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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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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

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

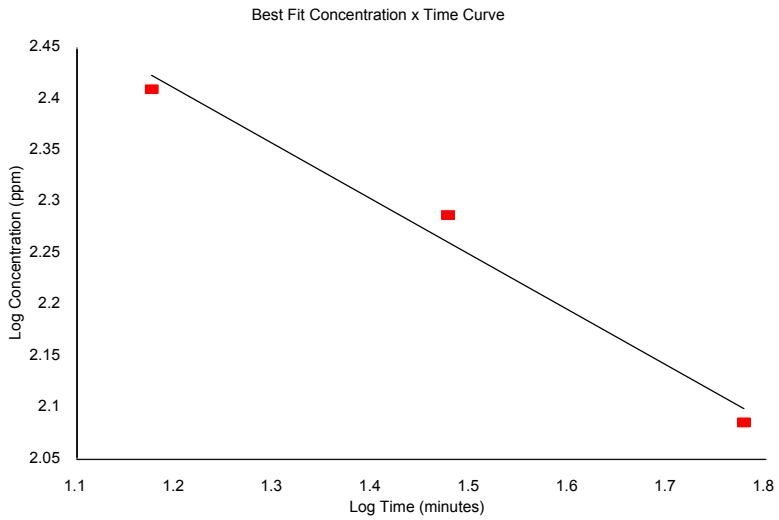

FIGURE A-1 LC_{50} values for chlorine pentafluoride in the rat. Source: Darmer et al. 1972.

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

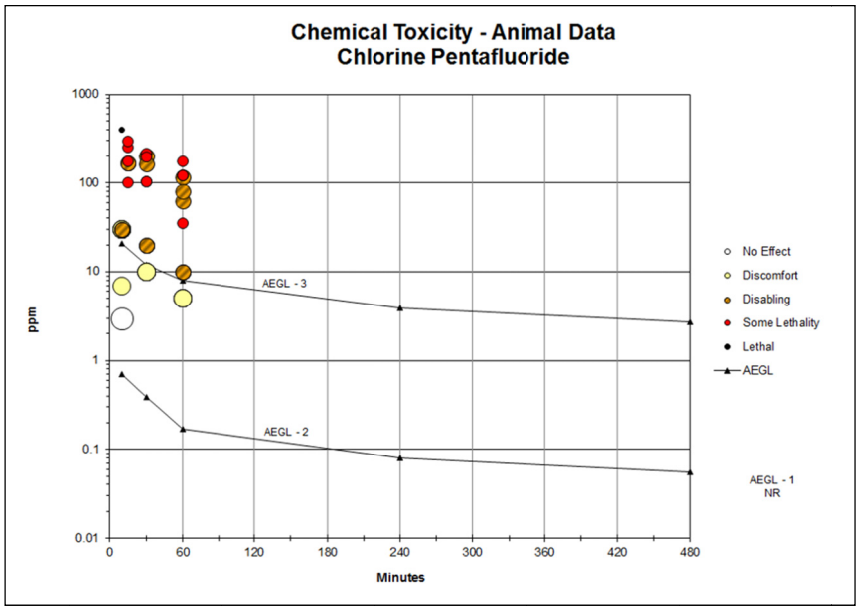

FIGURE C-1 Category plot of toxicity data and AEGL values for chlorine pentafluoride.

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.

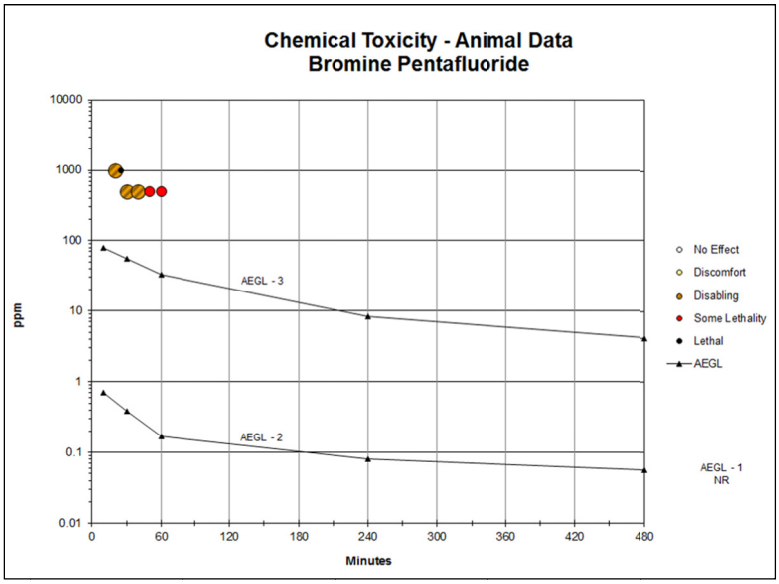

FIGURE C-2 Category plot of toxicity data and AEGL values for bromine pentafluoride.

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.