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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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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

2

Carbonyl Fluoride[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

TABLE 2-1 AEGL Values for Carbonyl Fluoride

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

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

1. INTRODUCTION

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

TABLE 2-2 Chemical and Physical Properties of Carbonyl Fluoride

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

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

2.2. Nonlethal Toxicity

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

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

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

2.6. Summary

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

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

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

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

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

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

3.2. Nonlethal Toxicity

3.2.1. Rats

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

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

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

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

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

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

3.3. Repeated Dose Toxicity

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

3.4. Developmental and Reproductive Toxicity

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

3.5. Genotoxicity

No data on the genotoxicity of carbonyl fluoride were found.

3.6. Chronic Toxicity and Carcinogenicity

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

3.7. Summary

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

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

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

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

4.2. Mechanism of Toxicity

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

4.3. Structure-Activity Relationships

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

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

4.4. Other Relevant Information

No additional relevant information on carbonyl fluoride was found.

4.4.1. Species Variability

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

4.4.2. Susceptible Populations

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

4.4.3. Concentration-Exposure Duration Relationship

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

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues for carbonyl fluoride were identified.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

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

5.2. Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1 Values

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

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

6.3. Derivation of AEGL-2 Values

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

TABLE 2-4 AEGL-2 Values for Carbonyl Fluoride

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

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

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

7.3. Derivation of AEGL-3 Values

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

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

8. SUMMARY OF AEGLS

8.1. AEGLS Values and Toxicity End Points

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

8.2. Other Standards and Guidelines

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

TABLE 2-5 AEGL-3 Values for Carbonyl Fluoride

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

TABLE 2-6 AEGL Values for Carbonyl Fluoride

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

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

TABLE 2-7 AEGL Values for Phosgene and Hydrogen Fluoride

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

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

TABLE 2-8 Standards and Guidelines for Carbonyl Fluoride

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

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

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

8.3. Data Adequacy and Research Needs

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

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CARBONYL FLUORIDE

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

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

Calculations:

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

Derivation of AEGL-3 Values

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

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

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

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR CARBONYL FLUORIDE

Derivation Summary

AEGL-1 VALUES

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

AEGL-2 VALUES

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

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

AEGL-3 VALUES

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

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

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

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

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

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

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

(Continued)

AEGL-3 VALUES Continued

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

APPENDIX D

BENCHMARK DOSE CALCULATIONS

BMDS MODEL RUN $BMCL_{05}$

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

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

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

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

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

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

Analysis of Deviance Table

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

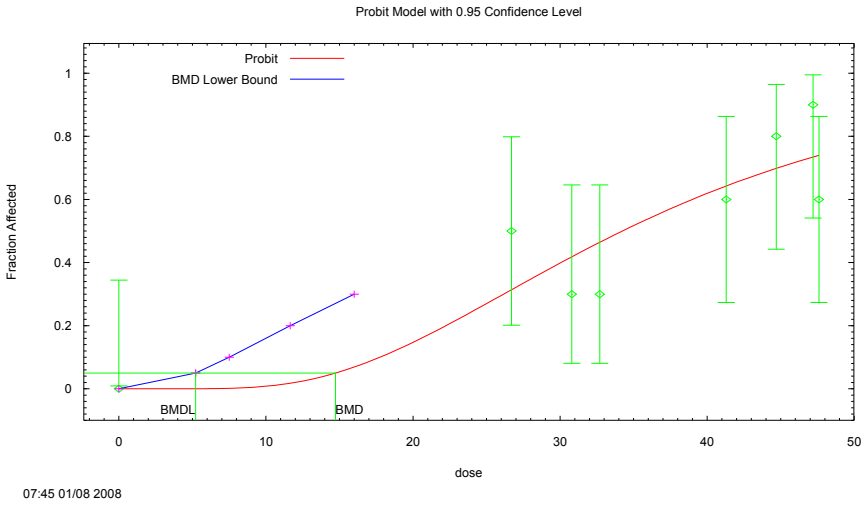
AIC: 92.1812

Goodness of Fit

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

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

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



BMDS MODEL RUN BMC_{01}

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

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

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

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

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

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

Analysis of Deviance Table

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

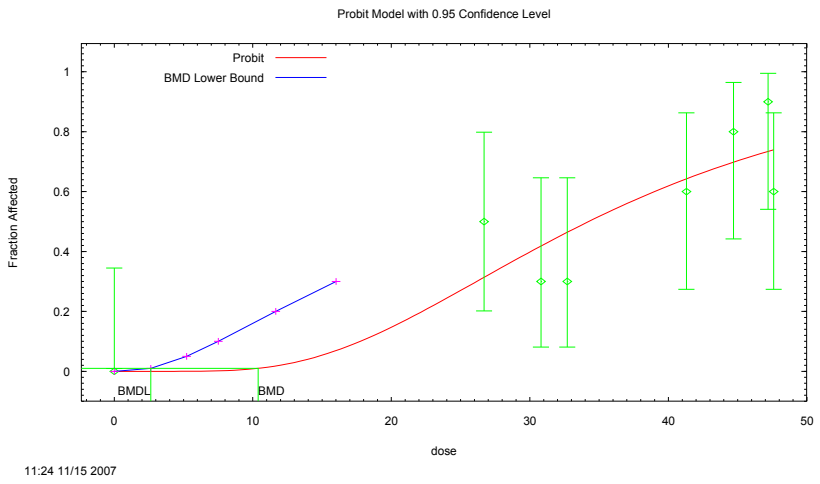
AIC: 92.1812

Goodness of Fit

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

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

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



APPENDIX E

CATEGORY PLOT FOR CARBONYL FLUORIDE

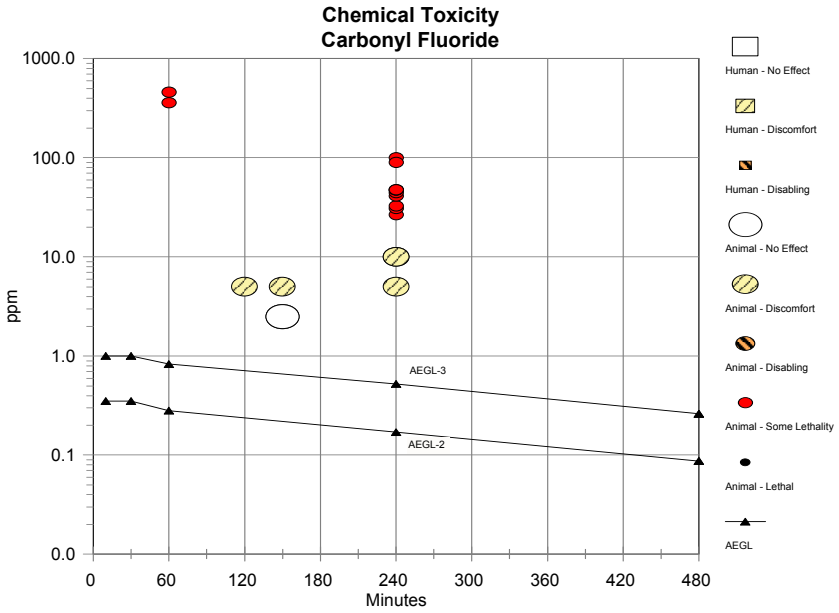


FIGURE E-1 Category plot of toxicity data and AEGL values for carbonyl fluoride.

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

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

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

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