Conc. (ppm)	Mortality ratio	Conc. (ppm)	Mortality ratio
60	0/4	16	0/4
100	2/4	21	1/4
120	2/4	32	3/4
140	4/4		

End point/Concentration/Rationale: $BMCL_{05}$ of 7.48 ppm; accounts for the variability due to the small number of test animals (four per group) and is typically used as the point-of-departure for AEGL-3 values. The $BMCL_{05}$ is below the 1-h nonlethal

(Continued)

AEGL-3 VALUES Continued

concentration of 16 ppm reported by Davis (1970) for rhesus monkeys and beagle dogs. It is also about one-third of the 1-h LC_{50} of 26 ppm determined by the method of Litchfield and Wilcoxon (1949), but more conservative than the 1-h LC_5 of 17 ppm calculated by that method.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, Davis (1970) evaluated the acute inhalation toxicity of oxygen difluoride in monkeys, dogs, rats, and mice. Larger species (dogs and monkeys) appeared to be less sensitive to the lethal effects of oxygen difluoride than smaller species (rats and mice). However, the study was conducted using a small number of animals (two males and two females per group). Therefore an interspecies uncertainty factor of 3 was applied.
Intraspecies: 3, consistent with the uncertainty factor application for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride, which all appear to cause tissue irritation by direct-contact mechanisms). Data in animals indicate that the primary target is the deep lung rather than the airways. Therefore, an intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in the toxic response to oxygen difluoride.

Modifying factor: 3 to account for the sparse data set on oxygen difluoride

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; an empirical value of 1.1 for the exponent n was derived using the software of ten Berge and the data from the studies by Lester and Adams (1965) and Davis (1970). Regression analysis of 1-h LC_{50} data from those studies resulted in a similar n value of 1.27.

Data adequacy: Lethality data are available for four species (monkeys, dogs, rats, and mice) and are sufficient for deriving AEGL-3 values. However, due to the sparse data set, a modifying factor of 3 was applied. Results of experiments indicate that larger species are less susceptible to oxygen difluoride than smaller species.

APPENDIX D

LETHALITY THRESHOLD AND BENCHMARK DOSE ANALYSIS FOR OXYGEN DIFLUORIDE

Davis (1970): Rhesus monkeys (4/group; 2 males, 2 females), 1-h exposure $BMCL_{05}$

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Tue Jan 30 08:44:51 2007

BMDS MODEL RUN

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

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

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

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
background = 0
intercept = -9.26036
slope = 2.85468

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-12.6489	5.97666
slope	3.8667	1.85849

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test DF	P-value
Full model	-4.49868			
Fitted model	-4.65729	0.317211	2	0.8533
Reduced model	-8.99736	8.99736	3	0.02933

AIC: 13.3146

Goodness of Fit Scaled

Dose	Est. Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	4	0
16.0000	0.0269	0.108	0	4	-0.3327
21.0000	0.1903	0.761	1	4	0.3039
32.0000	0.7740	3.096	3	4	-0.1148

Chi-square = 0.22 DF = 2 P-value = 0.8975

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

BMC = 17.216
BMCL = 7.48236

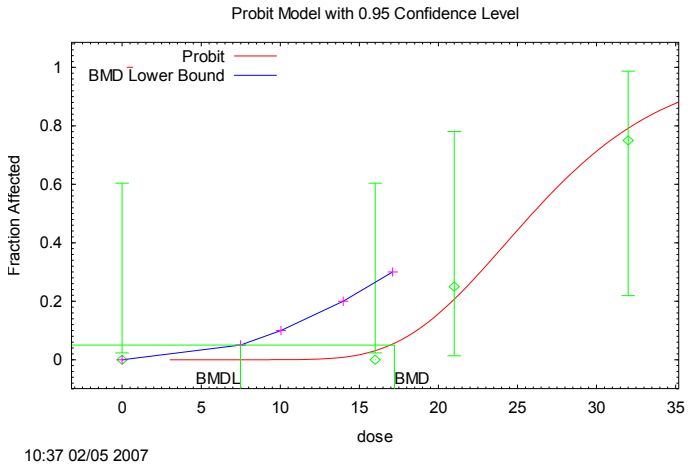


FIGURE D-1 Probit model $BMCL_{05}$.

Davis (1970): Rhesus monkeys (4/group; 2 males, 2 females), 1-h exposure BMC_{01}

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Wed Jan 31 10:38:01 2007

BMDS MODEL RUN

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

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

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

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
background = 0
intercept = -9.26036
slope = 2.85468

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-12.6489	5.97666
slope	3.8667	1.85849

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance	Test DF	P-value
Full model	-4.49868			
Fitted model	-4.65729	0.317211	1	0.5733
Reduced model	-7.63817	6.27898	2	0.0433

AIC: 13.3146

Goodness of Fit Scaled

Dose	Est. Prob.	Expected	Observed	Size	Residual
16.0000	0.0269	0.108	0	4	-0.3327
21.0000	0.1903	0.761	1	4	0.3039
32.0000	0.7740	3.096	3	4	-0.1148

Chi-square = 0.22 DF = 1 P-value = 0.6420

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 14.4341
BMCL = 4.22764

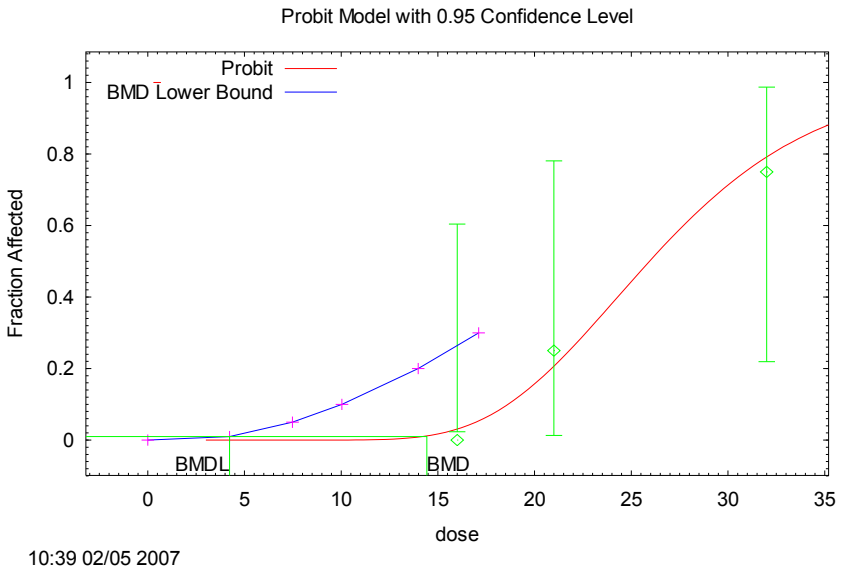


FIGURE D-2 Probit model BMC_{01}.

LC_{50} and Lethality Threshold - Litchfield-Wilcoxon

Davis (1970): Rhesus monkeys, 1-h exposure to oxygen difluoride

	Mortality	Observed %	Expected %	Observed-Expected	Chi-Square
16.000	0/4	0 (2.30)	3.37	-1.07	0.0035
21.000	1/4	25.00	18.45	6.55	0.0285
32.000	3/4	75.00	80.38	-5.38	0.0183

Values in parentheses are corrected for 0 or 100 percent Total = 0.0503

LC_{50} = 26.067(20.584 - 33.010)*
Slope = 1.27(1.02 - 1.58)*
*These values are 95 percent confidence limits

Total animals = 12Total doses = 3 Animals/dose = 4.00
Chi-square = total chi-square X animals/dose = 0.2013
Table value for Chi-square with 1 Degrees of Freedom = 3.8400

LC_{84} = 33.175 LC_{16} = 20.481 FED = 1.27 FS = 1.24 A = 1.10

Expected Lethal Dose Values

$LC_{0.1}$	9.545
$LC_{1.0}$	13.360
$LC_{5.0}$	16.986
LC_{10}	18.936
LC_{25}	22.217
LC_{50}	26.067
LC_{75}	30.583
LC_{90}	35.882
LC_{99}	50.857

APPENDIX E

CATEGORY PLOT FOR OXYGEN DIFLUORIDE

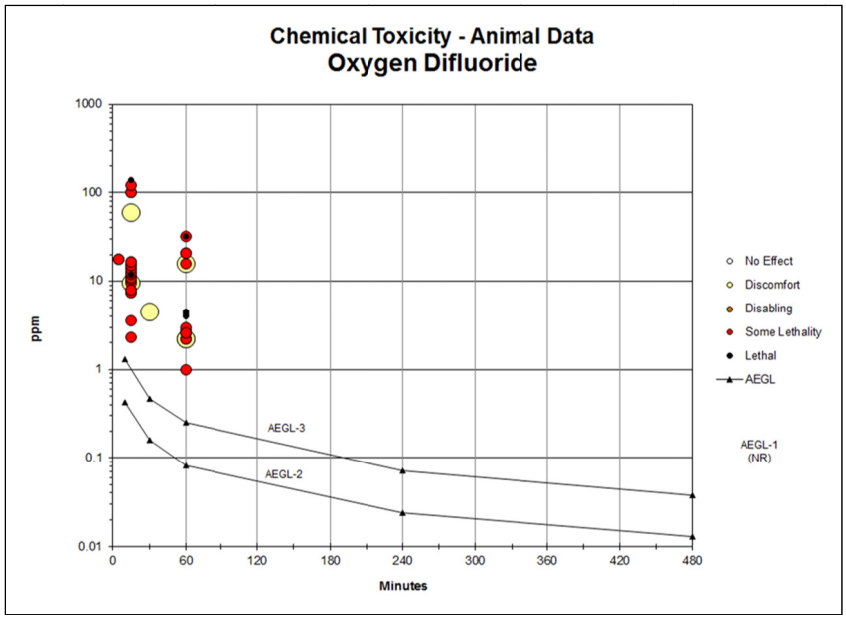


FIGURE E-1 Category plot of toxicity data and AEGL values for oxygen difluoride.

TABLE E-1 Data Used in Category Plot for Oxygen Difluoride

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.43	10	AEGL	
AEGL-2				0.16	30	AEGL	
AEGL-2				0.083	60	AEGL	
AEGL-2				0.024	240	AEGL	
AEGL-2				0.013	480	AEGL	
AEGL-3				1.3	10	AEGL	
AEGL-3				0.47	30	AEGL	
AEGL-3				0.25	60	AEGL	
AEGL-3				0.071	240	AEGL	
AEGL-3				0.038	480	AEGL	
Darmer et al. 1972	Rat	M	1	2.6	60	SL	LC_{50}
Davis 1970	Dog	B	1	60	15	1	Mortality: 0/4
Davis 1970	Dog	B	1	100	15	SL	Mortality: 3/4
Davis 1970	Dog	B	1	8.2	60	1	Mortality: 0/4
Davis 1970	Dog	B	1	16	60	SL	Mortality: 2/4
Davis 1970	Dog	B	1	21	60	SL	Mortality: 1/4
Davis 1970	Dog	B	1	32	60	3	Mortality: 4/4
Davis 1970	Monkey	B	1	60	15	1	Mortality: 0/4

Davis 1970	Monkey	B	1	100	15	SL	Mortality: 2/4
Davis 1970	Monkey	B	1	120	15	SL	Mortality: 2/4
Davis 1970	Monkey	B	1	140	15	3	Mortality: 4/4
Davis 1970	Monkey	B	1	16	60	1	Mortality: 0/4
Davis 1970	Monkey	B	1	21	60	SL	Mortality: 1/4
Davis 1970	Monkey	B	1	32	60	SL	Mortality: 3/4
Davis 1970	Mouse	M	1	7.5	15	SL	LC_{50}
Davis 1970	Mouse			7.5	15	SL	LC_{50}
Davis 1970	Mouse	M	1	9.5	15	SL	Mortality: 12/15
Davis 1970	Mouse	M	1	11.0	15	SL	Mortality: 8/15
Davis 1970	Mouse	M	1	11.9	15	3	Mortality: 15/15
Davis 1970	Mouse	M	1	15.2	15	SL	Mortality: 12/15
Davis 1970	Mouse	M	1	16.5	15	SL	Mortality: 14/15
Davis 1970	Mouse	M	1	1.0	60	SL	Mortality: 5/15
Davis 1970	Mouse	M	1	2.2	60	SL	Mortality: 8/15
Davis 1970	Mouse	M	1	2.2	60	SL	Mortality: 8/15
Davis 1970	Mouse	M	1	4.2	60	3	Mortality: 15/15
Davis 1970	Rat	M	1	9.5	15	1	Mortality: 0/10
Davis 1970	Rat	M	1	10.4	15	SL	Mortality: 1/10
Davis 1970	Rat	M	1	11.0	15	SL	Mortality: 3/10
Davis 1970	Rat	M	1	11.9	15	SL	Mortality: 1/10
Davis 1970	Rat	M	1	12.7	15	SL	LC_{50}
Davis 1970	Rat	M	1	13.8	15	SL	Mortality: 9/10
Davis 1970	Rat	M	1	15.2	15	SL	Mortality: 8/10

(Continued)

TABLE E-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Davis 1970	Rat	M	1	16.5	15	SL	Mortality: 9/10
Davis 1970	Rat	M	1	2.2	60	1	Mortality: 0/10
Davis 1970	Rat	M	1	2.2	60	1	Mortality: 0/10
Davis 1970	Rat			2.6	60	SL	LC_{50}
Davis 1970	Rat	M	1	2.7	60	SL	Mortality: 7/10
Davis 1970	Rat	M	1	3.0	60	SL	Mortality: 14/15
Davis 1970	Rat	M	1	4.0	60	3	Mortality: 10/10
Harrison and Mackenzie 1973	Rat	M	1	4.5	30	1	Respiratory distress
Harrison and Mackenzie 1973	Rat	M	1	4.5	60	3	Mortality: 4/4
Harrison and Mackenzie 1973	Rat			4.5	60	3	100% mortality
Lester and Adams 1965	Rat	B	1	17.6	5	SL	LC_{50}
Lester and Adams 1965	Rat	B	1	2.3	15	SL	$BMCL_{05}$
Lester and Adams 1965	Rat	B	1	3.6	15	SL	BMC_{01}
Lester and Adams 1965	Rat	B	1	8.0	15	SL	LC_{50}
Lester and Adams 1965	Rat	B	1	9.7	15	SL	Mortality: 7/10
Lester and Adams 1965	Rat	B	1	14.6	15	SL	Mortality: 7/10
Vernot et al. 1977	Rat	M	1	2.6	60	SL	LC_{50}

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