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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 20

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

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standing 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 nineteen volumes. This report is the twentieth volume in that series. The AEGL document for 12 chloroformates is published as an appendix in this report.

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 recom-

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

mendations 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. However, during the finalization process it was discovered that the AEGL values for the chloroformates needed to be rereviewed. The Department of Defense requested that the National Academies of Sciences, Engineering, and Medicine, convene a new committee to re-evaluate the AEGL values for the chloroformates and determine appropriate values for *n*-propyl chloroformate and isopropyl chloroformate.

The committee's report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Academies' Report Review Committee. The purpose of the 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 of 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 thank the following for their review of the report: Edward Bishop, HDR Engineering, Inc.; Glenn Millner, Center for Toxicology and Environmental Health, LLC; and Neeraja Erraguntla, American Chemistry Council.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Kenneth Still, Portland State University, he was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the author committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke from EPA. The committee also acknowledges Elizabeth Boyle, the project director for her work this project. Other staff members who contributed to this effort are Susan Martel (Senior Program Officer, Board on Environmental Studies and Toxicology), 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 Orin Luke (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.

George Rusch, *Chair*
Committee on Acute Exposure Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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Summary

This report contains updated values for *n*-propyl chloroformate, isopropyl chloroformate, ethyl chlorothioformate, as well as the AEGL values for the other 9 chloroformates included in the Interim Acute Exposure Guideline Levels (AEGLs) for Selected Chloroformates. A summary of these AEGL values is presented in Table S-1. AEGL-1 values were not derived for any chloroformate because of insufficient toxicity data. No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for all chloroformates were calculated by taking a three-fold reduction in the AEGL-3 values. That approach is consistent with recommendations in the Standing Operating Procedures for Developing AEGLs for estimating a threshold for irreversible effects (NRC 2001). AEGL-3 values were based on lethality data on the individual chloroformates, although the toxicity data for chloroformates were sparse. Respiratory effects associated with direct-acting irritation and corrosion (nasal irritation, pulmonary inflammation, pulmonary edema, and emphysema and associated lethality) have been observed in humans and animals for several of the chloroformates. Interspecies and intraspecies uncertainty factors of 3 (for a total uncertainty factor of 10) were used for calculating the AEGL values for the chloroformates. Those values were chosen because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal of entry (respiratory tract). The AEGL values for *n*-propyl chloroformate were determined on the basis of structural similarity to isopropyl chloroformate, and the AEGL values for isobutyl chloroformate and *sec*-butyl chloroformate were determined on the basis of structural analogy to *n*-butyl chloroformate.

REFERENCE

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances. Washington, DC: National Academy Press.

TABLE S-1 AEGL Values for Selected Chloroformates[a]

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Classification	10 min	30 min	1 h	4 h	8 h
Methyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)
AEGL-3 (lethal)	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)
Ethyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (8.8 mg/m^3)	1.6 ppm (7.0 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.88 mg/m^3)
AEGL-3 (lethal)	8.8 ppm (39 mg/m^3)	6.1 ppm (27 mg/m^3)	4.8 ppm (21 mg/m^3)	1.2 ppm (5.3 mg/m^3)	0.60 ppm (2.6 mg/m^3)
Isopropyl chloroformate and n-*propyl chloroformate*					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	3.7 ppm (19 mg/m^3)	3.7 ppm (19 mg/m^3)	3.0 ppm (15 mg/m^3)	1.9 ppm (9.5 mg/m^3)	1.3 ppm (6.5 mg/m^3)
AEGL-3 (lethal)	11 ppm (55 mg/m^3)	11 ppm (55 mg/m^3)	9.1 ppm (46 mg/m^3)	5.7 ppm (29 mg/m^3)	3.8 ppm (19 mg/m^3)
Allyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.3 ppm (6.4 mg/m^3)	0.87 ppm (4.3 mg/m^3)	0.70 ppm (3.4 mg/m^3)	0.18 ppm (0.88 mg/m^3)	0.09 ppm (0.44 mg/m^3)
AEGL-3 (lethal)	3.8 ppm (19 mg/m^3)	2.6 ppm (13 mg/m^3)	2.1 ppm (10 mg/m^3)	0.53 ppm (2.6 mg/m^3)	0.26 ppm (1.3 mg/m^3)
n-*Butyl chloroformate, isobutyl chloroformate, and* sec-*butyl chloroformate*					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)
AEGL-3 (lethal)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)
Benzyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)
AEGL-3 (lethal)	3.7 ppm (26 mg/m^3)	3.7 ppm (26 mg/m^3)	2.9 ppm (20 mg/m^3)	1.9 ppm (13 mg/m^3)	0.93 ppm (6.5 mg/m^3)

Phenyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.06 ppm (0.38 mg/m^3)
AEGL-3 (lethal)	0.72 ppm (4.6 mg/m^3)	0.72 ppm (4.6 mg/m^3)	0.57 ppm (3.6 mg/m^3)	0.36 ppm (2.3 mg/m^3)	0.18 ppm (1.2 mg/m^3)
2-Ethylhexyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)
AEGL-3 (lethal)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)
Ethyl chlorothioformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.80 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)
AEGL-3 (lethal)	3.0 ppm (15 mg/m^3)	3.0 ppm (15 mg/m^3)	2.4 ppm (12 mg/m^3)	1.5 ppm (7.6 mg/m^3)	0.75 ppm (3.8 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

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Introduction

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

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.

The contents of this report come from a document that was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Heather Carlson-Lynch (SRC, Inc.), and Chemical Manager Ernest V. Falke (U.S. Environmental Protection Agency). The National Advisory Committee on Acute Exposure Guideline Levels 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. However, during the finalization process it was discovered that the AEGL values for *n*-propyl chloroformate and isopropyl chloroformate relied on studies performed by Industrial Bio-Test, a company that is now known to have improperly conducted and reported some of its studies. The Department of Defense requested that the National Academies of Sciences, Engineering, and Medicine, convene a new committee to re-evaluate the AEGL values for the chloroformates and determine appropriate values for *n*-propyl chloroformate and isopropyl chloroformate.

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 2001), 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 both experienced scientific judgment and clear and

transparent criteria. 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.

STATEMENT OF TASK

An ad hoc committee will review and update the technical support document on acute exposure guideline levels (AEGLs) for selected chloroformates. The update will focus on establishing AEGL-3 values for *n*-propyl chloroformate and isopropyl chloroformate, but will also consider whether any new data are available that would affect the proposed values for the other 10 chloroformates.

APPROACH TO THE STUDY

The National Academies convened the Committee on Acute Exposure Guideline Levels for Chloroformates in 2016. Members of the committee have expertise in general toxicology, inhalation toxicology, industrial hygiene, occupational health, and risk assessment. One public meeting was held to familiarize the committee members with the history and importance of AEGLs and to discuss the approach to revising and updating the chloroformate AEGL values.

ORGANIZATION OF THE REPORT

This report is organized into two additional chapters and five appendixes. Chapter 2 is divided into 11 sections, one that provides, general information on selected chloroformates, and then separate sections that discuss the AEGLs for methyl chloroformate (Section 2), ethyl chloroformate (Section 3), isopropyl chloroformate (Section 4), *n*-propyl chloroformate (Section 5), allyl chloroformate (Section 6), *n*-butyl chloroformate, isobutyl chloroformate, and *sec*-butyl

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chloroflormate (Section 7), benzyl chloroformate (Section 8), phenyl chloroformate (Section 9), 2-ethylhexyl chloroformate (Section 10), and ethyl chlorothioformate (Section 11). Appendix A provides biographical information on the committee members, Appendix B provides the benchmark calculations, Appendix C provides the derivation summaries, Appendix D provides the category plots.

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Chloroformates Acute
Exposure Guideline Levels

1. GENERAL INFORMATION ON SELECTED CHLOROFORMATES

The bases of the AEGL values for the following chloroformates are described in this report: methyl chloroformate, ethyl chloroformate, isopropyl chloroformate, *n*-propyl chloroformate, allyl chloroformate, *n*-butyl chloroformate, isobutyl chloroformate, *sec*-butyl chloroformate, benzyl chloroformate, phenyl chloroformate, 2-ethylhexyl chloroformate, and ethyl chlorothioformate. Information relevant to all 12 compounds is presented first, and is followed by separate sections on the individual chemicals.

1.1. General Physical and Chemical Properties

Selected physicochemical properties of the chloroformates are presented in Table 2-1. Chloroformates are clear, colorless liquids with relatively low freezing points and relatively high boiling points (>100°C). The chloroformates are reactive compounds possessing both acid chloride and alkyl substituents. The alkyl substituent is responsible for the thermal stability of the chloroformate in the following order of decreasing stability: aryl (e.g., benzyl chloroformate, phenyl chloroformate) > primary alkyl (e.g., methyl chloroformate, ethyl chloroformate, *n*-propyl chloroformate, *n*-butyl chloroformate) > secondary alkyl (e.g., isopropyl chloroformate, isobutyl chloroformate) > tertiary alkyl (Kreutzberger 2001).

Chloroformates are soluble in organic solvents, and hydrolyze in water. Hydrolysis products of the chloroformates, except ethyl chlorothioformate, are an alcohol (ROH), carbon dioxide, and hydrogen chloride; hydrolysis products of ethyl chlorothioformate are ethyl mercaptan, carbon dioxide, and hydrogen chloride. Specific alcohol hydrolysis products for each chloroformate are listed in Table 2-1. Lower chloroformates (such as methyl and ethyl chloroformate) hydrolyze more rapidly in water at room temperature, and the higher and aromatic chloroformates hydrolyze more slowly at room temperature (Kreutzberger 2001). Measured hydrolysis half-life in water for methyl, ethyl, propyl, isopropyl, and phenyl chloroformate range from 1.4 to 53.2 min (Queen 1967). Rates for the

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TABLE 2-1 General Chemical and Physical Properties of Selected Chloroformates[a]

Chloroformate	Molecular Weight	Solubility in Water	Hydrolysis Half-time, min (°C)	Hydrolysis Products (with CO_2)	Estimated Atmospheric Half-time	Vapor Pressure, mm Hg (°C)	Vapor Density, g/L (air = 1)	Boiling Point, °C	Flash Point, °C	Flamability Limits[i] Lower explosive limit	Upper explosive limit
Methyl chloroformate	94.5	Slightly soluble (hydrolyzes)	20.5 (25)[b]	Methanol, HCl	74 d at 5 × 10⁵ OH, photooxidation	108.5 (25)	3.26	71.0	12.2	–	6.7%
Ethyl chloroformate	108.53	Gradually decomposes	33.0 (25)[b]	Ethanol, HCl	11 d, photooxidation	22.4 (25)	3.7	95	27.8	–	–
Isopropyl chloroformate	122.55	Hydrolyzes	5.6 (25)[b]	Isopropanol, HCl	5 d, photooxidation	100 (47)	4.2	104.6	27.8	Flammable; may be ignited by heat, sparks or flame.	Flammable; may be ignited by heat, sparks or flame.
n-Propyl chloroformate	122.55	–	29.4 (25)[b]	*n*-Propanol, HCl	–	20 (25)	4.2	112.4	34.4	–	–
Allyl chloroformate	120.54	Hydrolyzes	–	Allyl alcohol, HCl	14 h, photooxidation; 23 h, reaction with ozone	20 (25)	4.2	110	31.1	–	–
n-Butyl chloroformate	136.58[c]	Poorly soluble (hydrolyzes)[d]	–	*n*-Butanol, HCl	–	5.3 (20)[d]	4.7[g]	142[e]	46.0	–	–
Isobutyl chloroformate	136.58[c]	Gradually decomposes[f]	–	Isobutanol, HCl	–	16.5 (20)[g]	4.7[g]	130[f]	39.4[f]	–	–
sec-Butyl chloroformate	136.58[c]	_	–	*sec*-Butanol, HCl	–	–	–	–	35.6	–	–
Benzyl chloroformate	170.60	Decomposes	–	Benzyl alcohol, HCl	–	7 (85-87)	1[h]	152	80	–	–

(Continued)

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TABLE 2-1 Continued

Chloroformate	Molecular Weight	Solubility in Water	Hydrolysis Half-time, min (°C)	Hydrolysis Products (with CO_2)	Estimated Atmospheric Half-time	Vapor Pressure, mm Hg (°C)	Vapor Density, g/L (air = 1)	Boiling Point, °C	Flash Point, °C	Flamability Limits[l]	
										Lower explosive limit	Upper explosive limit
Phenyl chloroformate	156.6[g]	Decomposes[g]	1.4 (19.6)[b]	Phenol, HCl	–	0.68 (20)[g]	5.41[g]	188-189[g]	69[g]	–	–
2-Ethylhexyl chloroformate	192.71[i]	Decomposes[i]	–	2-Ethyl-1-hexanol, HCl	–	1 (45)[i]	>1	208[c]	NA	–	–
Ethyl chlorothioformate	124.59	Decomposes[j]	4.3 (4.6)[k]	Ethyl mercaptan, HCl	–	8.3 (21)[j]	–	132[j]	51.7[j]	–	–

Additional chemical and physical data for individual chloroformates are presented in their respective sections.
[a]Source is HSDB (2003a,b, 2013, 2014a,b,c,d) except where noted.
[b]Calculated from empirical rate constants reported by Queen (1967).
[c]Kreutzberger (2001).
[d]BG Chemie (2005).
[e]Bohm and Beth-Hubner (2006).
[f]O'Neil et al. (2001a,b).
[g]IPCS (2005a,b,c).
[h]IPCS (2004).
[i]Chemical Book (2016).
[j]Stauffer Chemical Company (1983).
[k]Calculated from empirical rate constant reported by Queen et al. (1970).
[l]https://cameochemicals.noaa.gov.

other chloroformates were not found. Data on atmospheric hydrolysis, the effect of relative humidity on hydrolysis rates, and persistence in the atmosphere of chloroformates were not available. However, data obtained from a study for structurally-similar and hydrolytically active acetyl chlorides (e.g., chloroacetyl chloride, phosgene, and trichloroacetyl chloride) indicate that gas-phase hydrolysis in an atmosphere of 40% humidity is much less than in water (Butler and Snelson 1979). A comparison of the hydrolysis half-times, vapor pressures, boiling points, flash points, and flammability limits are presented in Table 2-1.

A comparison of the chemical structures are presented in Figure 2-1.

1.2. Production and Use

Chloroformates are produced by the reaction of phosgene with alcohols or phenols. The alkyl chloroformates of low molecular weight alcohols are prepared by reaction of anhydrous alcohols with a molar excess of chlorine-free phosgene at low temperature. Hydrogen chloride is evolved during the reaction and is collected in a tower with recovered excess phosgene (Kreutzberger 2001).
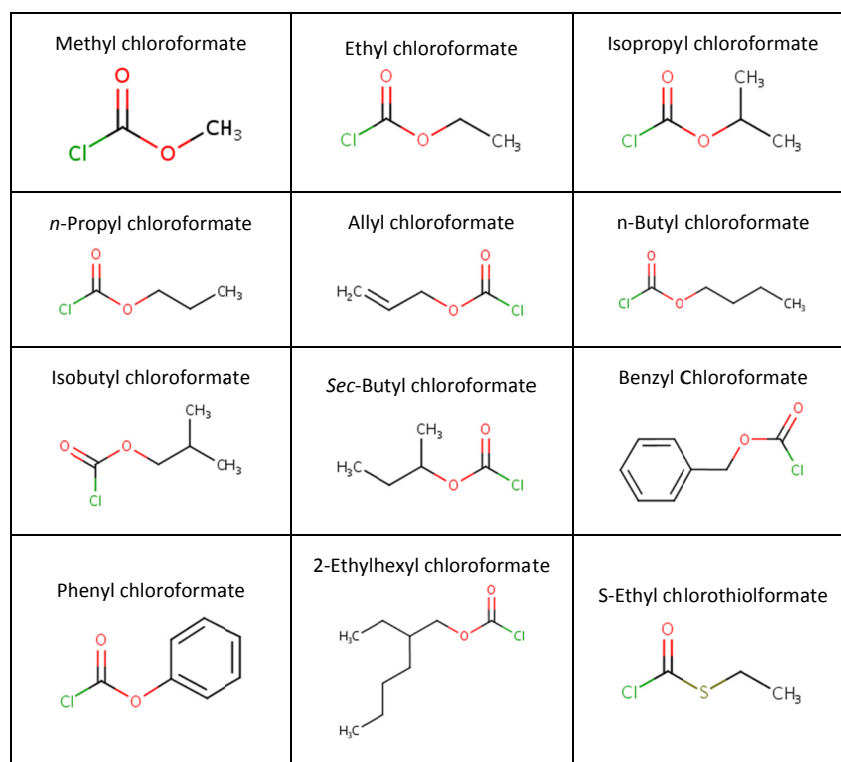

FIGURE 2-1 Structures. Source: ChemIDPlus 2012.

Chloroformates are used as intermediates in the synthesis of pesticides, herbicides, perfumes, pharmaceuticals, foods, polymers, and dyes. They are also used for conversion to peroxydicarbonates, which then serve as free radical initiators for polymerization of vinyl chloride, ethylene, and other unsaturated monomers (Kreutzberger 2001).

1.3. Absorption, Metabolism, Disposition, and Excretion

No specific information about the absorption, metabolism, disposition, and excretion of the chloroformates was found.

1.4. Mechanism of Toxicity

Chloroformates hydrolyze in water or moist air to produce a parent alcohol or mercaptan compound (used in the production of each chloroformate), hydrogen chloride, and carbon dioxide. Thus, exposures to chloroformates are most likely to a mixture of the parent compound and its hydrolysis products. Chloroformates are direct-acting contact irritants, and are corrosive to the eyes, skin, gastrointestinal tract, and the respiratory tract. Inhalation may result in coughing, labored breathing, sore throat, unconsciousness, convulsions, and death. Pulmonary edema frequently occurs, and its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion. Delayed pulmonary edema resulting in hospitalization and requiring treatment has occurred in people accidentally exposed to unknown concentrations of methyl chloroformate (Schuckmann 1972; Penkovitch and Anikin 1988) and ethyl chloroformate (Bowra 1981). According to AIHA (2006a), a fatality with pulmonary edema occurred after a worker was exposed to methyl chloroformate at an estimated concentration of 40,000 ppm. Ingestion of chloroformates may result in a burning sensation of the digestive tract, nausea, vomiting, and abdominal pain (Kreutzberger 2001).

Table 2-2 provides a comparison of 1-h and 4-h rat LC_{50} (lethal concentration, 50% lethality) values for the chloroformates and their hydrolysis products. A comparison of the toxicity data suggests that the toxicity of the chloroformates cannot be readily predicted from the toxicity of any particular hydrolysis product and supports the suggestion that the toxicity likely reflects exposure to a mixture of parent compound and hydrolysis products.

1.5. Concurrent-Exposure Issues

No information about exposure to chloroformates in conjunction with other chemicals that might be found concurrently in the workplace or the environment was found.

TABLE 2-2 Rat LC_{50} Values (ppm) for Selected Chloroformates and Their Hydrolysis Products

	1 h		4 h	
	Chloroformate[a]	Alcohol[b,c]	Chloroformate[a]	Alcohol[b,c]
Methyl chloroformate	88-123	>145,000	15-52	64,000
Ethyl chloroformate	145-200	–	–	–
Isopropyl chloroformate	300	–	–	29,600
n-Propyl chloroformate	410	–	–	–
Allyl chloroformate	65.1	1,060	–	165
n-Butyl chloroformate	200 (LC_{40})	–	–	8,000
Isobutyl chloroformate	–	–	–	8,000
sec-Butyl chloroformate	–	–	–	–
Benzyl chloroformate	–	–	85	16,800
Phenyl chloroformate	–	–	30	–
2-Ethylhexyl chloroformate	–	–	33.9	–
Ethyl chlorothioformate	–	–	45	2,770 (mercaptan)
Hydrogen chloride[b]	3,124		–	

[a]See sections on the individual chloroformates for the sources of the LC_{50} values.
[b]HSDB (2003a,b, 2013, 2014a,b,c,d) is source of the alcohol and hydrogen chloride LC_{50} values.
[c]Alcohol, phenol, or mercaptan hydrolysis product is shown in Table 2-1.

1.6. Species Sensitivity

No information about differences in the acute toxicity of the chloroformates between species was available. However, because the chloroformates are highly reactive in nature and are direct-acting irritants, little interspecies variability is expected. RD_{50} (concentration of a substance that reduces the respiratory rate by 50%) data on methyl, ethyl, propyl, isopropyl, isobutyl, *sec*-butyl, and phenyl chloroformate suggest that the mouse may be more sensitive than the rat. However, the difference could be an artifact of the stressful testing procedure used with the mice, which were restrained during the exposure period, and not indicative of increased sensitivity to chloroformates.

1.7. Temporal Extrapolation

The concentration-exposure time 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). Insufficient

data were available for deriving an empirical value for n for any of the twelve chloroformates. In the absence of chemical-specific data, a default value of n = 3 was used to extrapolate from longer to shorter durations, and a default value of n = 1 was used to extrapolate from shorter to longer durations, to provide AEGL values that are protective of human health (NRC 2001).

1.8. Data Quality

The literature search, study selection, and evidence integration follows the methods outlined in the AEGLs standing operating procedure (NRC 2001). Although the AEGLs standing operating procedure outlines methods to ensure consistency and transparency, they are not formal systematic review procedures. However, several studies on the chloroformates were conducted by Industrial Bio-Test Laboratories, Inc. (IBT). In 1976 FDA found significant deficiencies and discrepancies in reports and study procedures, which called into question the validity of IBT studies. This led to a number of investigations of IBT by government agencies, the closure of the firm and criminal convictions of some of IBT staff for fraud or falsifying data. In a post hoc audit program of IBT studies conducted by the U.S. Environmental Protection Agency and the Canadian Health and Welfare Department (EPA 1983), 618 of 867 non-acute toxicity studies (including subacute, sub-chronic, carcinogenicity, reproductive toxicity, genotoxicity, and neurotoxicity studies) were reported to be invalid (OECD 2007). Although the focus of this audit was on repeated-dose and long-term studies, in its Manual for Investigation of HPV Chemicals, the Organisation for Economic Co-operation and Development (OECD) reports that significant discrepancies and deficiencies in acute toxicity studies also were found (OECD 2007).

OECD (2007) outlined specific criteria for using data generated by IBT, and recommended rejecting a study when either a regulatory or internal audit revealed problems with respect to the reliability of the findings or when the findings of unaudited studies are inconsistent with data collected by reputable laboratories. OECD (2007) further recommended that unaudited studies should not be used as key studies, but instead be used with caution and considered only as weak evidence if supported by data from reputable laboratories. OECD (2007) also noted that if an IBT study is consistent with a well conducted and reliable study, the IBT results may be used to increase confidence in characterization of a substance's toxicity.

In reviewing IBT studies for this report, the general recommendations of OECD (2007) were followed. First and foremost, no IBT studies were used as the principal or key study in deriving AEGLs for any of the chloroformates. In cases where IBT study reports were available, they were reviewed (but not formally audited), and if the findings were consistent with other studies of reputable validity, the results of the IBT studies are included and referred to as providing supporting evidence.

1.9. Special Considerations

A summary of the AEGL values for the chloroformates reviewed in this document is presented in Table 2-3. AEGL-1 values were not derived for any chloroformate because of insufficient toxicity data. As discussed in Section 1.4 (Mechanism of Toxicity), exposures to the chloroformates are most likely to a mixture of the parent compound and its hydrolysis products. Therefore, using AEGL-values for hydrogen chloride as the basis for establishing AEGL values for the chloroformates was considered inappropriate. Furthermore, AEGL-1 values for hydrogen chloride (shown in Table 2-4) approach or exceed the AEGL-2 and AEGL-3 values for the chloroformates.

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for all chloroformates were calculated by taking a three-fold reduction in the AEGL-3 values. That approach is consistent with recommendations in the Standing Operating Procedures for Developing AEGLs for estimating a threshold for irreversible effects (NRC 2001). AEGL-3 values were based on lethality data on the individual chloroformates, although the toxicity data for chloroformates were sparse. Respiratory effects associated with direct-acting irritation and corrosion (nasal irritation, pulmonary inflammation, pulmonary edema, and emphysema and associated lethality) have been observed in humans and animals for several of the chloroformates. Interspecies and intraspecies uncertainty factors of 3 (for a total uncertainty factor of 10) were used for calculating the AEGL values for the chloroformates. Those values were chosen because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal of entry (respiratory tract). The AEGL values for *n*-propyl chloroformate were determined on the basis of structural similarity to isopropyl chloroformate, and the AEGL values for isobutyl chloroformate and *sec*-butyl chloroformate were determined on the basis of structural analogy to *n*-butyl chloroformate.

2. METHYL CHLOROFORMATE

2.1. Summary

Data on methy chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

No acute inhalation data appropriate for deriving AEGL-2 values for methyl chloroformate were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on methyl chloroformate provide evidence of a steep curve. In studies of rats exposed to methyl chloroformate for 4 h,

TABLE 2-3 AEGL Values for Selected Chloroformates[a]

Classification	10 min	30 min	1 h	4 h	8 h
Methyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)
AEGL-3 (lethal)	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)
Ethyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (8.8 mg/m^3)	1.6 ppm (7.0 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.88 mg/m^3)
AEGL-3 (lethal)	8.8 ppm (39 mg/m^3)	6.1 ppm (27 mg/m^3)	4.8 ppm (21 mg/m^3)	1.2 ppm (5.3 mg/m^3)	0.60 ppm (2.6 mg/m^3)
Isopropyl chloroformate and n-*propyl chloroformate*					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	3.7 ppm (19 mg/m^3)	3.7 ppm (19 mg/m^3)	3.0 ppm (15 mg/m^3)	1.9 ppm (9.5 mg/m^3)	1.3 ppm (6.5 mg/m^3)
AEGL-3 (lethal)	11 ppm (55 mg/m^3)	11 ppm (55 mg/m^3)	9.1 ppm (46 mg/m^3)	5.7 ppm (29 mg/m^3)	3.8 ppm (19 mg/m^3)
Allyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.3 ppm (6.4 mg/m^3)	0.87 ppm (4.3 mg/m^3)	0.70 ppm (3.4 mg/m^3)	0.18 ppm (0.88 mg/m^3)	0.09 ppm (0.44 mg/m^3)
AEGL-3 (lethal)	3.8 ppm (19 mg/m^3)	2.6 ppm (13 mg/m^3)	2.1 ppm (10 mg/m^3)	0.53 ppm (2.6 mg/m^3)	0.26 ppm (1.3 mg/m^3)
n-*Butyl chloroformate, isobutyl chloroformate, and* sec-*butyl chloroformate*					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)
AEGL-3 (lethal)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)

TABLE 2-3 Continued

Benzyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)
AEGL-3 (lethal)	3.7 ppm (26 mg/m^3)	3.7 ppm (26 mg/m^3)	2.9 ppm (20 mg/m^3)	1.9 ppm (13 mg/m^3)	0.93 ppm (6.5 mg/m^3)
Phenyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.06 ppm (0.38 mg/m^3)
AEGL-3 (lethal)	0.72 ppm (4.6 mg/m^3)	0.72 ppm (4.6 mg/m^3)	0.57 ppm (3.6 mg/m^3)	0.36 ppm (2.3 mg/m^3)	0.18 ppm (1.2 mg/m^3)
2-Ethylhexyl chloroformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)
AEGL-3 (lethal)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)
Ethyl chlorothioformate					
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.80 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)
AEGL-3 (lethal)	3.0 ppm (15 mg/m^3)	3.0 ppm (15 mg/m^3)	2.4 ppm (15 mg/m^3)	1.51 ppm (7.6 mg/m^3)	0.75 ppm (3.8 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.

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

TABLE 2-4 AEGL Values for Chloroformate Hydrolysis Products

Classification	10 min	30 min	1 h	4 h	8 h
Hydrogen chloride (NRC 2004)					
AEGL-1 (nondisabling)	1.8 ppm (2.7 mg/m^3)	1.8 ppm (2.7 mg/m^3)	1.8 ppm (2.7 mg/m^3)	1.8 ppm (2.7 mg/m^3)	1.8 ppm (2.7 mg/m^3)
AEGL-2 (disabling)	100 ppm (156 mg/m^3)	43 ppm (65 mg/m^3)	22 ppm (33 mg/m^3)	11 ppm (17 mg/m^3)	11 ppm (17 mg/m^3)
AEGL-3 (lethal)	620 ppm (937 mg/m^3)	210 ppm (313 mg/m^3)	100 ppm (155 mg/m^3)	26 ppm (38 mg/m^3)	26 ppm (39 mg/m^3)

Hoeschst (Hollander et al. 1986) reported an LC_{50} of 51-53 ppm, no mortality at 45 ppm, and 80% mortality at 57 ppm. In another study using rats, the 1-h LC_{50} was 100 ppm, and rats exposed at 26 ppm for 1 h were clinically normal and had no mortality (Fisher et al. 1981a).

Using lethality data from Hoechst (Hollander et al. 1986), a 4-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 42.4 ppm was calculated (see Appendix A) and used as the point-of-departure for deriving AEGL-3 values for methyl chloroformate. That concentration is considered a threshold for lethality and is supported by data that no deaths occurred in rats exposed to methyl chloroformate at 45 ppm for 4 h (Hollander et al. 1986). The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations in rats of nasal irritation and respiratory effects (e.g., pulmonary congestion, pulmonary edema, and increased pulmonary weights) in short-term repeated-exposure studies of methyl chloroformate (Gage 1970; Kenny et al. 1992; BASF 1993, 1999a). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (42.4 ppm). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on methyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (10 min, 30 min, and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. Time scaling from 4 h to 10 min is supported by a 1-h LC_{50} study (IBT 1975); utilizing the $BMCL_{05}$ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from the study by Hoechst (Hollander et al. 1986).

The AEGL values for methyl chloroformate are presented in Table 2-5.

TABLE 2-5 AEGL Values for Methyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)	One-third the AEGL-3 values
AEGL-3 (lethal)	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)	Estimated lethality threshold (4-h $BMCL_{05}$) in rats (Hollander et al. 1986)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

2.2. Chemical and Physical Properties

Methyl chloroformate hydrolyzes in water to form methanol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of methyl chloroformate are presented in Table 2-6.

2.3. Human Toxicity Data

2.3.1. Acute Lethality

No data on human deaths from exposure to methyl chloroformate were found.

2.3.2. Nonlethal Toxicity

2.3.2.1. Case Reports

A healthy 41-year-old chemical production worker inhaled 2-3 breaths of an atmosphere containing methyl chloroformate in the vicinity of leaking equipment (Schuckmann 1972). The concentration of methyl chloroformate in the discharge was not reported. The worker left the contaminated area immediately because of a penetrating odor and coworkers' warnings. About an hour after exposure, he experienced slight ocular irritation and an irritating cough and reported to the medical facility at the factory. Auscultation of lungs was largely unremarkable; isolated respiratory sounds were found in the upper

TABLE 2-6 Chemical and Physical Properties of Methyl Chloroformate

Parameter	Value	Reference
Common name	Methyl chloroformate	HSDB 2014a
Synonyms	Carbonochloridic acid, methylethyl ester; chlorocarbonic acid, methylethyl ester; chloroformic acid methyl ester; formic acid, chloro-, methyl ester; methyl chlorocarbonate; K-stoff; methoxycarbonyl chloride; TL 438	HSDB 2014a
CAS registry no.	79-22-1	HSDB 2014a
Chemical formula	$C_2H_3ClO_2$	HSDB 2014a
Molecular weight	94.5	HSDB 2014a
Physical state	Colorless liquid	HSDB 2014a
Melting point	-81°C	HSDB 2014a
Boiling point	71.0°C	HSDB 2014a
Flash point	12.2°C	HSDB 2014a

Density
  Vapor
  Liquid
	
	3.26 g/L (air = 1)
	1.223 g/cm^3 (water = 1)
		HSDB 2014a

Solubility	Slightly soluble (hydrolyzes) in water; soluble in chloroform, benzene, alcohol, ether	HSDB 2014a
Vapor pressure	108.5 mm Hg at 25°C	HSDB 2014a
Hydrolysis half-life	20.5 min at 25°C	Queen 1967
Estimated atmospheric half-time	74 d at 5×10^5 OH, photooxidation	HSDB 2014a
Conversion factors in air	1 mg/m^3 = 0.26 ppm 1 ppm = 3.9 mg/m^3	–

lobes. The next day (about 24 h later), a follow-up examination was performed. The worker reported increasing cough since early morning and presented with abnormal respiratory sounds in the upper lung lobes during auscultation. A codeine preparation (Codipront) was prescribed and a follow-up examination was scheduled for the next day. However, the worker returned in the afternoon of the same day because of increasingly severe signs and symptoms as the day progressed, as evidenced by extensive abnormal sounds in the upper lung lobes, moderate dyspnea, and a temperature of 37.2°C. The worker was kept for observation overnight, with an oxygen supply, a bronchodilator (Brondilat), and 40 mg Urbason intravenously. During the night the symptoms receded and the worker slept well to the early morning hours. The cough resumed and auscultation showed slight dry rales in the right lower lung lobe. The worker was sent home after treatment with Omnicillin and Codipront. Examination performed the next day revealed no notable complaints. The following day,

however, the worker complained of a severely irritating cough and dyspnea; slight cyanosis of the lips was also observed. Auscultation of the lungs, revealing rales in all lung areas, confirmed the subjective findings. The worker was then admitted to the factory's medical facility and stayed there for about three days. Urbason, Brondilat, and Hostacyclin were administered during this time period. The symptoms started to recede, although a morning cough persisted, and drug treatment was discontinued.

In another report, a 46-year-old male worker was exposed to methyl chloroformate while repairing a methyl chloroformate pipeline (Penkovitch and Anikin 1988). The liquid soaked his clothing and penetrated to the skin; he reported itching and burning. He was wearing a gas mask during the accident; thus, no inhalation exposure occurred until he removed the gas mask in the shower room. He then reported a sharp, choking smell and developed burning of the eyes, tearing, sore throat, and a cough while showering for 3-5 min. Methyl chloroformate concentrations were not reported. He returned to his home and reported no abnormal symptoms for 4-5 h. He then developed a sore, burning throat, chills, asthma, and productive cough. The asthma and cough progressed, and he was admitted to a hospital 22 h after the accident. He presented with pulmonary edema which resolved within 24 h after treatment with Prednisolone and Lasix.

AIHA (2006a) described a report of individual injuries and a fatality in workers exposed to methyl chloroformates; the primary reports (Hey and Thiess1968 and Thiess and Hey 1968) were in German and were not translated. AIHA (2006a) indicated that the nonfatal symptoms consisted of ocular irritation, laryngitis, and dry, racking cough, all of which resolved within 1-2 h. In the fatal case, severe pulmonary edema and death ensued after exposure to a concentration estimated by the study authors to be about 40,000 ppm (AIHA 2006a).

2.3.3. Developmental and Reproductive Toxicity

No developmental or reproductive studies of acute human exposure to methyl chloroformate were available.

2.3.4. Genotoxicity

No genotoxic studies of acute human exposure to methyl chloroformate were available.

2.3.5. Carcinogenicity

No carcinogenicity studies of human exposure to methyl chloroformate were available.

2.3.6. Summary

Case reports of methyl chloroformate toxicity are available; however, details of exposure concentration and duration were not available. Signs of exposure included ocular and upper respiratory irritation followed by a latent period which ultimately led to pulmonary edema. For the workers in these reports, the latency periods were 36 h (Schuckmann 1972) and 22 h (Penkovitch and Anikin 1988). No human data on lethality, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity on methyl chloroformate were found.

2.4. Animal Toxicity Data

2.4.1. Acute Lethality

2.4.1.1. Rats

Groups of five male and five female Charles River albino rats were exposed to methyl chloroformate vapor at 0, 145, 173, 233, or 274 ppm (nominal concentrations) for 1 h, followed by a 14-day observation period (IBT 1975). Vapor was generated by bubbling clean, dry air through undiluted methyl chloroformate in a gas washing bottle. The resulting air-vapor mixture was then introduced into the exposure chamber. The 1-h LC_{50} was determined to be 163 ppm, and the calculated $BMCL_{05}$ is 74 ppm. Male rats appeared to be more sensitive than females. Hypoactivity, ptosis, ruffed fur, enophthalmus, and dyspnea were observed in all rats during exposure. Evidence of acute bronchiolitis followed by fibrosis of the pulmonary parenchyma was observed in animals killed on day 14 post-exposure and in rats that died during the experiment. Data from this study are summarized in Table 2-7.

TABLE 2-7 Mortality in Charles River Albino Rats Exposed to Methyl Chloroformate for 1 Hour

Concentration, ppm	Males	Females	Males and Females
0	0/5	0/5	0/10
145	4/5	0/5	4/10
173	5/5	2/5	7/10
233	5/5	4/5	9/10
274	5/5	1/5	6/10
$BMCL_{05}$	–	–	74 ppm
LC_{50}	–	–	163 ppm

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Adapted from IBT 1975.

In another study, groups of 10 male Sprague Dawley rats were exposed to methyl chloroformate at 735, 2,947, 9610, or 66,235 ppm (nominal concentrations) for 1 h (WARF Institute, Inc. 1972). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air flow was used. Methyl chloroformate was administered into the incoming air stream just before it entered the chamber port, and exposure concentrations were calculated by dividing the total amount sprayed into the chamber by the total cubic feet of air circulated through the chamber. All animals died within 18 h of exposure (see Table 2-8).

Groups of five male and five female Fischer 344 rats (main group) were exposed to methyl chloroformate vapor at 0, 26, 110, 133, 159, or 192 ppm for 1 h in a 3-ft wide Hinner-style chamber (Fisher et al. 1981a). Chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. In addition 10, 10, and 20 rats/sex (satellite rats) were exposed concurrently to methyl chloroformate at 26, 110, or 133 ppm, respectively. One male and one female satellite rat in each exposure group and two male and two female rats in the three lower-exposure groups were killed 4 h, 24 h, 9 days, or 10 days after exposure. All other surviving animals were killed 14 days after exposure. The LC_{50} values were 100 ppm for females and 92-123 ppm for males at 14-days post-exposure. Respiratory distress occurred in all main group rats exposed at 110, 133, 159, and 192 ppm during the first 24 h after exposure. Respiratory distress resolved within 24 h in the 110-ppm group; however, the effect persisted through day 14 in the other exposure groups and was accompanied by lethargy, weakness, and inactivity. Concentration-related red or clear ocular and nasal discharge and gross pulmonary lesions were observed in rats exposed at 110, 133, 159, and 192 ppm. Controls and rats in the 26-ppm group were clinically normal. Rats in the satellite group responded similarly to corresponding rats in the main group. In the main study group, decreased mean body weight and body weight gain were observed in the 110-, 133-, 159-, and 192-ppm rats and correlated with poor clinical status prior to death or study termination. No effect on body weight was observed in rats exposed at 26 ppm. Lesions found in satellite rats exposed at 110 and 133 ppm were comparable at all three sacrifice times and included severe degeneration, necrosis, erosion, and ulceration of the nasal turbinates and tracheal mucosal epithelia; alveolar hemorrhage; and erosion of bronchial and bronchiolar epithelia. Effects were similar. By day 9 or 10, the nasal turbinate effects had resolved, but regeneration was incomplete and purulent rhinitis persisted. Other respiratory tract and pulmonary lesions seen at 4 and 24 h resolved after 9 or 10 days. Pulmonary edema was observed in some rats in the 110-, 133-, 159-, and 192-ppm groups. No pulmonary edema was observed in controls or in the group exposed at 26 ppm.

Vernot et al. (1977) reported a 1-h LC_{50} of 88 ppm (64-123 ppm) for male and 103 ppm (90-118 ppm) for female Sprague-Dawley rats. Experiments were performed in bell jars using groups of five rats per concentration; concentrations were determined analytically. No further experimental details were available.

TABLE 2-8 Mortality in Sprague-Dawley Rats Exposed to Methyl Chloroformate for 1 Hour

Concentration, ppm	Results
735	10/10 dead after 20 min of exposure
2,947	9/10 dead at end of 1-h exposure; 1/10 dead 2-min post-exposure
9,610	5/10 dead at end of 1-h exposure; 5/10 dead 10-min post-exposure
66,235	All 10 animals survived
	7/10 dead 3-h post-exposure; 3/10 dead within 18-h post-exposure

Source: Adapted from WARF Institute, Inc. 1972.

Groups of five male and five female SPF Wistar rats were exposed to methyl chloroformate at 35, 45, 57, or 73 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (Hollander et al. 1986). The whole body exposures were performed in a 2.25-m^3 exposure chamber operated under dynamic flow conditions. Methyl chloroformate concentrations were measured every 15 min during exposure using a single beam photometer, and were measured analytically every 120 min using gas chromatography. Clinical signs observed in all treatment groups in a concentration-related manner included palpebral fissure narrowed or closed; increased grooming; squatting posture; accelerated, irregular, and jerky respiration; gasping; drowsiness; staggering movements; wimpering and crackling breathing sounds; sneezing; and piloerection. Body weight gain was reduced in both sexes after exposure, but animals surviving to study termination regained initial body weight. There were no gross treatment-related effects at necropsy in animals surviving to study termination. Gross examination of animals that died during the study showed dark red to black lungs, foamy liquid in the lungs, red aqueous liquid in the thoracic cavity, and distended gastrointestinal tracts. Histopathologic examination showed increased permeability in the alveolar septa and corresponding damage to bronchial epithelium; this effect was found in all treatment groups. Four-hour LC_{50} values of 51 ppm and 53 ppm were calculated for males and females, respectively. A combined male and female $BMCL_{05}$ of 42.4 ppm and combined male and female BMC_{01} of 47.8 ppm were calculated. Mortality data are summarized in Table 2-9.

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to methyl chloroformate at nominal concentrations of 16, 65, 96, or 127 ppm (analytic concentrations were 1.5, 13.7, 33.6, and 31.0 ppm, respectively) for 4 h, followed by a 14-day observation period (BASF 1980a). Whole body exposures were conducted in a 200-L glass-steel inhalation chamber. Analytic concentrations were measured by gas chromatography. Clinical signs in the 65-, 96-, and 127-ppm groups included dyspnea, gasping, blistering in front of noses, red ocular and nasal discharge and encrustations, ruffled and sticky fur, staggering, distended abdomen, poor general state, attempts to escape, impaired coordination, salivation, and squatting posture. Animals in the 16-ppm group exhibited jerky respiration and

eyelid closure. Body weight gain was initially decreased in the three highest concentration groups; this effect resolved in surviving animals by day 14 post-exposure. Four hour LC_{50} values of 13 ppm and 18 ppm were calculated for males and females, respectively. A combined male and female LC_{50} value of 15 ppm was also calculated. Data from this study are summarized in Table 2-10. The LC_{50} values calculated from this study are 3-4 times lower than those found in the Hoechst (Hollander et al. 1986) study and are inconsistent with other data (see Table 2-12).

Death occurred in 12/12 rats exposed to methyl chloroformate vapor (20°C) at 37,500 ppm for 3 min (BASF 1981a). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, and gasping. Pulmonary emphysema with petechial hemorrhages and dilation on the right side of the heart were observed at necropsy.

TABLE 2-9 Mortality in SPF Wistar Rats Exposed to Methyl Chloroformate for 4 Hours

Concentration, ppm	Males	Females	Males and Females
35	0/5	0/5	0/10
45	0/5	0/5	0/10
57	5/5	3/5	8/10
73	5/5	5/5	10/10
LC_{50}	51 ppm	53 ppm	–
$BMCL_{05}$	–	–	42.4 ppm
BMC_{01}	–	–	47.8 ppm

Abbreviations: BMC_{05}, benchmark concentration, 1% response; $BMCL_{01}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Hollander et al. 1986.

TABLE 2-10 Mortality in Sprague-Dawley Rats Exposed to Methyl Chloroformate for 4 Hours

Nominal Concentration, ppm	Analytic Concentration, ppm	Males	Females	Males and Females
16	1.5	0/10	0/10	0/20
65	13.7	5/10	3/10	8/20
96	33.6	10/10	7/10	17/20
127	31.0	10/10	10/10	20/20
LC_{50}	–	13 ppm	18 ppm	15 ppm

Abbreviations: LC_{50}, lethal concentration, 50% lethality.
Source: Adapted from BASF 1980a.

Death occurred in 11/12, 5/6, and 6/6 rats exposed to an "atmosphere enriched or saturated" with methyl chloroformate vapor (20°C) for 3, 10, and 30 min, respectively (BASF 1978). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, corneal opacity, dyspnea, and convulsions. Pulmonary edema and emphysema and bilateral dilation of the heart were found at necropsy.

Death occurred in 10/10 rats exposed to an "atmosphere enriched or saturated" with methyl chloroformate vapor (20°C) for 3 min (Hollander and Weigand 1985). Clinical signs included jerky respiration, extreme excitation, and severe corneal opacity. Pleural hemorrhages were found at necropsy.

The following oral LD_{50} values for methyl chloroformate were reported: 190 mg/kg for male Sprague-Dawley rats (Vernot et al. 1977); 110 mg/kg for female Sprague-Dawley rats (Vernot et al. 1977); 313 mg/kg for male and female Sprague-Dawley rats (BASF 1981b); and 220 mg/kg (WARF Institute Inc. 1972). A dermal LD_{50} value of 894 mg/kg was reported for male and female Sprague-Dawley rats (BASF 1981c). In another study, a dermal LD_{50} of more than 2 mL/kg was reported for male rats (WARF Institute, Inc. 1972).

A 4-week repeated exposure study (BASF 1993) described both lethal and nonlethal effects in rats (see Section 2.3.2 [Repeated Exposure] for details of the study).

2.4.1.2. Mice

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to methyl chloroformate aerosol at nominal concentrations of 0, 16.5, 25, 35, 50, 75, or 125 ppm for 30 min (Carpenter 1982a). The mice were then removed and exposed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously during both the exposure and recovery periods. Undiluted methyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9-L stainless steel chamber which was continuously evacuated at a rate of 20 L/min. An RD_{50} (concentration that reduced the respiratory rate by 50%) of 52.4 ppm was calculated. Results of this study are summarized in Table 2-11.

Gurova et al. (1977) reported a 2-h LC_{50} of 47 ppm for mice. No other experimental details were available.

2.4.2. Repeated Exposure

In an inhalation range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to methyl chloroformate at 0, 1.9, 6.2, or 19.5 ppm for 6 h/day for 5 days (Kenny et al. 1992). No treatment-related effects were observed in the 1.9-ppm group. Clinical signs in the 6.2- and 19.5-ppm groups included blinking, licking the inside of the mouth, ruffled fur,

and sneezing. In the 19.5-ppm group, males sneezed and had noisy nasal breathing in between exposures. Decreased body weight was accompanied by decreased food and water consumption in rats exposed at 19.5 ppm. Rats were necropsied 3 days post-exposure. Lungs failed to collapse in 1/5 males and 3/5 females in the 6.2-ppm group and 5/5 females in the 19.5-ppm group. Petechial bleeding was found in the lungs of 1/5 males in the 6.2-ppm group and 5/5 males and 1/5 females in the 19.5-ppm group. Pulmonary weight was increased in all high-concentration females; organ weights were not examined in males because of experimental error during necropsy. Inflammatory and erosive mucous membrane lesions were found in the nose, larynx, and trachea, and bronchiolitis and pneumonia were observed in high-concentration rats. Focal epithelial hyperplasia of the nasal mucosa was found in the 6.2- and 19.5-ppm groups. Comparison of histologic findings in a satellite group examined immediately after 3 days of exposure suggested that regeneration and repair of epithelial lesions had occurred in animals examined 3 days post-exposure.

In a repeated-exposure study, groups of five male and five female Sprague-Dawley rats were exposed to methyl chloroformate at 0, 0.13, 0.38, 1.01, 3.1, or 8.8 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1993). Mortality was occurred in 2/5 male and 1/5 female rats at 8.8 ppm during the final week of exposure. Clinical signs, observed only at 8.8 ppm, included blinking, hunched posture, rapid breathing pattern, and noisy breathing. Decreased body weight gain and food consumption were also observed in the 8.8-ppm animal. Increased packed cell volume, increased hemoglobin concentration, increased red cell count, increased neutrophil count, increased total protein, decreased albumin, increased globulin, decreased albumin-to-globulin ratio, and increased cholesterol were observed at 8.8 ppm as well. In addition, uncollapsed lungs, pulmonary congestion, enlarged tracheobronchial and medistinal lymph nodes, and increased pulmonary weight were observed at necropsy in rats exposed at 8.8 ppm. Histopathologic lesions of the nasal turbinates were observed at 3.1 and 8.8 ppm, whereas lesions were observed in the larynx of animals exposed at 1.01, 3.1, and 8.8 ppm.

TABLE 2-11 Effects in Male Swiss-Webster Mice Exposed to Methyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rate, Control/Exposed	Decrease in Respiratory Rate, %	Mortality
16.5	265/230	13.2	–
25	250/180	26	–
35	285/190	33.3	–
50	270/140	46.3	1/4 (<6 h)
75	275/100	63.6	1/4 (<6 h)
125	250/50	80	4/4 (<5 h)
125	280/50	82.1	3/4 (<20 h)

Source: Carpenter 1982a.

Groups of 10 male and 10 female Wistar rats were exposed to methyl chloroformate at 0, 0.40, 2.15, 3.98, or 7.83 ppm for 6 h/day, 5 days/week for 3, 10, 20, or 65 exposures (90-day study with interim necropsies after 3, 14, and 28 study days; satellite groups also contained 10 rats/sex/concentration) (BASF 1999a). In addition clinical evaluations and complete necropsy, cell proliferation measurements were performed in four female rats per group. 5-Bromo-2′-deoxyuridine was administered to these females via subcutaneously implanted minipumps. Pumps remained in the animals for 8 h or 3 days for evaluation of cell proliferation in the nasal cavity and laryngeal epithelia. Four male rats in the 7.83-ppm group died; deaths occurred after 24, 32, 36, and 41 exposures. Clinical signs were observed only in high-concentration animals and included rubbing of snout, sneezing, nasal crusts and abnormal respiration in the animals that died, and general morbidity. Decreased body weight and body weight gain were noted in males in the 3.98- and 7.83-ppm groups killed after three exposures and at study termination. At necropsy, gross effects were observed only in the 7.83-ppm group and included red foci in the lungs. Animals in the high-concentration group, except for those killed after three exposures, had increased pulmonary weights. Concentration and duration-related histologic effects were restricted to the respiratory tract and occurred in 2.15-, 3.98-, and 7.83-ppm animals at all sacrifice times. Nasal and laryngeal squamous cell metaplasia was found at 2.15, 3.98, and 7.83 ppm. Focal epithelial hyperplasia and squamous cell metaplasia and hyperplasia of the trachea and lungs occurred at 3.98 and 7.83 ppm. No histopathologic effects were found in the 0.40-ppm group. Cell proliferation was increased at 2.15 ppm after 20 and 65 days, and at 3.98 and 7.83 ppm after 10, 20, and 65 days. The significant increases occurred in the respiratory and transitional cell epithelium of the nose and in the ciliated and squamous epithelium of the larynx. No cell proliferation was observed at 0.40 ppm.

Groups of four male and four female Alderly Park SPF rats were exposed to methyl chloroformate vapor in isopropanol at 1, 5, or 20 ppm for 6 h for 15 exposures (Gage 1970). The vapor concentrations were produced by injecting liquid at a known rate into a metered stream of air with a controlled fluid-feed atomizer. No effects were observed at 1 ppm. Nasal irritation and lethargy were observed at 5 ppm, and nasal irritation, respiratory difficulty, weight loss, lethargy, and poor condition were observed at 20 ppm. Distended lungs and pulmonary hemorrhage, and renal congestion were found at autopsy in the 20-ppm group. No further details were provided.

2.4.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding animal exposure to methyl chloroformate were not available.

2.4.4. Genotoxicity

Methyl chloroformate was negative in Ames bacterial reverse-mutation-assay tests with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence or absence of S9 mix (Hoechst 1977; Miltenburger 1985; BASF 1988a). Methyl chloroformate induced chromosome aberrations in Chinese hamster V79 cells in the presence of S9 mix; no increase in aberrations occurred in the absence of S9 mix (Miltenburger 1986).

2.4.5. Carcinogenicity

No carcinogenicity data on methyl chloroformate were found.

2.4.6. Summary

Animal toxicity data on methyl chloroformate include acute and repeated-exposure inhalation studies. Rat 1-h LC_{50} values were relatively consistent between studies as follows: 163 ppm for male and female Charles River rats (IBT1975); 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al. 1981a); and 88 ppm and 103 ppm for male and female Sprague Dawley rats, respectively (Vernot et al. 1977). Rat 4-h LC_{50} values were reported to be 51-53 ppm (Hollander et al. 1986) and 15 ppm (BASF 1980a); however, the 15-ppm value is an outlier when compared to other available data. Signs of toxicity included body weight loss, weakness and lethargy, respiratory distress, hematologic effects consistent with decreased oxygen availability (assumed secondary to pulmonary congestion and edema), and bronchiolitis, fibrosis, and pulmonary edema. A 30-min RD_{50} of 47.2 ppm (nominal concentration) was reported for male Swiss-Webster mice (Carpenter 1982a). Methyl chloroformate did not induce mutations in an Ames bacterial reverse mutation assay (Hoechst 1977; Miltenburger 1985; BASF 1988a) but did induce chromosomal aberrations in Chinese hamster V79 cells in the presence of S9 mix (Miltenburger 1986). No data concerning developmental or reproductive toxicity or carcinogenicity of methyl chloroformate were found in the literature. Animal data on methyl chloroformate are summarized in Table 2-12.

2.5. Data Analysis for AEGL-1

2.5.1. Human Data Relevant to AEGL-1

No human data on methyl chloroformate consistent with the definition of AEGL-1 were available.

TABLE 2-12 Summary of Inhalation Toxicity Studies of Methyl Chloroformate

Species	Concentration, ppm	Exposure Duration	Effect	Reference
Acute Exposure				
Rat	37,500	3 min	12/12 dead	BASF 1978
Rat	735 (nominal)	20 min	10/10 dead	WARF Institute, Inc. 1972
Rat	26	1 h	No effects	Fisher et al. 1981a
Rat	74 (nominal)	1 h	$BMCL_{05}$	IBT 1975
Rat-male	88	1 h	LC_{50}	Vernot et al. 1977
Rat-male	92-123	1 h	LC_{50}	Fisher et al. 1981a
Rat-female	100	1 h	LC_{50}	Fisher et al. 1981a
Rat-female	103	1 h	LC_{50}	Vernot et al. 1977
Rat	163 (nominal)	1 h	LC_{50}	IBT 1975
Rat	2,974 (nominal)	1 h	10/10 dead	WARF Institute, Inc. 1972
Rat	15	4 h	LC_{50}	BASF 1980a
Rat	42.4	4 h	$BMCL_{05}$	Hollander et al. 1986
Rat-male	51	4 h	LC_{50}	Hollander et al. 1986
Rat-female	53	4 h	LC_{50}	Hollander et al. 1986
Mouse	52.4	30 min	RD_{50}	Carpenter 1982a
Repeated Exposure				
Rat	0.40	6 h/d, 3 d	No effects	BASF 1999a
Rat	2.15	6 h/d, 3 d	Histopathology	BASF 1999a
Rat	3.98	6 h/d, 3 d	Histopathology, decreased body weight	BASF 1999a
Rat	7.83	6 h/d, 3 d	Clinical signs, histopathology, decreased body weight	BASF 1999a
Rat	1.9	6 h/d, 5 d	No effects	Kenny et al. 1992
Rat	6.2	6 h/d, 5 d	Clinical signs consistent with irritation, focal epithelia hyperplasia, petechial lung bleeding	Kenny et al. 1992

Rat	19.5	6 h/d, 5 d	Clinical signs consistent with irritation, focal epithelia hyperplasia, inflammatory and erosive mucous membrane changes, petechial lung bleeding, increased lung weight, pneumonia	Kenny et al. 1992
Rat	0.40	6 h/d, 5 d/wk, 2 wk	No effects	BASF 1999a
Rat	2.15	6 h/d, 5 d/wk, 2 wk	Histopathology	BASF 1999a
Rat	3.98	6 h/d, 5 d/wk, 2 wk	Histopathology, cell proliferation	BASF 1999a
Rat	7.83	6 h/d, 5 d/wk, 2 wk	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF 1999a
Rat	1	6 h, 15 exposures	No effects	Gage 1970
Rat	5	6 h, 15 exposures	Nasal irritation, lethargy	Gage 1970
Rat	20	6 h, 15 exposures	Nasal irritation, respiratory difficulty, lethargy, lung pathology, renal congestion	Gage 1970
Rat	0.13	6 h/d, 5 d/wk, 4 wk	No effects	BASF 1993
Rat	0.38	6 h/d, 5 d/wk, 4 wk	No effects	BASF 1993
Rat	0.40	6 h/d, 5 d/wk, 4 wk	No effects	BASF 1999a
Rat	1.01	6 h/d, 5 d/wk, 4 wk	Larynx lesions	BASF 1993
Rat	2.15	6 h/d, 5 d/wk, 4 wk	Histopathology, cell proliferation	BASF 1999a
Rat	3.1	6 h/d, 5 d/wk, 4 wk	Nasal turbinate histopathology, larynx lesions	BASF 1993
Rat	3.98	6 h/d, 5 d/wk, 4 wk	Histopathology, cell proliferation	BASF 1999a
Rat	7.83	6 h/d, 5 d/wk, 4 wk	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF 1999a
Rat	8.8	6 h/d, 5 d/wk, 4 wk	3/10 deaths in final week of exposure, clinical signs, decreased body weight, hematologic effects, pulmonary congestion, increased lung weight, nasal turbinate histopathology, larynx lesions	BASF 1993
Rat	0.40	6 h/d, 5 d/wk, 13 wk	No effects	BASF 1999a
Rat	2.15	6 h/d, 5 d/wk, 13 wk	Histopathology, cell proliferation	BASF 1999a

(Continued)

TABLE 2-12 Continued

Species	Concentration, ppm	Exposure Duration	Effect	Reference
Rat	3.98	6 h/d, 5 d/wk, 13 wk	Histopathology, cell proliferation, decreased body weight	BASF 1999a
Rat	7.83	6 h/d, 5 d/wk, 13 wk	4/10 deaths-males (after 24, 32, 36, or 41 exposures), clinical signs, histopathology, cell proliferation, increased lung weight, decreased body weight	BASF 1999a

Abbreviations: $BMCL_{01}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality; RD_{50}, concentration that reduces the respiratory rate by 50%.

2.5.2. Animal Data Relevant to AEGL-1

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

2.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for methyl chloroformate. Therefore, AEGL-1 values are not recommended.

2.6. Data Analysis for AEGL-2

2.6.1. Human Data Relevant to AEGL-2

Case reports of human poisonings with methyl chloroformate include descriptions of effects consistent with the definition of AEGL-2. However, because reliable concentration and exposure duration information were not available, the data are not appropriate for deriving AEGL-2 values.

2.6.2. Animal Data Relevant to AEGL-2

No acute animal data on methyl chloroformate consistent with the definition of AEGL-2 were available.

2.6.3. Derivation of AEGL-2 Values

No acute inhalation data appropriate for deriving AEGL-2 values for methyl chloroformate were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on methyl chloroformate provide evidence of such a curve. In studies of rats exposed to methyl chloroformate for 4 h, Hollander et al. (1986) reported an LC_{50} of 51-53 ppm, no mortality at 45 ppm, and 80% mortality at 57 ppm. In another study using rats, the 1-h LC_{50} was 100 ppm, and rats exposed at 26 ppm for 1 h were clinically normal and had no mortality (Fisher et al. 1981a). The AEGL-2 values for methyl chloroformate are presented in Table 2-13.

The AEGL-2 values are further supported by the results of repeated-exposure studies. No deaths occurred in rats repeatedly exposed to methyl chloroformate at 3.1 ppm and only histopathologic changes in the nasal turbinates and lesions of the larynx were found. Larynx lesions were the only finding in rats exposed at 1.01 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1993).

TABLE 2-13 AEGL-2 Values for Methyl Chloroformate

10 min	30 min	1 h	4 h	8 h
4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)

2.7. Data Analysis for AEGL-3

2.7.1. Human Data Relevant to AEGL-3

Human lethality data on methyl chloroformate were anecdotal and lacked reliable concentration and exposure duration information. Thus, those reports were not appropriate for establishing AEGL-3 values.

2.7.2. Animal Data Relevant to AEGL-3

Rat 1-h LC_{50} values for methyl chloroformate were: 163 ppm for male and female Charles River rats (IBT 1975); 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al. 1981a); and 88 ppm and 103 ppm for male and female Sprague Dawley rats, respectively (Vernot et al. 1977). Exposure of male and female Fischer-344 rats to methyl chloroformate at 26 ppm methyl chloroformate 1 h resulted in no deaths (Fisher et al. 1981a). Four-hour LC_{50} values of 51 ppm and 53 ppm were calculated for male and female Wistar rats, respectively; a combined male and female $BMCL_{05}$ value of 42.4 ppm and combined male and female BMC_{01} (benchmark concentration, 1% response) value of 47.8 ppm were also calculated (Hollander et al. 1986).

2.7.3. Derivation of AEGL-3 Values

The calculated 4-h $BMCL_{05}$ value of 42.4 ppm for methyl chloroformate in rats (Hollander et al. 1986) was the point-of-departure for AEGL-3 values. The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary congestion, pulmonary edema, and increased lung weights) in short-term repeated exposure rat studies of methyl chloroformate (Gage 1970; Kenny et al. 1992; BASF 1993, 1999a). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to

the estimated threshold for lethality (42.4 ppm). Time scaling was performed using the equation $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.1 (ten Berge et al. 1986). Data on methyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 min, 30 min, and 1 h) and n = 1 when extrapolating from shorter to longer durations (8 h) were used. Time scaling a 4-h point-of-departure to a 10-min AEGL-3 value is supported by a 1-h LC_{50} study (IBT 1975); a 10-min AEGL-3 value calculated on the basis of a $BMCL_{05}$ from the study would be 13 ppm, which supports the time-scaled value of 12 ppm calculated from the study by Hoechst (Hollander et al. 1986). The AEGL-3 values for methyl chloroformate are presented in Table 2-14; the calculations are presented in Appendix B.

The AEGL-3 values are further supported by the results of repeated-exposure studies. No deaths occurred in rats exposed to methyl chloroformate at 7.8 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1999a), and no deaths occurred until week 4 in rats exposed at 8.8 ppm for 6 h/day, 5 days/week for 4 weeks) (BASF 1993).

2.8. Summary of AEGLs

2.8.1. AEGL Values and Toxicity End Points

The AEGL values for methyl chloroformate are presented in Table 2-15. Data were insufficient for deriving AEGL-1 values. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on an estimated 4-h lethality threshold in rats. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

2.8.2. Other Standards and Guidelines

The American Industrial Hygiene Association (AIHA) has developed emergency response planning guidelines (ERPGs) for methyl chloroformate (see Table 2-16). The ERPGs are very similar to the corresponding 1-h AEGL values. No other exposure standards or guidelines exposure have been established for methyl chloroformate.

TABLE 2-14 AEGL-3 Values for Methyl Chloroformate

10 min	30 min	1 h	4 h	8 h
12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)

TABLE 2-15 AEGL Values for Methyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)
AEGL-3 (lethal)	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-16 Standards and Guidelines for Methyl Chloroformate

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)
AEGL-3	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)
EPRG-1 (AIHA)[b]	–	–	NA[c]	–	–
EPRG-2 (AIHA)[b]	–	–	2 ppm (7.8 mg/m^3)	–	–
EPRG-3 (AIHA)[b]	–	–	5 ppm (19.5 mg/m^3)	–	–

[a]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.
[b]ERPG-1 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2006a, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor.
EPRG-2 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2006a, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
EPRG-3 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013) is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.
[c]NA, not appropriate. Classified by AIHA as not appropriate because the odor threshold is above the EPRG-2 level.

2.8.3. Data Adequacy and Research Needs

The only human data on methyl chloroformate are from anecdotal reports. Animal data include acute and repeated-exposure rat inhalation studies and a mouse RD_{50} study. Support provided by the repeated-exposure studies adds to confidence in the AEGL values.

3. ETHYL CHLOROFORMATE

3.1. Summary

Data on ethyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

No acute inhalation data appropriate for deriving AEGL-2 values for ethyl chloroformate were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on ethyl chloroformate provide evidence of a steep curve. Fisher et al. (1981b) report a 1-h rat LC_{50} of 189-200 ppm, and that rats exposed at 47 ppm for 1 h were clinically normal and had no mortality.

For AEGL-3 values, an estimate of the threshold for lethality was used as the point-of-departure. The threshold was estimated by taking one-third of the most conservative 1-h LC_{50} value (145 ppm $\div$ 3 = 48 ppm) in rats (Vernot et al. 1977). That concentration is also supported by the study by Fisher et al. (1981b), which reported no deaths in rats exposed to ethyl chloroformate 47 ppm for 1 h. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations in rats of respiratory effects (e.g., pulmonary congestion, pulmonary edema, and emphysema) in lethality studies of ethyl chloroformate (BASF 1970a,b; Gage 1970; WARF Institute, Inc. 1978; Fisher et al. 1981b). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (48 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate. The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on ethyl chloroformate were insufficient for calculating

an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 and 30 min) and n = 1 when extrapolating from shorter to longer durations (4 and 8 h) were used.

The AEGL values for ethyl chloroformate are presented in Table 2-17.

3.2. Chemical and Physical Properties

Ethyl chloroformate hydrolyzes in water to form ethanol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of ethyl chloroformate are presented in Table 2-18.

3.3. Human Toxicity Data

3.3.1. Acute Lethality

Information concerning death in humans after inhalation exposure to ethyl chloroformate was not available.

3.3.2. Nonlethal Toxicity

3.3.2.1. Case Report

A chemical operator employed in the manufacture of polyvinyl chloride was splashed with an undetermined amount of ethyl chloroformate when a plastic hose blew off a pump that was dispensing ethyl chloroformate (Bowra 1981). The worker was wearing a polyvinyl chloride apron, safety shoes, long gloves, and a full-face fresh-air mask, which helped to restrict exposure to ethyl chloroformate to an area on his right thigh. He showered in a domestic shower, and developed ocular irritation and cough, presumably because the warmth and humidity of the shower room produced ethyl chloroformate fumes from his discarded clothing. Symptoms subsided until 3.5 h after the incident when he began to experience chest tightness and difficulty breathing. He was slightly cyanotic, had audible crepitations at the base of his right lung, and had a reddened area on the right thigh. He was hospitalized and subsequently developed pulmonary edema. He received medical treatment and his symptoms resolved over the next few days, with no long-term effects.

3.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies of acute human exposure to ethyl chloroformate were not available.

TABLE 2-17 AEGL Values for Ethyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	2.9 ppm (13 mg/m³)	2.0 ppm (8.8 mg/m³)	1.6 ppm (7.0 mg/m³)	0.40 ppm (1.8 mg/m³)	0.20 ppm (0.88 mg/m³)	One-third the AEGL-3 values
AEGL-3 (lethal)	8.8 ppm (39 mg/m³)	6.1 ppm (27 mg/m³)	4.8 ppm (21 mg/m³)	1.2 ppm (5.3 mg/m³)	0.60 ppm (2.6 mg/m³)	Estimated lethality threshold in the rat after a 1-h exposure (Vernot et al. 1977)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

TABLE 2-18 Chemical and Physical Properties of Ethyl Chloroformate

Parameter	Value	Reference
Common name	Ethyl chloroformate	HSDB 2003a
Synonyms	Ethyl chlorocarbonate	HSDB 2003a
CAS registry no.	541-41-3	HSDB 2003a
Chemical formula	$C_3H_5ClO_2$	HSDB 2003a
Molecular weight	108.5	HSDB 2003a
Physical state	Water-white liquid	HSDB 2003a
Melting point	-80.6°C	HSDB 2003a
Boiling point	95°C	HSDB 2003a
Flash point	27.8°C	HSDB 2003a
Vapor density	3.7 g/L (air = 1)	HSDB 2003a
Density/specific gravity	1.403 g/cm³	HSDB 2003a
Solubility	Gradually decomposes in water	HSDB 2003a
Vapor pressure	22.4 mm Hg at 25°C	HSDB 2003a
Hydrolysis half-life	33.0 min at 25°C	Queen 1967
Estimated atmospheric half-time	11 d, photooxidation	HSDB 2003a
Conversion factors in air	1 mg/m³ = 0.23 ppm 1 ppm = 4.4 mg/m³	–

3.3.4. Genotoxicity

Genotoxicity studies of acute human exposure to ethyl chloroformate were not available.

3.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to ethyl chloroformate were not available.

3.3.6. Summary

Information on human exposure to ethyl chloroformate is available from a single occupational case report. The report suggests that ethyl chloroformate is a respiratory-tract irritant and is capable of inducing delayed pulmonary edema, but no exposure concentration or duration information was available. No humans studies of the developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of ethyl chloroformate were available.

3.4. Animal Toxicity Data

3.4.1. Acute Lethality

3.4.1.1. Rats

Groups of 10 male Sprague Dawley rats were exposed to ethyl chloroformate at 365 or 730 ppm (nominal concentrations) for 1 h (WARF Institute, Inc. 1978). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air flow was used. Ethyl chloroformate was administered into the incoming air stream just before it entered the chamber port, and exposure concentrations were calculated by dividing the total amount sprayed into the chamber by the total cubic feet of air circulated through the chamber. Within 1 min, and throughout the 1-h exposure period, animals in both groups had closed eyes and were gasping. Animals in the 730-ppm group fell into a semi-conscious state after 10 min of exposure, and all were dead 1-2 h after exposure. All animals in the 365-ppm group died within 24 h after exposure. Hemorrhage in all lung lobes and in the trachea were found at gross necropsy.

Groups of five male and five female Fischer-344 rats were exposed to ethyl chloroformate vapor at 0, 47, 153, 180, 245, or 270 ppm for 1 h in a 3-foot wide Hinner-style chamber, followed by a 14-day observation period (Fisher et al. 1981b). Chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. The LC_{50} values were 189 ppm (164-216 ppm) for male rats and 200 ppm (173-232 ppm) for female rats after 14-days post-exposure.

Controls and rats in the 47-ppm group were clinically normal and had no treatment-related effects at necropsy. Body weight gain was decreased in surviving males and females in the 153- and 180-ppm groups at day 7 and at termination. All rats in the 245- and 270-ppm groups died before the scheduled sacrifice. Average relative lung weight of animals in the 245- and 270-ppm groups was approximately 3-times greater than that of controls, and corroborating lesions indicative of acute alveolar hemorrhage were observed. Relative lung weight was also increased (magnitude not specified) in the 153- and 180-ppm groups. Red lung coloration was observed in one male and one female in the 153-ppm group, and two females and one male in the 180-ppm group.

Vernot et al. (1977) reported 1-h LC_{50}s of 145 ppm (140-150 ppm) for male and 170 ppm (150-180) ppm for female Sprague-Dawley rats. Experiments were performed in bell jars using groups of five rats per concentrations; concentrations were determined analytically. No further experimental details were available.

Death occurred in 9/10 rats exposed to ethyl chloroformate at 200 ppm for 1 h (BASF 1970a). Clinical signs included mucous membrane irritation and gasping. Pulmonary congestion and edema were found at necropsy.

Death occurred in 11/12 rats exposed to an "atmosphere enriched or saturated" with ethyl chloroformate vapor (20°C) for 3 min (BASF 1970b). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, and gasping. Pulmonary congestion, pulmonary edema, and emphysema were found at necropsy.

Groups of four male and four female Alderly Park SPF rats were exposed to ethyl chloroformate vapor in isopropanol for 6 h at 1 ppm (20 exposures), 5 ppm (20 exposures), or 20 ppm (10 exposures) (Gage 1970). The vapor concen-trations were produced by injecting liquid at a known rate into a metered stream of air with a controlled fluid-feed atomizer. No effects were observed at 1 ppm, decreased weight gain was observed at 5 ppm, and nasal irritation, respiratory difficulty, weight loss, and poor condition were observed at 20 ppm. Distended lungs and pulmonary hemorrhage were found at necropsy in the 20-ppm group. No further details were provided.

Several oral LD_{50} values have been reported, including 470 mg/kg (Vernot et al. 1977) and 411 mg/kg (WARF Institute, Inc. 1978) for male rats; 614 mg/kg for female Wistar rats (Hoechst 1975); and 244 mg/kg for an unspecified sex and strain of rat (BASF 1970c). Dermal LD_{50} values have been reported to be greater than 2 mL/kg for male rats (WARF Institute, Inc. 1978) and 7,120 mg/kg for New Zealand white rabbits (Vernot et al. 1977).

3.4.1.2. Mice

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to ethyl chloroformate aerosol at concentrations of 0, 25, 50, 100, or 200 ppm for 30 min (Carpenter 1982b). The mice were then removed and exposed to fresh air for a 10-min recovery period,

and respiratory rates were monitored continuously during both the exposure and recovery periods. Undiluted ethyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9-L stainless steel chamber that was continuously evacuated at a rate of 20 L/min. An RD_{50} (concentration that reduced the respiratory rate by 50%) of 77.5 ± 5.4 ppm was calculated. Results of this study are summarized in Table 2-19.

3.4.2. Developmental and Reproductive Toxicity

Studies concerning the developmental and reproductive toxicity of ethyl chloroformate were not found.

3.4.3. Genotoxicity

Ethyl chloroformate was negative in a preincubation test both with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (BASF 1988b).

3.4.4. Carcinogenicity

Groups of 50 male Sprague-Dawley rats were exposed to ethyl chloroformate by inhalation at concentrations of 1.5, 3.0, or 6.0 ppm for 6 h/day, 5 days/week for a total of 30 exposures (Sellakumar et al. 1987). No treatment-related effect on life span was observed. One animal in the 6.0-ppm group developed a squamous cell carcinoma of the nasal mucosa; the time to tumor appearance was 700 days. No nasal tumors were noted at 1.5 or 3.0 ppm. Ethyl chloroformate has not been assessed for carcinogenicity by the International Agency for Research on Cancer (IARC) or the National Toxicology Program (NTP).

TABLE 2-19 Effects in Male Mice Exposed to Ethyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
25	285/255	11	0/4
50	280/235	52	0/4
100	260/120	54	3/4
200	215/55	74	4/4

Source: Adapted from Carpenter 1982b.

Van Duuren et al. (1987) investigated the carcinogenicity of ethyl chloroformate in female ICR/Ha Swiss mice by dermal and subcutaneous administration. Groups of 30-50 mice were treated dermally with 3.0, 4.3, or 5.5 mg of ethyl chloroformate in acetone three times per week for 18-22 months. Tumor incidence was 0/50, 1/30, and 0/50, for the 3.0-, 4.3-, and 5.5-mg groups, respectively. In a dermal initiation-promotion assay, mice were administered a single 5.5 mg dose of ethyl chloroformate, followed 2 weeks later by thrice weekly applications of phorbol mysterate acetate (as a promoter) for 18-22 months. Tumors were found in 6/50 animals (four papillomas, two squamous cell carcinomas), suggesting that ethyl chloroformate may be a tumor promoter. In another study, mice were injected in the left flank once weekly with 0.3 or 1.1 mg of ethyl chloroformate in 0.1 mL of tricaprylin for 18-22 months. Tumor incidence was 1/50 in the 0.3-mg group (squamous cell carcinoma) and 0/50 in the 1.1-mg group.

3.4.5. Summary

Animal toxicity data for ethyl chloroformate are sparse. One-hour LC_{50} values were relatively consistent between studies as follows: 189 ppm and 200 ppm for male and female Fischer-344 rats, respectively (Fisher et al. 1981b) and 145 ppm and 170 ppm for male and female Sprague Dawley rats, respectively (Vernot et al. 1977). Signs of toxicity included decreased body weight gain, respiratory distress, increased lung weight, and pulmonary edema. A 30-min RD_{50} of 77.5 ppm (nominal concentration) was reported for male Swiss-Webster mice (Carpenter 1982b). No data on the developmental or reproductive toxicity of ethyl chloroformate were available. Ethyl chloroformate was negative in the Ames assay. Carcinogenicity data suggest that ethyl chloroformate may be a tumor promoter by the dermal route (Van Duuren et al. 1987). Animal data on ethyl chloroformate are summarized in Table 2-20.

3.5. Data Analysis for AEGL-1

3.5.1. Human Data Relevant to AEGL-1

No human data on ethyl chloroformate consistent with the definition of AEGL-1 were available.

3.5.2. Animal Data Relevant to AEGL-1

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

TABLE 2-20 Summary of Acute Inhalation Toxicity Studies of
Ethyl Chloroformate

Species	Concentration, ppm	Exposure Duration	Effect	Reference
Rat	47	1 h	No effects	Fisher et al. 1981b
Rat-male	145	1 h	LC_{50}	Vernot et al. 1977
Rat-female	170	1 h	LC_{50}	Vernot et al. 1977
Rat-male	189	1 h	LC_{50}	Fisher et al. 1981b
Rat-female	200	1 h	LC_{50}	Fisher et al. 1981b
Rat	245	1 h	10/10 dead	Fisher et al. 1981b
Rat	270	1 h	10/10 dead	Fisher et al. 1981b
Rat	365 (nominal)	1 h	10/10 dead	WARF Institute, Inc. 1978
Rat	730 (nominal)	1 h	10/10 dead	WARF Institute, Inc. 1978
Mouse	77.5 (nominal)	30 min	RD_{50}	Carpenter 1982b

Abbreviations: LC_{50}, lethal concentration, 50% lethality; RD_{50}, concentration that reduces
respiratory rate by 50%.

3.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for ethyl chloroformate,
so no values are recommended.

3.6. Data Analysis for AEGL-2

3.6.1. Human Data Relevant to AEGL-2

No appropriate human data on ethyl chloroformate consistent with the
definition of AEGL-2 were available.

3.6.2. Animal Data Relevant to AEGL-2

No animal data on ethyl chloroformate consistent with the definition of
AEGL-2 were available.

3.6.3. Derivation of AEGL-2 Values

No acute inhalation data appropriate for deriving AEGL-2 values for ethyl
chloroformate were available. Thus, the AEGL-2 values were calculated by tak-
ing one-third of the AEGL-3 values. That approached is used to estimate a
threshold for irreversible effects if a chemical has a steep concentration-response
curve (NRC 2001). Lethality data on ethyl chloroformate provide evidence of a
steep curve. Fisher et al. (1981b) report a 1-h rat LC_{50} of 189-200 ppm, and that

rats exposed at 47 ppm for 1 h were clinically normal and had no mortality. The AEGL-2 values for ethyl chloroformate are presented in Table 2-21.

3.7. Data Analysis for AEGL-3

3.7.1. Human Data Relevant to AEGL-3

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

3.7.2. Animal Data Relevant to AEGL-3

Rat 1-hour LC_{50} values for ethyl chloroformate were: 189 ppm and 200 ppm for male and female Fischer-344 rats, respectively (Fisher et al. 1981b), and 145 ppm and 170 ppm for male and female Sprague Dawley rats, respectively (Vernot et al. 1977). Exposure of male and female Fischer-344 rats to ethyl chloroformate at 47 ppm for 1 h resulted in no deaths (Fisher et al. 1981b).

3.7.3. Derivation of AEGL-3 Values

One-third of the most conservative 1-h LC_{50} value in rats (145 ppm ÷ 3 = 48 ppm) (Vernot et al., 1977) will be used as the point-of-departure for ethyl chloroformate AEGL-3 values. That concentration is considered a threshold for lethality and is supported by the study by Fisher et al. (1981b) that reported no deaths in rats exposed to ethyl chloroformate at 47 ppm for 1 h.

The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations in rats of respiratory effects (e.g., pulmonary congestion, pulmonary edema, and emphysema) in lethality studies of ethyl chloroformate (BASF 1970a,b; Gage 1970; WARF Institute, Inc. 1978; Fisher et al. 1981b). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic

TABLE 2-21 AEGL-2 Values for Ethyl Chloroformate

10 min	30 min	1 h	4 h	8 h
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm
(13 mg/m^3)	(8.8 mg/m^3)	(7.0 mg/m^3)	(1.8 mg/m^3)	(0.88 mg/m^3)

variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (48 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on ethyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 and 30 min) and n = 1 when extrapolating from shorter to longer durations (4 and 8 h) were used. The AEGL-3 values for ethyl chloroformate are presented in Table 2-22; the calculations are presented in Appendix B.

3.8. Summary of AEGLs

3.8.1. AEGL Values and Toxicity End Points

The AEGL values for ethyl chloroformate are presented in Table 2-23. Data were insufficient for deriving AEGL-1 values. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on an estimated 1-h lethality threshold in rats. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

3.8.2. Other Standards and Guidelines

The American Industrial Hygiene Association (AIHA) has developed emergency response planning guidelines (ERGPs) for ethyl chloroformate (see Table 2-24). The ERPG-2 and ERPG-3 values are slightly higher than the 1-h AEGL-2 and AEGL-3 values. In support of the ERPG-3 value, AIHA (2006b) cites the nonlethal concentrations of 47 ppm for 1 h and of 20 ppm for repeated 6-h exposures identified in the study by Gage (1970). The rationale for the ERPG-2 value cites data from a 20-day repeated-exposure study in rats that found only weight loss at 5 ppm (Gage 1970). AIHA notes that concentrations greater than 5 ppm could result in respiratory and ocular irritation sufficient to impair escape. No other exposure standards were found for ethyl chloroformate.

TABLE 2-22 AEGL-3 Values for Ethyl Chloroformate

10 min	30 min	1 h	4 h	8 h
8.8 ppm (39 mg/m^3)	6.1 ppm (27 mg/m^3)	4.8 ppm (21 mg/m^3)	1.2 ppm (5.3 mg/m^3)	0.60 ppm (2.6 mg/m^3)

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TABLE 2-23 AEGL Values for Ethyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	2.9 ppm (13 mg/m³)	2.0 ppm (8.8 mg/m³)	1.6 ppm (7.0 mg/m³)	0.40 ppm (1.8 mg/m³)	0.20 ppm (0.88 mg/m³)
AEGL-3 (lethal)	8.8 ppm (39 mg/m³)	6.1 ppm (27 mg/m³)	4.8 ppm (21 mg/m³)	1.2 ppm (5.3 mg/m³)	0.60 ppm (2.6 mg/m³)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-24 Standards and Guidelines for Ethyl Chloroformate

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	2.9 ppm (13 mg/m³)	2.0 ppm (8.8 mg/m³)	1.6 ppm (7.0 mg/m³)	0.40 ppm (1.8 mg/m³)	0.20 ppm (0.88 mg/m³)
AEGL-3	8.8 ppm (39 mg/m³)	6.1 ppm (27 mg/m³)	4.8 ppm (21 mg/m³)	1.2 ppm (5.3 mg/m³)	0.60 ppm (2.6 mg/m³)
EPRG-1 (AIHA)[b]	–	–	ID[c]	–	–
EPRG-2 (AIHA)[b]	–	–	5 ppm (22 mg/m³)	–	–
EPRG-3 (AIHA)[b]	–	–	10 ppm (44 mg/m³)	–	–

[a]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.
[b]ERPG-1 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2006b, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor.
EPRG-2 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2006b, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
EPRG-3 (emergency response planning guidelines) (AIHA 2006b, 2013) is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.
[c]ID: AIHA did not derive an EPRG-1 value because of insufficient data (lack of data on odor threshold and minor irritation).

3.8.3. Data Adequacy and Research Needs

Animal data on ethyl chloroformate include acute rat inhalation studies and a mouse RD_{50} study. The consistency results observed in the rat LC_{50} studies adds to confidence in the AEGL values.

4. ISOPROPYL CHLOROFORMATE

4.1. Summary

Data on isopropyl chloroformate were insufficient to derive of AEGL-1 values, so no values are recommended.

No acute inhalation data appropriate for deriving AEGL-2 values for isopropyl chloroformate were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001).

The point-of-departure was based on the 5-day repeated exposure study by Collins and Proctor (1984). In that study, there were no deaths in Sprague-Dawley rats from exposure to isopropyl chloroformate at 50 ppm for 6 h/day for 5 days, whereas exposure at 100 ppm for 6 h/day for 5 days resulted in deaths of 3/4 males (after 2, 4, and 5 days of treatment) and 3/4 females (after 3, 3, and 5 days of treatment). A concentration of 50 ppm was selected as the point-of-departure because there were no observed deaths in rats at 50 ppm (i.e., lethality threshold). The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this point-of-departure is provided by the acute isopropyl chloroformate study conducted by Industrial Bio-Test Laboratories, Inc. (IBT 1970b). This study could not be used as the basis of the point of departure, due to the afformentioned issues with IBT studies. Supporting information for this mode of action comes from observations in rats of nasal irritation and respiratory effects (e.g., pulmonary inflammation, pulmonary edema, and emphysema) in short-term repeated-exposure studies of isopropyl chloroformate (Gage 1970; Collins and Proctor 1984). The 10- and 30-minute AEGL-3 of 11 ppm extrapolated from the 6-h point of departure of 50 ppm in rats are consistent with values that can potentially be derived from the estimated 15-min LC_{50} of 283-345 ppm based on the results in mice by Anderson (1984). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to

the estimated threshold for lethality (50 ppm). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on isopropyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations and $n = 1$ when extrapolating from shorter to longer durations were used. The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 6-h repeated exposure to a 10-min exposure value. The AEGL values for isopropyl chloroformate are presented in Table 2-25.

4.2. Chemical and Physical Properties

Isopropyl chloroformate hydrolyzes in water to form isopropanol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of isopropyl chloroformate are present in Table 2-26.

4.3. Human Toxicity Data

4.3.1. Acute Lethality

Information on human deaths after exposure to isopropyl chloroformate was not available.

4.3.2. Nonlethal Toxicity

Short-term, task-specific industrial hygiene monitoring for isopropyl chloroformate was conducted at a resins plant (Martin 1994). The monitoring was conducted to evaluate potential employee exposure during tank-truck unloading operations. Although employees wore full-face supplied-air respirators, neoprene gloves, rubber boots, and neoprene clothing, exposures were considered possible. The study was conducted to determine if PPE should be used during these operations. Thus the employees involved in the evaluation did wear PPE as potential exposure levels were unknown and since it was determined that the levels could exceed allowable levels, PPE was mandated for this operation Concentrations of isopropyl chloroformate measured from four personal monitors were 0.2-4.6 ppm for the sampled activity (20-40 min); measurements from two area samples were 0.06 and 1.7 ppm.

4.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies on acute human exposure to isopropyl chloroformate were not available.

TABLE 2-25 AEGL Values for Isopropyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	3.7 ppm (19 mg/m³)	3.7 ppm (19 mg/m³)	3.0 ppm (15 mg/m³)	1.9 ppm (9.5 mg/m³)	1.3 ppm (6.5 mg/m³)	One-third the AEGL-3 value
AEGL-3 (lethal)	11 ppm (55 mg/m³)	11 ppm (55 mg/m³)	9.1 ppm (46 mg/m³)	5.7 ppm (29 mg/m³)	3.8 ppm (19 mg/m³)	No lethality in rat in repeated-exposure study (Collins and Proctor 1984)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-26 Chemical and Physical Properties of Isopropyl Chloroformate

Parameter	Value	Reference
Common name	Isopropyl chloroformate	HSDB 2014b
Synonyms	Carbonochloride acid, 1-methylethyl ester; carbonochloridic acid, 1-methylethyl ester; chloroformic acid isopropyl ester; formic acid, chloro-, isopropyl ester; isopropyl chlorocarbonate; isopropyl chloromethonate	HSDB 2014b
CAS registry no.	108-23-6	HSDB 2014b
Chemical formula	$C_4H_7ClO_2$	HSDB 2014b
Molecular weight	122.55	HSDB 2014b
Physical state	Colorless liquid	HSDB 2014b
Boiling point	104.6°C	HSDB 2014b
Flash point	27.8°C	HSDB 2014b
Vapor density	4.2 g/L (air = 1)	HSDB 2014b
Density/specific gravity	1.08 g/cm³	HSDB 2014b
Solubility	Soluble in ether; hydrolyzes in water	HSDB 2014b
Vapor pressure	100 mm Hg at 47°C	HSDB 2014b
Hydrolysis half-life	4.6 min at 25°C	Queen 1967
Estimated atmospheric half-time	5 d, photooxidation	HSDB 2014b
Conversion factors in air	1 mg/m³ = 0.20 ppm 1 ppm = 5.0 mg/m³	–

4.3.4. Genotoxicity

Genotoxicity studies regarding acute human exposure to isopropyl chloroformate were not available.

4.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to isopropyl chloroformate were not available.

4.3.6. Summary

No human data on the lethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of isopropyl chloroformate were available. One industrial hygiene report was available, but was not informative about potential health effects.

4.4. Animal Toxicity Data

4.4.1. Acute Lethality

4.4.1.1. Rats

Groups of five male and five female young adult Charles River albino rats were exposed to nominal concentrations of isopropyl chloroformate vapor at 300, 1,640, or 15,600 ppm for up to 1 h (IBT 1970b). Vapor was generated by bubbling clean, dry air through undiluted isopropyl chloroformate (8-10°C) in a water bath. The resulting vapor was mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was then introduced into the top of a 70-L Plexiglass inhalation chamber, dispersed by a baffle plate, and removed at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the isopropyl chloroformate vaporized by the total volume of air used during each inhalation exposure. Animals in the mid- and high-exposure groups started gasping for breath within 15 min of exposure and exhibited convulsions and salivation. Low-concentration animals exhibited gasping and slight salivation. Necropsy of animals that died revealed moderate to severe pulmonary hyperemia. Rats that survived the 14-day observation period exhibited no gross abnormalities at necropsy. The 1-h LC_{50} was 300 ppm. Data from this study are summarized in Table 2-27. As noted in Section 1.8, studies conducted by Industrial Bio-Test Laboratories are of questionable validity. Although the study of isopropyl chloroformate has not been externally audited, and the raw data from the study are not available, the study report was reviewed, but it was not used as a primary study for derivation of AEGLs.

TABLE 2-27 Effects in Rats Exposed to Isopropyl Chloroformate for Up to 1 Hour

Nominal Concentration, ppm	Exposure Duration, min	Mortality	Time of Death After Initiation of Exposure
300	60	5/10	2 h, 2 h, 2 h, 2 d, and 10 d
1,640	60	10/10	40, 48, 48, 52, 57, 60, 65, 67, 70, and 70 min
15,600	41	10/10	17, 17, 24, 24, 35, 37, 37, 37, 37, and 41 min

Source: IBT 1970b.

In a limited study, no deaths occurred among 12 rats exposed to isopropyl chloroformate vapor at 200 ppm for 1 h (BASF 1968a). Clinical signs included slight mucosal irritation. No abnormalities were found at necropsy. BASF (1968a) did not have sufficient details about its design or the findings, so the study was considered inadequate to serve as the basis for AEGL-3 values.

Death occurred in 12/12 and 6/6 rats exposed to an "atmosphere saturated" with isopropyl chloroformate vapor for 3 or 10 min, respectively (BASF 1968b). Clinical signs included vigorous escape behavior, dyspnea, and convulsions. No abnormalities were found at necropsy.

In a repeated-exposure study (Collins and Proctor 1984), groups of four male and four female Sprague-Dawley rats were exposed to isopropyl chloroformate (analytic concentrations) at 0, 25, 50, or 100 ppm for 6 h/day for 5 days. Three high-concentration males died after 2, 4, and 5 days of treatment, respectively, and three high-concentration females died after 3, 3, and 4 days of treatment, respectively. Clinical observations on the day before death included lethargy, labored breathing, staining around the muzzle, muscular weakness, and low body temperature. At necropsy, uncollapsed lungs, fluid-filled tracheas, and red discoloration of various tissues (associated with lack of exsanguination) were observed. This study is described in more detail in Section 4.4.2.

Groups of four male and four female Alderly Park SPF rats were exposed to isopropyl chloroformate vapor in isopropanol at 5 ppm (unspecified exposure duration, 20 ppm (20 6-h exposures), 50 ppm (11 6-h exposures), or 200 ppm (1 5-h exposure) (Gage 1970). The vapor concentrations were produced by injecting liquid isopropyl chloroformate at a known rate into a metered stream of air with a controlled fluid-feed atomizer. No effects were observed at 5 ppm, and nasal irritation was observed at 20 ppm. At 50 ppm, respiratory difficulty, weight loss, and one death with pulmonary hemorrhage were observed. Two male rats died at 200 ppm. No further details of the study were available.

In an acute oral toxicity study (IBT 1971), groups of two male and two female Charles River albino rats were administered isopropyl chloroformate by gavage at 118.5, 177.8, 266.7, or 400 mg/kg and observed up to 14 days. No deaths occurred at the low dose, two animals died at 177.8 mg/kg, and all

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animals died in the two highest dose groups. Deaths occurred between 1 h and 5 days post-exposure. Hypoactivity, muscular weakness, ptosis, hyperpnea, and ruffled fur were observed. Hemorrhages were found in the stomachs of animals that died during the study. An LD_{50} (lethal dose, 50% lethality) of 177.8 mg/kg was calculated. An approximate oral LD_{50} of 800 mg/kg was reported in rats (BASF 1968c).

4.4.1.2. Mice

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to isopropyl chloroformate at nominal concentrations of 0, 50, 75, 100, 200, or 500 ppm for 30 min (Carpenter 1982c). Although these exposures were generated as aerosols, the exposure was to the vapor based on the chemical vapor pressure. The mice were then removed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously during both the exposure and recovery periods. Undiluted isopropyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9-L stainless steel chamber, which was continuously evacuated at a rate of 20 L/min. An RD_{50} of 104 ppm was calculated. Data from this study are summarized in Table 2-28.

In another study (Anderson 1984), groups of four male Swiss-Webster mice were exposed head only to isopropyl chloroformate vapor at nominal concentrations of 0, 177, 306, 443, or 883 ppm for 15 min. The vapor was introduced through a Harvard apparatus syringe drive into a Pitt No. 1 generator. The glass exposure chamber had a capacity of 2.2 L, and air flow was 8.8 L/mine. Baseline respiratory rates of each mouse were recorded for 10 min before exposure. Respiratory rates were recorded after 5 and 10 min of exposure, and the percentage in respiratory depression was calculated from these values. Animals were killed 24 h after exposure. Lung and body weights were obtained at time of death or at necropsy. The 15-min RD_{50} was calculated to be 375 ppm, and the 15-min LC_{50} was estimated to be about 283-345 ppm. Concentration-related increases in lung weight, indicative of pulmonary edema, were observed in treated animals compared to controls. The data from this study are summarized in Table 2-29.

4.4.2. Nonlethal Toxicity

Collins and Proctor (1984) exposed groups of four male and four female Sprague-Dawley rats to isopropyl chloroformate vapor at 0, 25, 50, or 100 ppm (analytical) for 6 h/day for 5 days. Isopropyl chloroformate vapor was generated using a sintered glass bubbler supplied with pre-dried compressed air. Chamber concentrations were achieved by adjusting the rate of air flow through the generator. The whole-body exposures were conducted in 600-L stainless-steel

and glass chambers. Actual test concentrations were determined hourly during treatment with an infrared gas analyzer, and nominal chamber concentrations were determined daily by calculating the amount of isopropyl chloroformate consumed per liter of air passing through the chamber. Mean daily measured chamber concentrations were 25, 50, and 100 ppm and corresponding nominal concentrations were 22, 42, and 86 ppm, respectively. The investigators attribute these differences to the low accuracy of the orifice plate system used to measure flow rate through the chamber. Three high-concentration males (after 2, 4, and 5 days of treatment) and three high-concentration females (after 3, 3, and 5 days of treatment) died during the exposure period. Clinical observations on the day before death included lethargy, labored breathing, staining around the muzzle, muscular weakness, and low body temperature. Treatment-related body weight loss was observed post-exposure in the mid- and high-concentration males and females and decreased body weight gain was observed in low-concentration males. Concentration-related increases ($p < 0.02$) in lung weight were observed in all treatment groups compared with controls. In animals surviving to the end of the study, enlarged bronchial lymph nodes were observed at necropsy in several animals in all concentration groups. Focal alveolar edema and bronchiolitis were observed in several mid-concentration and all high-concentration animals. Peribronchiolar mononuclear cell infiltrate was observed in low- and mid-concentration animals and is assumed to have preceded the bronchiolitis observed in the high-concentration animals. Animals from all three treatment groups exhibited focal pulmonary emphysema.

4.4.3. Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies of isopropyl chloroformate were available.

TABLE 2-28 Effects in Mice Exposed to Isopropyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
50	320/260	19	1/4
75	225/150	33	3/4
100	260/110	58	4/4
200	275/55	80	4/4
500	–	100	4/4 (during exposure)

Source: Carpenter 1982c.

TABLE 2-29 Effects in Mice Exposed to Isopropyl Chloroformate for 15 Minutes

Concentration, ppm		Decrease in Respiratory Rate, %			Mean Lung Weight, g	Lung:Body Weight Ratio (×100)	Mortality Within 24 h
Nominal	Analytic	5 min	10 min	Average			
0	0	–	–	–	0.17	0.62	0/4
177	141	20	16	18	0.26	0.9	0/4
306	283	35	40	38	0.35	1.29	2/4[a]
443	345	45	41	43	0.39	1.23	2/4[b]
883	730	70	85	76	0.45	1.45	4/4[c]

[a]Deaths 2 h or more after exposure.
[b]All deaths within 3 h of exposure.
[c]All deaths within 3 h of exposure.
Source: Anderson 1984.

4.4.4. Genotoxicity

Isopropyl chloroformate was negative in the standard plate test and preincubation test both with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *Eschericha coli* WP2 uvrA (BASF 1999b).

4.4.5. Carcinogenicity

Animal carcinogenicity data on isopropyl chloroformate were not available.

4.4.6. Summary

Animal toxicity data on isopropyl chloroformate are sparse. The chemical affected the respiratory rate of male Swiss-Webster mice; a 30-min RD_{50} of 104 ppm (nominal concentration) was reported by Carpenter (1982c) and a 15-min RD_{50} of 375 ppm (analytic concentration) was reported by Anderson (1984). For lethality, a 15-min LC_{50} of 283-345 ppm was estimated for male Swiss-Webster mice (Anderson 1984) and a 1-h LC_{50} of 300 ppm was calculated for Charles River albino rats (IBT 1970b). Repeated exposure to isopropyl chloroformate at 100 ppm resulted in death in Sprague-Dawley rats. At 25 and 50 ppm concentrations, body weight loss, increased pulmonary weight, and bronchiolitis were observed. Increased pulmonary weight and edema were consistently observed at necropsy in most studies. Isopropyl chloroformate was negative in the Ames assay. No developmental toxicity, reproductive toxicity, or carcinogenicity study of isopropyl chloroformate were available. Animal inhalation data on isopropyl chloroformate are summarized in Table 2-30.

TABLE 2-30 Summary of Inhalation Toxicity Studies of Isopropyl Chloroformate

Species	Concentration, ppm[a]	Exposure Duration	Effect	Reference
Acute Exposure				
Rat	15,600 (nominal)	17-41 min	10/10 dead	IBT 1970b
Rat	1,640 (nominal)	40-60 min	10/10 dead	IBT 1970b
Rat	200 (approximate)	1 h	0/12 dead	BASF 1968a
Rat	300 (nominal)	1 h	LC_{50}	IBT 1970b
Rat	200 (nominal)	5 h	2/8 dead	Gage 1970
Mouse	283-345 (analytical)	15 min	LC_{50}	Anderson 1984
Mouse	375 (analytical)	15 min	RD_{50}	Anderson 1984
Mouse	104 (nominal)	30 min	RD_{50}	Carpenter 1982c
Repeated Exposure				
Rat	20 (nominal)	6 h/d, 20 d	Nasal irritation.	Gage 1970
Rat	50 (nominal)	6 h/d, 11 d	Respiratory difficulty, weight loss, pulmonary hemorrhage, 1/8 dead.	Gage 1970
Rat	25 (analytical)	6 h/d, 5 d	Decreased body weight gain, increased pulmonary weight, enlarged bronchial lymph nodes, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema.	Collins and Proctor 1984
Rat	50 (analytical)	6 h/d, 5 d	Body weight loss, increased pulmonary weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema.	Collins and Proctor 1984
Rat	100 (analytical)	6 h/d, 5 d	Body weight loss, increased pulmonary weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, focal pulmonary emphysema, deaths in 3/4 males and 3/4 females.	Collins and Proctor 1984

[a]The calculated equilibrium vapor concentration of isopropyl chloroformate is 45,800 ppm; this concentration is well above the highest reported nominal concentration (15,600 ppm) tested.

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4.5. Data Analysis for AEGL-1

4.5.1. Human Data Relevant to AEGL-1

No human data on isopropyl chloroformate consistent with the definition of AEGL-1 were available.

4.5.2. Animal Data Relevant to AEGL-1

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

4.5.3. Derivation of AEGL-1 Values

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

4.6. Data Analysis of AEGL-2

4.6.1. Human Data Relevant to AEGL-2

No human data on isopropyl chloroformate consistent with the definition of AEGL-2 were available.

4.6.2. Animal Data Relevant to AEGL-2

No acute animal data on isopropyl chloroformate consistent with the definition of AEGL-2 were available.

4.6.3. Derivation of AEGL-2 Values

No appropriate acute inhalation data on isopropyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). The AEGL-2 values for isopropyl chloroformate are presented in Table 2-31. The values are supported by the study by Gage (1970), which reported only nasal irritation in rats exposed to isopropyl chloroformate at 20 ppm for 6 h/day for 20 days.

TABLE 2-31 AEGL-2 Values for Isopropyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm	3.7 ppm	3.0 ppm	1.9 ppm	1.3 ppm
19 mg/m^3)	(19 mg/m^3)	(15 mg/m^3)	(9.5 mg/m^3)	(6.5 mg/m^3)

4.7. Data Analysis for AEGL-3

4.7.1. Human Data Relevant to AEGL-3

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

4.7.2. Animal Data Relevant to AEGL-3

A 1-h LC_{50} value of 300 ppm was calculated from a study in rats by Industrial Bio-Test Laboratories, Inc. (IBT 1970b). A 15-min mouse LC_{50} of 283-345 ppm was estimated (Anderson 1984).

4.7.3. Derivation of AEGL-3 Values

The only study that provided enough information to obtain a concentration-response relationship for lethality associated with isopropyl chloroformate was one conducted by Industrial Bio-Test Laboratories, Inc. (IBT 1970b). However, as noted in Section 1.8, some studies performed by this laboratory have been discredited because of deficiencies in study conduct and discrepancies between raw data and study reports (OECD 2007). Therefore, this study was not used as a primary study for derivation of AEGL values. In the absence of suitable acute exposure studies, the point-of-departure was based on the 5-day repeated exposure study by Collins and Proctor (1984). In that study, there were no deaths from exposure to isopropyl chloroformate at 50 ppm for 6 h/day for 5 days, whereas exposure at 100 ppm resulted in deaths of 3/4 males (after 2, 4, and 5 days of treatment) and 3/4 females (after 3, 3, and 5 days of treatment). A 6-h concentration of 50 ppm was selected as the point-of-departure, which also is supported by the BASF (1968a) study that reported no deaths among 12 rats exposed to isopropyl chloroformate at approximately 200 ppm for 1 h. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations in rats of nasal irritation and respiratory effects (e.g., pulmonary inflammation, pulmonary edema, and emphysema) in short-term repeated-exposure studies of isopropyl chloroformate (Gage 1970; Collins and Proctor 1984). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are

unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (50 ppm). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on isopropyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (10 and 30 min) and $n = 1$ when extrapolating from shorter to longer durations (4 and 8 h) were used. The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 6-h repeated exposure to a 10-min exposure value. The AEGL-3 values for isopropyl chloroformate are presented in Table 2-32; the calculations are presented in Appendix B. The 10- and 30-min AEGL-3 of 11 ppm extrapolated from the 6-h point of departure of 50 ppm in rats are consistent with values that can potentially be derived from the estimated 15-min LC_{50} of 283-345 ppm based on the results in mice by Anderson (1984) (see Table 2-30).

4.8. Summary of AEGLs

4.8.1. AEGL Values and Toxicity End Points

The AEGL values for isopropyl chloroformate are presented in Table 2-33. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were estimated by dividing the AEGL-3 values by 3, and AEGL-3 values were based a nonlethal concentration identified in a repeated-exposure study. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

4.8.2. Other Standards and Guidelines

The following standards are available for isopropyl chloroformate and are presented in Table 2-34. The American Industrial Hygiene Association (AIHA 2004, 2013) derived emergency response planning guidelines (ERPG-2 and ERPG-3) for isopropyl chloroformate that are slightly higher than the 1-h AEGL-2 and AEGL-3 values. The ERPG-2 of 5 ppm is based in part on the RD_{50} of 104 ppm in mice (Carpenter 1982c) and in part on the repeated exposure study in rats in which 20 ppm resulted in nasal irritation and 5 ppm was a no-observed-effect level (Gage 1970). The ERPG-3 of 20 ppm is based on the following lethality data: 5-h LC_{50} of 200 ppm in rats and 1-h LC_{50} of 299 ppm, both values attributed to personal communication; and deaths in 6/8 rats exposed to isopropyl chloroformate at 100 ppm for 6 h/day in a repeated-exposure study, cited as Bio-Research Laboratories Ltd. (1984). These data correspond to studies cited herein as Gage (1970) and Collins and Proctor (1984). AIHA (2004) indi-

cated that the ERPG-3 would protect against the effects of the hydrogen chloride decomposition product. No further information on the derivation of the ERPGs was provided.

TABLE 2-32 AEGL-3 Values for Isopropyl Chloroformate

10 min	30 min	1 h	4 h	8 h
11 ppm ($55 \ mg/m^3$)	11 ppm ($55 \ mg/m^3$)	9.1 ppm ($46 \ mg/m^3$)	5.7 ppm ($29 \ mg/m^3$)	3.8 ppm ($19 \ mg/m^3$)

TABLE 2-33 AEGL Values for Isopropyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	3.7 ppm ($19 \ mg/m^3$)	3.7 ppm ($19 \ mg/m^3$)	3.0 ppm ($15 \ mg/m^3$)	1.9 ppm ($9.5 \ mg/m^3$)	1.3 ppm ($6.5 \ mg/m^3$)
AEGL-3 (lethal)	11 ppm ($55 \ mg/m^3$)	11 ppm ($55 \ mg/m^3$)	9.1 ppm ($46 \ mg/m^3$)	5.7 ppm ($29 \ mg/m^3$)	3.8 ppm ($19 \ mg/m^3$)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-34 Standards and Guidelines for Isopropyl Chloroformate

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	3.7 ppm ($19 \ mg/m^3$)	3.7 ppm ($19 \ mg/m^3$)	3.0 ppm ($15 \ mg/m^3$)	1.9 ppm ($9.5 \ mg/m^3$)	1.3 ppm ($6.5 \ mg/m^3$)
AEGL-3	11 ppm ($55 \ mg/m^3$)	11 ppm ($55 \ mg/m^3$)	9.1 ppm ($46 \ mg/m^3$)	5.7 ppm ($29 \ mg/m^3$)	3.8 ppm ($19 \ mg/m^3$)
ERPG-1 (AIHA)[b]	–	–	ID[c]	–	–
ERPG-2 (AIHA)[b]	–	–	5 ppm ($25 \ mg/m^3$)	–	–
ERPG-3 (AIHA)[b]	–	–	20 ppm ($100 \ mg/m^3$)	–	–

[a]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.
[b]ERPG-1 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2004, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor.

EPRG-2 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2004, 2013) is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

EPRG-3 (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2004, 2013) is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.

[c]AIHA did not derive an EPRG-1 value for isopropyl chloroformate because of insufficient data (lack of data on odor threshold and minor irritation).

4.8.3. Data Adequacy and Research Needs

The database on isopropyl chloroformate is sparse. The most reliable data for estimating AEGL-3 values are from a repeated-exposure study in rats. The results of that study are supported by acute inhalation studies in rats and mice, although, as noted above, limitations precluded use of any of these as a primary study for derivation of AEGLs.

Acute inhalation lethality studies of isopropyl chloroformate conducted in accordance with current testing standards would help provide confirmation of the available animal toxicity data and provide chemical-specific acute 1-hour inhalation toxicity data to support the AEGL values.

5. *n*-PROPYL CHLOROFORMATE

5.1. Summary

Data on *n*-propyl chloroformate were insufficient to derive AEGL-1 values, so no values are recommended.

No appropriate acute inhalation data consistent with the definition of AEGL-2 or AEGL-3 were available on *n*-propyl chloroformate. However, this chemical is a structural analog of isopropyl chloroformate and has similar physical/chemical parameters. The two compounds produce similar adverse effects and appear to be of similar toxicity as demonstrated by Industrial Bio-Test Laboratories, Inc. (IBT 1970a) studies. Studies by IBT, while of uncertain quality, suggested 1-h LC_{50} values of 410 ppm for *n*-propyl chloroformate and 300 ppm for isopropyl chloroformate. As noted in Section 1.8, no IBT studies were used as the principal or key study in deriving AEGLs for any of the chloroformates. In cases where IBT study reports were available, they were reviewed (but not formally audited), and if the findings were consistent with other studies of reputable validity, the results of the IBT studies are included and referred to as providing supporting evidence. The IBT LC_{50} studies support the use of isopropyl chloroformate AEGL values for *n*-propyl chloroformate.

The database for isopropyl chloroformate is more robust, including studies conducted by other laboratories as well as repeated exposure studies. Because of the sparseness of the database on *n*-propyl chloroformate and the uncertainties associated with the quality of the available data, the AEGL-2 values for isopropyl chloroformate were adopted as surrogates for *n*-propyl chloroformate.

For AEGL-3 values, the only data on *n*-propyl chloroformate that provided an indication of a dose-response relationship for lethality was from a study conducted by Industrial Bio-Test Laboratories, Inc. (IBT 1970a). As noted in Section 1.8, the validity of the studies conducted by that laboratory is of questionable validity. The study of *n*-propyl chloroformate has not been externally audited, and the raw data from the study are not available. Because of this, the study was considered inadequate for use in deriving AEGL-3 values. A study by BASF (1970a) did not have sufficient details about its design or the findings, so the study also was considered inadequate to serve as the basis for AEGL-3 values. Because of the sparseness of the database and uncertainties in the quality of the available data for *n*-propyl chloroformate, AEGL-3 values for the isopropyl chloroformate were adopted as surrogates for *n*-propyl chloroformate (see Section 5 for details on how the values for isopropyl chloroformate were determined). The AEGL values for *n*-propyl chloroformate are presented in Table 2-35.

5.2. Chemical and Physical Properties

Propyl chloroformate hydrolyzes in water to form *n*-propanol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of *n*-propyl chloroformate presented in Table 2-36.

TABLE 2-35 AEGL Values for *n*-Propyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	3.7 ppm (19 mg/m^3)	3.7 ppm (19 mg/m^3)	3.0 ppm (15 mg/m^3)	1.9 ppm (9.5 mg/m^3)	1.3 ppm (6.5 mg/m^3)	By analogy to isopropyl chloroformate
AEGL-3 (lethal)	11 ppm (55 mg/m^3)	11 ppm (55 mg/m^3)	9.1 ppm (46 mg/m^3)	5.7 ppm (29 mg/m^3)	3.8 ppm (19 mg/m^3)	By analogy to isopropyl chloroformate

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

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TABLE 2-36 Chemical and Physical Properties of Propyl Chloroformate

Parameter	Data	Reference
Common name	Propyl chloroformate	HSDB 2014c
Synonyms	Carbonochloridic acid, propyl ester; formic acid, chloro-, propyl ester; propyl chlorocarbonate; *n*-propyl chloroformate	HSDB 2014c
CAS registry no.	109-61-5	HSDB 2014c
Chemical formula	$C_4H_7ClO_2$	HSDB 2014c
Molecular weight	122.55	HSDB 2014c
Physical state	Colorless liquid	HSDB 2014c
Boiling Point	112.4°C	HSDB 2014c
Flash point	35.4°C	HSDB 2014c
Vapor density	4.2 g/L (air = 1)	HSDB 2014c
Density/specific gravity	1.09 g/cm^3	HSDB 2014c
Solubility	Miscible in chloroform, benzene, ether	HSDB 2014c
Vapor pressure	20 mm Hg at 25°C	HSDB 2014c
Hydrolysis half-life	29.4 min at 25°C	Queen 1967
Estimated atmospheric half-time	–	–
Conversion Factors in Air	1 mg/m^3 = 0.20 ppm 1 ppm = 5.0 mg/m^3	–

5.3. Human Toxicity Data

5.3.1. Acute Lethality

No information on human lethality from exposure to *n*-propyl chloroformate was found.

5.3.2. Nonlethal Toxicity

No information about the nonlethal human toxicity from exposure to *n*-propyl chloroformate was found.

5.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies on acute human exposure to *n*-propyl chloroformate were not available.

5.3.4. Genotoxicity

Genotoxicity studies on acute human exposure to *n*-propyl chloroformate were not available.

5.3.5. Carcinogenicity

Carcinogenicity studies on human exposure to *n*-propyl chloroformate were not available.

5.3.6. Summary

Data concerning human exposure to *n*-propyl chloroformate are not available.

5.4. Animal Toxicity Data

5.4.1. Acute Lethality

5.4.1.1. Rats

Groups of five male and five female young adult Charles River albino rats (320 g, average weight) were exposed to nominal concentrations of *n*-propyl chloroformate vapor at 249, 333, 1,000, 3,077, or 21,538 ppm for 1 h (IBT 1970a). Vapor was generated by bubbling clean, dry air through undiluted *n*-propyl chloroformate. The resulting vapor was mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was then introduced into the top of a 70-L Plexiglass inhalation chamber, dispersed by a baffle plate, and removed at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the *n*-propyl chloroformate vaporized by the total volume of air used during each inhalation exposure. No adverse effects were observed in the 249-ppm group during exposure. Bloody nasal discharge and dyspnea were observed in the 333-ppm group near the end of the exposure period, while hyperactivity, clear nasal discharge, dyspnea, and salivation were observed in the 1,000-, 3,077-, and 21,538-ppm groups. No adverse effects on body weight were observed in any animals that survived the 14-day observation period; however, necropsy revealed slight to moderate hyperemia in these animals. Necropsy of animals that died during the study revealed moderate to severe pulmonary hyperemia. A 1-h LC_{50} of 410 ppm, $BMCL_{05}$ of 216 ppm, and BMC_{01} of 229 ppm were calculated. Results from this study are summarized in Table 2-37.

As noted in Section 1.8, the validity of the studies conducted by Industrial Bio-Test Laboratories is of questionable validity. The study of *n*-propyl chloroformate has not been externally audited, and the raw data from the study are not available.

In a limited study, death occurred in 3/10 rats exposed to *n*-propyl chloroformate at 200 ppm for 1 h (BASF 1970d). Clinical signs included restlessness, mucous membrane irritation, and dyspnea. Acute pulmonary emphysema was observed at necropsy. However, the report did not have sufficient details about its study design or the findings, so the study was considered inadequate to serve as the basis for AEGL-3 values.In another report, Death occurred in 12/12 rats exposed to an "atmosphere enriched or saturated" with *n*-propyl chloroformate vapor (20°C) for 3 min (BASF 1970e). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, and gasping. Pulmonary congestion and edema were found at necropsy.

An oral LD_{50} value for *n*-propyl chloroformate of 650 mg/kg was reported for Charles River albino rats (IBT 1970a). Oral LD_{50} values of 1,212 mg/kg (BASF 1980b) and 872 mg/kg (BASF 1970f) were reported for Sprague-Dawley rats.

TABLE 2-37 Effect in Rats Exposed to *n*-Propyl Chloroformate for 1 Hour

Nominal Concentration, ppm	Mortality	Time of Death, Post-Exposure	Observations at Necropsy	Observations During Exposure
249	0/10	Not applicable	Slight to moderate pulmonary hyperemia	None
333	2/10	Within 60 min	Slight to moderate pulmonary hyperemia in survivors; moderate to severe pulmonary hyperemia in decedents	Bloody nasal discharge; dyspnea
1,000	10/10	Within 60 min	Moderate to severe pulmonary hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation
3,077	10/10	Within 60 min	Moderate to severe pulmonary hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation
21,538	10/10	Within 30 min	Moderate to severe pulmonary hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation

Source: Data from IBT 1970a.

5.4.1.2. Mice

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to *n*-propyl chloroformate aerosol at concentrations of 0, 25, 50, 75, or 100 ppm for 30 min (Carpenter 1982b). The mice were then removed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously. Undiluted *n*-propyl chloro-formate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 6-L stainless steel chamber which was continuously evacuated at a rate of 18.3 L/min. An RD_{50} of 83.5 ± 2.17 ppm was calculated. Although RD_{50} values are not used in the development of AEGL values, an RD_{50} was reported, the data was reported and no dose response relationship was observed, limiting its usefulness in development of an AEGL3. Results of the study are summarized in Table 2-38.

5.4.2. Nonlethal Toxicity

5.4.2.1. Rabbits

Corneal opacity and iridal and conjunctival irritation were observed within 1 min after the eyes of albino rabbits were instilled with 0.1 mL of undiluted *n*-propyl chloroformate (IBT 1970a). The irritation became progressively worse, and maximum damage was present in all ocular tissues within 3-7 days. No improvement was observed after 14 days, so the chemical is considered extremely irritating to the eyes of albino rabbits.

Propyl chloroformate is also considered extremely irritating to the skin of albino rabbits (IBT 1970a). Severe erythema, edema, and burns were observed after dermal exposure of rabbits to 0.5 mL of undiluted *n*-propyl chloroformate for 24 h. Effects persisted through the 72-h observation period.

5.4.3. Developmental and Reproductive Toxicity

No information concerning the developmental or reproductive toxicity of *n*-propyl chloroformate was found.

TABLE 2-38 Effects in Male Swiss-Webster Mice Exposed to Propyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
25	255/225	12	0/4
50	280/205	27	1/4
75	270/150	44	2/4
100	245/95	61	0/4

Source: Carpenter 1982b.

5.4.4. Genotoxicity

Propyl chloroformate was negative in a preincubation test both with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (BASF 1988c).

5.4.5. Carcinogenicity

No information on the carcinogenicity of *n*-propyl chloroformate was found.

5.4.6. Summary

Animal toxicity data on *n*-propyl chloroformate is sparse. A 1-h LC_{50} of 410 ppm, $BMCL_{05}$ of 216 ppm, and BMC_{01} of 229 ppm were calculated for Charles River albino rats (IBT 1970a). *n*-Propyl chloroformate is severely irritating to the skin and eyes of albino rabbits (IBT 1970a).

5.5. Data Analysis for AEGL-1

5.5.1. Human Data Relevant to AEGL-1

No human data on *n*-propyl chloroformate consistent with the definition of AEGL-1 were available.

5.5.2. Animal Data Relevant to AEGL-1

No animal data on *n*-propyl chloroformate consistent with the definition of AEGL-1 were available.

5.5.3. Derivation of AEGL-1 Values

AEGL-1 values for *n*-propyl chloroformate are not recommended because of insufficient data.

5.6. Data Analysis for AEGL-2

5.6.1. Human Data Relevant to AEGL-2

No human data on *n*-propyl chloroformate consistent with the definition of AEGL-2 were available.

5.6.2. Animal Data Relevant to AEGL-2

No animal data on *n*-propyl chloroformate consistent with the definition of AEGL-2 were available.

5.6.3. Derivation of AEGL-2 Values

Chemical-specific data were insufficient to derive AEGL-2 values for *n*-propyl chloroformate. However, *n*-propyl chloroformate is a structural analog of isopropyl chloroformate, and the two compounds appear to be of similar toxicity (see Section 5.7.3). The database for isopropyl chloroformate is more robust, and includes studies conducted by laboratories other than IBT, as well as repeated exposure studies. Given the sparseness of the database and the uncertainties in the quality of the available data for *n*-propyl chloroformate, AEGL-2 values for isopropyl chloroformate were adopted as surrogates for *n*-propyl chloroformate (see Section 4 for how the isopropyl chloroformate values were determined). The AEGL-2 values for *n*-propyl chloroformate are presented in Table 2-39.

5.7. Data Analysis for AEGL-3

5.7.1. Human Data Relevant to AEGL-3

No human data on *n*-propyl chloroformate consistent with the definition of AEGL-3 were available.

5.7.2. Animal Data Relevant to AEGL-3

A 1-h rat LC_{50} of 410 ppm and $BMCL_{05}$ of 216 ppm were calculated; no deaths were noted at 249 ppm (IBT 1970a). The limited BASF (1970d) reported mortalities in 3/10 rats exposed to *n*-propyl chloroformate at 200 ppm for 1 h. This study was inadequate to serve as the basis for AEGL-3 values because it did not provide sufficient details about its study design or the findings, and other concentrations were not tested.

TABLE 2-39 AEGL-2 Values for *n*-Propyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm	3.7 ppm	3.0 ppm	1.9 ppm	1.3 ppm
(19 mg/m^3)	(19 mg/m^3)	(15 mg/m^3)	(9.5 mg/m^3)	(6.5 mg/m^3)

5.7.3. Derivation of AEGL-3 Values

Propyl chloroformate is a structural analog of isopropyl chloroformate, and the two compounds appear to be of similar toxicity. Given the sparseness of the database and uncertainties in the quality of the available data for *n*-propyl chloroformate, AEGL-3 values for isopropyl chloroformate were adopted as surrogates for *n*-propyl chloroformate (see Section 5 for how the isopropyl chloroformate values were determined). The AEGL-3 values for *n*-propyl chloroformate are presented in Table 2-40.

5.8. Summary of AEGLs

5.8.1. AEGL Values and Toxicity End Points

The AEGL values for *n*-propyl chloroformate are presented in Table 2-41. AEGL-1 values are not recommended because of insufficient data. Data were also insufficient for deriving AEGL-2 and AEGL-3 values, so the AEGL values for isopropyl chloroformate were adopted for *n*-propyl chloroformate, as available data indicate that the two chemicals have similar toxicity.

5.8.2. Other Standards and Guidelines

No other exposure standards or guidelines for *n*-propyl chloroformate were found.

TABLE 2-40 AEGL-3 Values for *n*-Propyl Chloroformate

10 min	30 min	1 h	4 h	8 h
11 ppm (55 mg/m^3)	11 ppm (55 mg/m^3)	9.1 ppm (46 mg/m^3)	5.7 ppm (29 mg/m^3)	3.8 ppm (19 mg/m^3)

TABLE 2-41 AEGL Values for *n*-Propyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	3.7 ppm (19 mg/m^3)	3.7 ppm (19 mg/m^3)	3.0 ppm (15 mg/m^3)	1.9 ppm (9.5 mg/m^3)	1.3 ppm (6.5 mg/m^3)
AEGL-3 (lethal)	11 ppm (55 mg/m^3)	11 ppm (55 mg/m^3)	9.1 ppm (46 mg/m^3)	5.7 ppm (29 mg/m^3)	3.8 ppm (19 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

5.8.3. Data Adequacy and Research Needs

Data on *n*-propyl chloroformate are sparse. Human data are not available. Animal data include two rat acute inhalation lethality studies (one of uncertain quality [IBT 1970a] and one with inadequate reporting [BASF 1970d]) and one mouse RD50 study. AEGLs for *n*-propyl chloroformate were therefore based on analogy to its structural analog, isopropyl chloroformate, which has a more robust database. Although, as noted in Section 1.8 and above, the IBT 1970a study was of limited usefulness and could not be relied upon as a primary study for derivation of AEGLs, the toxic effects and the LC_{50} value reported in this 1-hour acute inhalation study provide supporting evidence for the *n*-propyl chloroformate AEGL values.

Acute inhalation lethality studies of *n*-propyl chloroformate conducted in accordance with current testing standards would help provide confirmation of the available animal toxicity lethality data and provide chemical-specific data to support the AEGL values.

6. ALLYL CHLOROFORMATE

6.1. Summary

Data on allyl chloroformate were insufficient to derive AEGL-1 values, so no values are recommended.

No appropriate acute inhalation data consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on allyl chloroformate provide evidence of a steep curve. The incidence of mortality in rats exposed to allyl chloroformate for 1 h was 0/10 at 33.7 ppm, 6/10 at 65 ppm, and 10/10 at 175.7 ppm (Stillmeadow Inc. 1987).

Lethality data from a study by Stillmeadow Inc. (1987) was used to calculate a 1-h rat $BMCL_{05}$ of 21 ppm to be used as the lethality threshold point-of-departure for calculating AEGL-3 values. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or

corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (21 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate. The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on allyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (10 and 30 min) and $n = 1$ when extrapolating from shorter to longer durations (4 and 8 h) were used. The AEGL values for allyl chloroformate are presented in Table 2-41.

6.2. Chemical and Physical Properties

Allyl chloroformate hydrolyzes in water to form allyl alcohol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of this chemical are presented in Table 2-42.

6.3. Human Toxicity Data

6.3.1. Acute Lethality

Information on human deaths after exposure to allyl chloroformate was not available.

TABLE 2-41 AEGL Values for Allyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR	Insufficient data.
AEGL-2 (disabling)	1.3 ppm (6.4 mg/m^3)	0.87 ppm (4.3 mg/m^3)	0.70 ppm (3.4 mg/m^3)	0.18 ppm (0.88 mg/m^3)	0.09 ppm (0.44 mg/m^3)	One-third the AEGL-3 values.
AEGL-3 (lethal)	3.8 ppm (19 mg/m^3)	2.6 ppm (13 mg/m^3)	2.1 ppm (10 mg/m^3)	0.53 ppm (2.6 mg/m^3)	0.26 ppm (1.3 mg/m^3)	1-h rat BMCL$_{05}$ (Stillmeadow Inc. 1987)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-42 Chemical and Physical Properties of Allyl Chloroformate

Parameter	Value
Common name	Allyl chloroformate
Synonyms	Chloroformic acid, allyl ester; allyl chlorocarbonate
CAS registry no.	2937-50-0
Chemical formula	$C_4H_5ClO_2$
Molecular weight	120.54
Physical state	Colorless liquid
Boiling point	110°C
Flash point	31.1°C
Vapor density	4.2 g/L (air = 1)
Density/specific gravity	1.14 g/cm^3
Solubility	Hydrolyzes in water
Vapor pressure	20 mm Hg at 25°C
Estimated atmospheric half-time	14 h, photooxidation; 23 h, reaction with ozone
Conversion factors in air	1 mg/m^3 = 0.20 ppm 1 ppm = 4.9 mg/m^3

Source: HSDB 2013.

6.3.2. Nonlethal Toxicity

Information concerning nonlethal toxicity in humans after exposure to allyl chloroformate was not available.

6.3.3. Developmental and Reproductive Toxicity

No human data on the developmental or reproductive toxicity of allyl chloroformate were available.

6.3.4. Genotoxicity

Genotoxicity studies on acute human exposure to allyl chloroformate were not available.

6.3.5. Carcinogenicity

Carcinogenicity studies on human exposure to allyl chloroformate were not available.

6.3.6. Summary

No human studies of the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of allyl chloroformate were available.

6.4. Animal Toxicity Data

6.4.1. Acute Lethality

6.4.1.1. Rats

Groups of five male and five female Sprague Dawley rats were exposed to allyl chloroformate at 33.7, 65.0, 77.7, 134.5, 175.7, or 233.3 ppm for 1 h, followed by a 14-day observation period (Stillmeadow Inc. 1987). Animals were exposed in a 200-L stainless steel dynamic flow inhalation chamber. Aerosol was generated by aspirating the allyl chloroformate through a pressure operated spray nozzle. The concentrated aerosol was then diluted with dried, filtered air and drawn into the exposure chamber. Air flow was maintained through the use of a calibrated critical orifice, and air flow was recorded at 30-min intervals during the exposure period. The concentration of allyl chloroformate in the exposure atmosphere was determined analytically at 30 and 60 min via gas chromatography. Clinical signs were observed in all exposure groups and included decreased activity, body tremors, constricted pupils, diarrhea, emaciation, epistaxis, gasping, lacrimation, nasal discharge, piloerection, polyuria, ptosis, respiratory gurgle, and salivation. Nine of the 10 rats exposed at 33.7 ppm gained weight over the 14-day observation period, and the tenth animal retained a constant weight. All eight of the rats exposed at higher concentrations and survived the 14-day observation period lost weight. Gross necropsy findings included discoloration of the lungs, pulmonary edema, clear fluid in the thoracic cavity, gastrointestinal tract distended with gas, and discoloration of gastrointestinal tract contents. An LC_{50} of 65.1 ppm, a $BMCL_{05}$ of 21 ppm, and a BMC_{01} of 25.7 ppm were calculated. Data from this study are summarized in Table 2-43.

6.4.2. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of allyl chloroformate was available.

6.4.3. Genotoxicity

No information on the genotoxicity of allyl chloroformate was available.

TABLE 2-43 Mortality in Sprague-Dawley Rats Exposed to Allyl Chloroformate for 1 Hour

Concentration, ppm	Males	Females	Males and Females
33.7	0/5	0/5	0/10
65.0	3/5	3/5	6/10
77.7	3/5	4/5	7/10
134.5	5/5	4/5	9/10
175.7	5/5	5/5	10/10
233.3	5/5	5/5	10/10
LC_{50}	–	–	65.1 ppm
$BMCL_{05}$	–	–	21 ppm
BMC_{01}	–	–	25.7 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Adapted from Stillmeadow Inc. 1987.

6.4.4. Carcinogenicity

No information on the carcinogenicity of allyl chloroformate was available.

6.4.5. Summary

Animal toxicity data on allyl chloroformate include one well-conducted rat lethality study, which described clinical signs consistent with severe irritation. Data from the study were used to estimate an LC_{50} of 65.1 ppm, a $BMCL_{05}$ of 21 ppm, and a BMC_{01} of 25.7 ppm. No studies of the reproductive toxicity, developmental toxicity, genotoxicity data, or carcinogenicity of allyl chloroformate were available.

6.5. Data Analysis for AEGL-1

6.5.1. Human Data Relevant to AEGL-1

No human data on allyl chloroformate consistent with the definition of AEGL-1 were available.

6.5.2. Animal Data Relevant to AEGL-1

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

6.5.3. Derivation of AEGL-1 Values

Data are insufficient to derive AEGL-1 values for allyl chloroformate, so no values are recommended.

6.6. Data Analysis for AEGL-2

6.6.1. Human Data Relevant to AEGL-2

No human data on allyl chloroformate consistent with the definition of AEGL-2 were available.

6.6.2. Animal Data Relevant to AEGL-2

No animal data on allyl chloroformate consistent with the definition of AEGL-2 were available.

6.6.3. Derivation of AEGL-2 Values

No appropriate acute inhalation data on allyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on allyl chloroformate provide evidence of a steep curve. The incidence of mortality in rats exposed to ally chloroformate for 1 h was 0/10 at 33.7 ppm, 6/10 at 65 ppm, and 10/10 at 175.7 ppm (Stillmeadow Inc. 1987). The AEGL-2 values for allyl chloroformate are presented in Table 2-44.

6.7. Data Analysis for AEGL-3

6.7.1. Human Data Relevant to AEGL-3

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

6.7.2. Animal Data Relevant to AEGL-3

A 1-h rat LC_{50} of 65.1 ppm and a $BMCL_{05}$ of 21 ppm were calculated for allyl chloroformate (Stillmeadow Inc. 1987).

6.7.3. Derivation of AEGL-3 Values

The calculated 1-h rat $BMCL_{05}$ of 21 ppm (Stillmeadow Inc. 1987) was the point-of-departure for deriving AEGL-3 values for allyl chloroformate. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (21 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on allyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 and 30 min) and n = 1 when extrapolating from shorter to longer durations (4 and 8 h) were used. The AEGL-3 values for allyl chloroformate are presented in Table 2-45; the calculations are presented in Appendix B.

TABLE 2-44 AEGL-2 Values for Allyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm
(6.4 mg/m^3)	(4.3 mg/m^3)	(3.4 mg/m^3)	(0.88 mg/m^3)	(0.44 mg/m^3)

TABLE 2-45 AEGL-3 Values for Allyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm
(19 mg/m^3)	(13 mg/m^3)	(10 mg/m^3)	(2.6 mg/m^3)	(1.3 mg/m^3)

6.8. Summary of AEGLs

6.8.1. AEGL Values and Toxicity End Points

The AEGL values for allyl chloroformate are presented in Table 2-46. Data were insufficient for deriving AEGL-1 values. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on a 1-h $BMCL_{05}$ for lethality in rats. A derivation summary and category plot of the AEGL values are presented in Appendixes C and D, respectively.

6.8.2. Other Standards and Guidelines

No other standards or guidelines for allyl chloroformate were found.

6.8.3. Data Adequacy and Research Needs

Only one study of allyl chloroformate was available.

7. *n*-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, AND *sec*-BUTYL CHLOROFLORMATE

7.1. Summary

Data on *n*-butyl, isobutyl, or *sec*-butyl chloroformate were insufficient to derive AEGL-1 values, so no values were recommended.

The AEGL-2 and AEGL-3 values for *n*-butyl, isobutyl, and *sec*-butyl chloroformate are the same. Only *n*-butyl chloroformate had sufficient data from which to derive values. Because isobutyl chloroformate and *sec*-butyl are structural analogs of *n*-butyl chloroformate and appear to have similar toxicity (Carpenter 1982b), the values derived for *n*-butyl chloroformate were applied to these two chemicals.

TABLE 2-46 AEGL Values for Allyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.3 ppm (6.4 mg/m³)	0.87 ppm (4.3 mg/m³)	0.70 ppm (3.4 mg/m³)	0.18 ppm (0.88 mg/m³)	0.09 ppm (0.44 mg/m³)
AEGL-3 (lethal)	3.8 ppm (19 mg/m³)	2.6 ppm (13 mg/m³)	2.1 ppm (10 mg/m³)	0.53 ppm (2.6 mg/m³)	0.26 ppm (1.3 mg/m³)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

No acute inhalation data on *n*-butyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). The AEGL-2 values are supported by results of repeated-exposure studies by HRC (1990), which found no effects in rats exposed to *n*-butyl chloroformate at 1.8 ppm for 6 h/day, 5 days/week for 4 weeks, or at 2.9 ppm for 6 h/day for 5 days.

For AEGL-3 values, the point-of-departure was the estimated lethality threshold for *n*-butyl chloroformate. The estimate was calculated by taking one-third of the concentration of *n*-butyl chloroformate at which 4/10 rats died after a 1-h exposure (200 ppm ÷ 3 = 66.7 ppm) (BASF 1970g). The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (66.7 ppm). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on *n*-butyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 and 30 min) and n = 1 when extrapolating from shorter to longer durations (4 and 8 h) were used. The AEGL-3 values are also supported by results from repeated exposure studies conducted by HRC (1990); no rats died when exposed to *n*-butyl chloroformate 5.1 ppm for 6 h/day, 5 days/week for 4 weeks or at 28.4 ppm for 6 h/day for 5 days. The AEGL values for *n*-butyl chloroformate are presented in Table 2-47.

7.2. Chemical and Physical Properties

n-Butyl, isobutyl, and *sec*-butyl chloroformate hydrolyze in water to form *n*-butanol, isobutanol, and *sec*-butanol, respectively, and carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of *n*-butyl chloroformate, isobutyl chloroformate, and *sec*-butyl chloroformate are presented in Tables 2-48, 2-49, and 2-50, respectively.

TABLE 2-47 AEGL Values for *n*-Butyl, Isobutyl, and *sec*-Butyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)	One-third AEGL-3 values
AEGL-3 (lethal)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)	Estimated 1-h lethality threshold in rats (BASF 1970g)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-48 Chemical and Physical Properties of *n*-Butyl Chloroformate

Parameter	Value	Reference
Common name	*n*-Butyl chloroformate	Kreutzberger 2001
Synonyms	Butyl chlorocarbonate; butoxycarbonyl chloride; chloroformic acid, butyl ester	BG Chemie 2005
CAS registry no.	592-34-7	Kreutzberger 2001
Chemical formula	$C_5H_9ClO_2$	Kreutzberger 2001
Molecular weight	136.58	Kreutzberger 2001
Physical state	Liquid	BG Chemie 2005
Boiling point	142°C	Bohm and Beth-Hubner 2006
Flash point	46.0°C	Kreutzberger 2001
Vapor density	4.7 g/L (air = 1)	IPCS 2005a
Density/specific gravity	1.06 g/cm^3	Kreutzberger 2001
Solubility	Poorly soluble (hydrolyzes) in water; miscible in ether; soluble in acetone and ethanol	BG Chemie 2005
Vapor pressure	5.3 mm Hg at 20°C	BG Chemie 2005
Conversion factors in air	1 mg/m^3 = 0.18 ppm 1 ppm = 5.6 mg/m^3	–

TABLE 2-49 Chemical and Physical Properties of Isobutyl Chloroformate

Parameter	Value	Reference
Common name	Isobutyl chloroformate	Kreutzberger 2001
Synonyms	Carbonochloridic acid, 2-methylpropyl ester; isobutyl chlorocarbonate	O'Neil et al. 2001a
CAS registry no.	543-27-1	O'Neil et al. 2001a
Chemical formula	$C_5H_{10}ClO_2$	O'Neil et al. 2001a
Molecular weight	136.58	O'Neil et al. 2001a
Physical state	Clear liquid	O'Neil et al. 2001a
Boiling point	130°C	O'Neil et al. 2001a
Flash point	39.4°C	O'Neil et al. 2001a
Vapor density	4.7 g/L (air = 1)	IPCS 2005b
Density/specific gravity	1.04 g/cm³	O'Neil et al. 2001a
Solubility	Miscible in chloroform, benzene, ether; gradually decomposes in water	O'Neil et al. 2001a
Conversion factors in air	1 mg/m³ = 0.18 ppm 1 ppm = 5.6 mg/m³	–

TABLE 2-50 Chemical and Physical Properties of *sec*-Butyl Chloroformate

Parameter	Values	Reference
Common name	*sec*-Butyl chloroformate	Kreutzberger 2001
Synonyms	Carbonochloridic acid, 1-methylpropyl ester	ChemIDplus 2012
CAS registry no.	17462-58-7	ChemIDPlus 2012
Chemical formula	$C_5H_9ClO_2$	Kreutzberger 2001
Molecular weight	136.58	Kreutzberger 2001
Physical state	Colorless liquid	Kreutzberger 2001
Flash point	35.6°C	Kreutzberger 2001
Density/specific gravity	1.049 g/cm³	Kreutzberger 2001
Conversion factors in air	1 mg/m³ = 0.18 ppm 1 ppm = 5.6 mg/m³	–

7.3. Human Toxicity Data

7.3.1. Acute Lethality

Information on death in humans after inhalation exposure to *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate was not available.

7.3.2. Nonlethal Toxicity

Information on the nonlethal toxicity of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate in humans was not available.

7.3.3. Developmental ad Reproductive Toxicity

No human data on the developmental or reproductive toxicity of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate were available.

7.3.4. Genotoxicity

No human genotoxicity studies of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate were available.

7.3.5. Carcinogenicity

No human carcinogenicity studies of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate were available.

7.3.6. Summary

No human data on the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate were available.

7.4 Animal Toxicity Data

7.4.1. Acute Lethality

7.4.1.1. n-*Butyl Chloroformate*

Death occurred in 4/10 rats exposed to *n*-butyl chloroformate at 200 ppm for 1 h (BASF 1970g). Dyspnea was observed, and pulmonary emphysema was found at necropsy.

Death occurred in 12/12 rats exposed for 3 min and 6/6 rats exposed for 10 min to an "atmosphere enriched or saturated" with *n*-butyl chloroformate vapor (20°C) (BASF 1970g). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, and gasping. Pulmonary congestion and edema with hydrothorax were found at necropsy.

Oral LD_{50} values of 1,325 mg/kg (administered in 10% aqueous traga-canth gum emulsion) and 2,120 mg/kg (administered in 20% aqueous tragacanth gum emulsion) were reported for rats (BASF 1970g). An oral LD_{50} of 2,610 mg/kg was reported for male and female Sprague-Dawley rats when *n*-butyl chloroformate was administered in olive oil (BASF 1980c).

7.4.2. Nonlethal Toxicity

7.4.2.1. n-*Butyl Chloroformate*

In an inhalation range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to *n*-butyl chloroformate at 0, 2.9, 9.9, or 28.4 ppm for 6 h/day for 5 days (HRC 1990). None of the rats died. A decrease in food consumption in a concentration-related manner was observed in all treatment groups. Clinical signs in the 9.9- and 28.4-ppm groups included concentration-dependent sneezing, rubbing the snout with paws, closed or partially closed eyes, rapid breathing, licking the inside of the mouth, and sniffing and noisy respiration between exposures. High-concentration rats also exhibited prone position, lack of reaction to acoustic stimuli, and hypoactivity (after the first exposure). Body weight loss was observed in high-concentration males throughout the study; whereas, high-concentration females showed initial body weight loss, followed by decreased body weight gain. Pulmonary weights were increased in high-concentration males and females and in mid-concentration females.

In a repeated-exposure study, groups of five male and five female Sprague-Dawley rats were exposed to *n*-butyl chloroformate at 0, 0.50, 1.8, or 5.1 ppm for 6 h/day, 5 days/week for 4 weeks (HRC 1990). None of the rats died. Piloerection was observed in the 5.1-ppm group during exposure. High-concentration males had increased pulmonary weight. Histologic examination of the lungs revealed minimal focal epithelial hyperplasia of the carina trachea in 1/5 males and 3/5 females and minimal focal crowding of epithelial cells in 3/5 males in the 5.1-ppm group. No other treatment-related effects were reported.

7.4.2.2. Isobutyl Chloroformate

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to isobutyl chloroformate aerosol at concentrations of 0, 25, 50, 100, 150, or 200 ppm for 30 min (Carpenter 1982b). The mice were then removed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously during both the exposure and recovery periods Undiluted isobutyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 6-L stainless steel chamber, which was continuously evacuated at 18.3 L/min. An RD_{50} of 97.0 ± 5.82 ppm was calculated. Results from this study are summarized in Table 2-51.

7.4.2.3. sec-*Butyl Chloroformate*

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to *sec*-butyl chloroformate aerosol at concentrations of 0, 50, 100, 150, or 200 ppm for 30 min (Carpenter 1982b). Although these exposures were generated as aerosols, the exposure was to the vapor based on the chemical vapor pressure. The mice were then removed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously. Undiluted *sec*-butyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a known rate. Aerosol was directed into a 6-L stainless steel chamber, which was continuously evacuated at 18.3 L/min. An RD_{50} of 117 ± 1.64 ppm was calculated. Results of this study are summarized in Table 2-52.

7.4.3. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate was found.

TABLE 2-51 Effects in Male Swiss-Webster Mice Exposed to Isobutyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
25	265/20	25	0/4
50	260/155	40	0/4
100	310/155	50	0/4
150	290/145	50	0/4
200	295/85	71	0/4

Source: Carpenter 1982b.

TABLE 2-52 Effects in Male Swiss-Webster Mice Exposed to *sec*-Butyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
50	195/175	10	0/4
100	280/165	41	0/4
150	295/130	55	0/4
200	225/40	82	1/4

Source: Carpenter 1982b.

7.4.4. Genotoxicity

n-Butyl chloroformate was negative in a preincubation test both with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (BASF 1988d), and was negative both with and without activation in a chromosome-aberration assay in Chinese hamster V79 cells (CCR 1990). No genotoxicity data on isobutyl chloroformate or *sec*-butyl chloroformate were available.

7.4.5. Carcinogenicity

No information on the carcinogenicity of *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate was available.

7.4.6. Summary

The lethal and nonlethal toxicity of *n*-butyl chloroformate have been studied only in rats. Clinical signs from exposure to *n*-butyl chloroformate were consistent with severe irritation and respiratory distress. Animal data on isobutyl chloroformate and *sec*-butyl chloroformate are available only from mouse RD_{50} studies. *n*-Butyl chloroformate was negative in both bacterial reverse-mutation and mammalian-cell chromosome-aberration assays; no genotoxicity data were available for isobutyl chloroformate or *sec*-butyl chloroformate. No developmental toxicity, reproductive toxicity, or carcinogenicity data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate were available.

7.5. Data Analysis for AEGL-1

7.5.1. Human Data Relevant to AEGL-1

No human data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate consistent with the definition of AEGL-1 were available.

7.5.2. Animal Data Relevant to AEGL-1

No animal data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate consistent with the definition of AEGL-1 were available.

7.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate, so no values are recommended.

7.6. Data Analysis for AEGL-2

7.6.1. Human Data Relevant to AEGL-2

No human data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate consistent with the definition of AEGL-2 were available.

7.6.2. Animal Data Relevant to AEGL-2

No animal data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate consistent with the definition of AEGL-2 were available.

7.6.3. Derivation of AEGL-2 Values

7.6.3.1. n-*Butyl Chloroformate*

No appropriate acute inhalation data on *n*-butyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approach is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). The AEGL-2 values for *n*-butyl chloroformate are presented in Table 2-53. The values are supported by results of repeated-exposure studies by HRC (1990), which found no effects in rats exposed to *n*-butyl chloroformate at 1.8 ppm for 6 h/day, 5 days/week for 4 weeks, or at 2.9 ppm for 6 h/day for 5 days.

7.6.3.2. Isobutyl Chloroformate and sec-*Butyl Chloroformate*

Chemical-specific data were insufficient to derive of AEGL-2 values for isobutyl chloroformate and *sec*-butyl chloroformate. Because these two compounds are structural analogs of *n*-butyl chloroformate, the AEGL-2 values for *n*-butyl chloroformate were adopted for them. Additionally, mouse RD_{50} data suggest that two chemicals have similar toxicity; the RD_{50} values from studies in male Swiss-Webster mice were 97 ppm for isobutyl chloroformate and 117 ppm for *sec*-butyl chloroformate (Carpenter 1982b). An RD_{50} was not located for *n*-butyl chloroformate.

TABLE 2-53 AEGL-2 Values for *n*-Butyl Chloroformate (and Isobutyl Chloroformate and *sec*-Butyl Chloroformate)

10 min	30 min	1 h	4 h	8 h
4.0 ppm (22 mg/m³)	2.8 ppm (33 mg/m³)	2.2 ppm (27 mg/m³)	0.57 ppm (6.7 mg/m³)	0.28 ppm (3.3 mg/m³)

7.7. Data Analysis for AEGL-3

7.7.1. Human Data Relevant to AEGL-3

No human data on *n*-butyl chloroformate, isobutyl chloroformate, or *sec*-butyl chloroformate consistent with the definition of AEGL-3 were available.

7.7.2. Animal Data Relevant to AEGL-3

Death occurred in 4/10 rats exposed to *n*-butyl chloroformate at 200 ppm for 1 h (BASF 1970g). No acute lethality data on isobutyl chloroformate or *sec*-butyl chloroformate were available.

7.7.3. Derivation of AEGL-3 Values

7.7.3.1. n-*Butyl Chloroformate*

A point-of-departure for deriving AEGL-3 values was estimated by taking one-third of the concentration of *n*-butyl chloroformate at which 4/10 rats died after a 1-h exposure (200 ppm ÷ 3 = 66.7 ppm) (BASF 1970g). The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (66.7 ppm). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on *n*-butyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (10 and 30 min) and n = 1 when extrapolating from shorter to longer durations (4 and 8 h) were used. The AEGL-3 values are also supported by results from repeated exposure studies conducted by HRC (1990); no rats died when exposed to *n*-butyl chloroformate 5.1 ppm for 6 h/day, 5 days/week for 4 weeks or at 28.4 ppm for 6 h/day for 5 days. The AEGL values for *n*-butyl chloroformate are presented in Table 2-54; the calculations are presented in Appendix B.

TABLE 2-54 AEGL-3 Values for *n*-Butyl Chloroformate (and Isobutyl Chloroformate and *sec*-Butyl Chloroformate

10 min	30 min	1 h	4 h	8 h
12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)

7.7.3.2. Isobutyl Chloroformate and sec-*Butyl Chloroformate*

Chemical-specific data were insufficient to derive of AEGL-3 values for isobutyl chloroformate and *sec*-butyl chloroformate. Because these two compounds are structural analogs of *n*-butyl chloroformate, the AEGL-3 values for *n*-butyl chloroformate were adopted for isobutyl chloroformate and *sec*-butyl chloroformate. Additionally, mouse RD_{50} data suggest that two chemicals have similar toxicity; the RD_{50} values from studies in male Swiss-Webster mice were 97 ppm for isobutyl chloroformate and 117 ppm for *sec*-butyl chloroformate (Carpenter 1982b).

7.8. Summary of AEGLs

7.8.1. AEGL Values and Toxicity End Points

Data were insufficient to derive AEGL-1 values for *n*-butyl, isobutyl, or *sec*-butyl chloroformate, so no values recommended.

For *n*-butyl chloroformate, no appropriate acute inhalation data consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approach is used to estimate a threshold for effects if a chemical has a steep concentration-response curve (NRC 2001). The AEGL-3 values for *n*-butyl chloroformate were derived on the basis of an estimated 1-h lethality threshold in rats. The AEGL values are presented in Table 2-55. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

No appropriate chemical-specific data consistent with the definition of AEGL-2 or AEGL-3 were available for isobutyl chloroformate and *sec*-butyl chloroformate. Because the two compounds are structural analogs of *n*-butyl chloroformate and appear to have similar toxicity (Carpenter 1982b), the values derived for *n*-butyl chloroformate were applied to these two chemicals.

7.8.2. Other Standards and Guidelines

No other exposure standards or guidelines for *n*-butyl, isobutyl, or *sec*-butyl chloroformate were found.

TABLE 2-55 AEGL Values for *n*-Butyl Chloroformate, Isobutyl Chloroformate, and *sec*-Butyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)
AEGL-3 (lethal)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

7.8.3. Data Adequacy and Research Needs

No human data *n*-butyl, isobutyl, or *sec*-butyl chloroformate were available, and the animal toxicity data were sparse.

8. BENZYL CHLOROFORMATE

8.1. Summary

Data on benzyl chloroformate were insufficient to derive AEGL-1 values, so no values are recommended.

No appropriate acute inhalation data on benzyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approach is used to estimate a threshold for effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on benzyl chloroformate provide evidence of a steep curve. Mortality rates in rats exposed to benzyl chloroformate for 4 h were 0/10 at 18.6 ppm and 5/10 at 84.6 ppm (BASF 1990a); clinical signs in surviving rats resolved (were reversible).

The experimental concentration of benzyl chloroformate causing no deaths in rats (18.6 ppm) after a 4-h exposure (BASF 1990a) was used as the point-of-departure for AEGL-3 values. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because

metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (18.6 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate. The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on benzyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (30 min and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for benzyl chloroformate are presented in Table 2-56.

8.2. Chemical and Physical Properties

Benzyl chloroformate hydrolyzes in water to form benzyl alcohol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of benzyl chloroformate are presented in Table 2-56.

8.3. Human Toxicity Data

8.3.1. Acute Lethality

Information on death in humans after inhalation exposure to benzyl chloroformate was not available.

8.3.2. Nonlethal Toxicity

Information on the nonlethal toxicity of benzyl chloroformate in humans was not available.

8.3.3. Developmental and Reproductive Toxicity

No human studies on the developmental or reproductive of benzyl chloroformate were available.

TABLE 2-56 AEGL Values for Benzyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	1.2 ppm (8.7 mg/m³)	1.2 ppm (8.7 mg/m³)	0.97 ppm (6.7 mg/m³)	0.63 ppm (4.3 mg/m³)	0.31 ppm (2.2 mg/m³)	One-third the AEGL-3 values
AEGL-3 (lethal)	3.7 ppm (26 mg/m³)	3.7 ppm (26 mg/m³)	2.9 ppm (20 mg/m³)	1.9 ppm (13 mg/m³)	0.93 ppm (6.5 mg/m³)	No death in rats exposed for 4 h (BASF 1990a)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 values is without adverse effects.

TABLE 2-56 Chemical and Physical Data on Benzyl Chloroformate

Parameter	Value	Reference
Common name	Benzyl chloroformate	HSDB 2014d
Synonyms	Carbonochloridic acid phenyl methyl ester; carbobenzoxy chlorode; chloroformic acid benzyl ester; benzyl carbonyl chloride	HSDB 2014d
CAS registry no.	501-53-1	HSDB 2014d
Chemical formula	$C_8H_7ClO_2$	HSDB 2014d
Molecular weight	170.60	HSDB 2014d
Physical state	Clear to pale yellow liquid	HSDB 2014d
Boiling point	152°C	HSDB 2014d
Flash point	80°C	HSDB 2014d
Vapor density	1 g/L (air = 1)	IPCS 2004
Density/specific gravity	1.22 g/cm³	HSDB 2014d
Solubility	Decomposes in water	O'Neil et al. 2001b
Vapor pressure	7 mm Hg at 85-87°C	HSDB 2014d
Conversion factors in air	1 mg/m³ = 0.14 ppm 1 ppm = 7.0 mg/m³	–

8.3.4. Genotoxicity

No genotoxicity studies on acute human exposure to benzyl chloroformate were available.

8.3.5. Carcinogenicity

No carcinogenicity studies on human exposure to benzyl chloroformate were available.

8.3.6. Summary

No reports on the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of benzyl chloroformate in humans were available.

8.4. Animal Toxicity Data

8.4.1. Acute Lethality

Groups of five male and five female SPF Wistar rats were exposed to benzyl chloroformate at 18.6 or 84.6 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (BASF 1990a). The nose-only exposures were performed in a 55-L glass-steel system; animals were restrained in tubes and their noses inserted into the chamber. Benzyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs during exposure included accelerated respiration and restlessness in the low-concentration group and irregular respiration, reddish nasal discharge, and restlessness in the high-concentration group. Clinical signs post-exposure included accelerated respiration and ruffled fur in the low-concentration group and intermittent respiration, respiratory sounds, reddish nasal discharge, aggressiveness (males only), ruffled fur, and deteriorated general state in the high-concentration group. All clinical signs resolved by day 2 post-exposure in the 18.6-ppm group and by day 5 post-exposure in survivors in the 84.6-ppm group. Body weight gain was decreased in high-concentration animals of both sexes during the first week after exposure; however, animals surviving to study termination had normal body weight. There were no gross treatment-related effects found at necropsy in animals surviving to study termination. Gross examination of animals that died during the study revealed pulmonary emphysema with hyperemia and tympanism of the intestinal tract. An approximate LC_{50} of 85 ppm was reported for male and female rats combined. Mortality data from this study are presented in Table 2-57.

Death occurred in 0/12, 1/6, and 4/6 rats exposed to an "atmosphere enriched or saturated" with benzyl chloroformate vapor (20°C) for 1, 3, or 8 h, respectively (BASF 1973). Clinical signs included vigorous escape behavior, mucous membrane irritation, and dyspnea. Pulmonary emphysema, dilation of the heart, and mottled liver were found at necropsy.

TABLE 2-57 Mortalilty in Rats Exposed to Benzyl Chloroformate for 4 Hours

	Males	Time to Death, Post-Exposure Day	Females	Time to Death, Days Post-Exposure	Males and Females
18.6 ppm	0/5	–	0/5	–	0/10
84.6 ppm	2/5	Both on day 14	3/5	1 on day of exposure; 2 on day 2	5/10

Source: BASF 1990a.

8.4.2. Nonlethal Toxicity

Information on nonlethal toxicity in animals exposed to benzyl chloroformate was not available.

8.4.3. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of benzyl chloroformate was found.

8.4.4. Genotoxicity

Benzyl chloroformate was negative in a reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of S9 mix (Allen and Panfili 1986).

8.4.5. Carcinogenicity

No information on the carcinogenicity of benzyl chloroformate was found.

8.4.6. Summary

Little animal toxicity data on benzyl chloroformate were available. An approximate 4-h rat LC_{50} of 85 ppm was reported and no deaths were reported in rats exposed at 18.6 ppm for 4 h. Benzyl chloroformate was nonmutagenic in a reverse-mutation assay. No information on the developmental or reproductive toxicity or carcinogenicity were available.

8.5. Data Analysis for AEGL-1

8.5.1. Human Data Relevant to AEGL-1

No human data on benzyl chloroformate consistent with the definition of AEGL-1 were available.

8.5.2. Animal Data Relevant to AEGL-1

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

8.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for benzyl chloroformate, so no values are recommended.

8.6. Data Analysis for AEGL-2

8.6.1. Human Data Relevant to AEGL-2

No human data on benzyl chloroformate consistent with the definition of AEGL-2 were available.

8.6.2. Animal Data Relevant to AEGL-2

No animal data on benzyl chloroformate consistent with the definition of AEGL-2 were available.

8.6.3. Derivation of AEGL-2 Values

No acute inhalation data on benzyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on benzyl chloroformate provide evidence of a steep curve; mortality rates in rats exposed for 4 h were 0/10 at 18.6 ppm and 5/10 at 84.6 ppm (BASF 1990a). Clinical signs in surviving rats resolved (were reversible). The AEGL-2 values for benzyl chloroformate are presented in Table 2-58.

8.7. Data Analysis for AEGL-3

8.7.1. Human Data Relevant to AEGL-3

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

TABLE 2-58 AEGL-2 Values for Benzyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)

8.7.2. Animal Data Relevant to AEGL-3

No deaths occurred in rats exposed to benzyl chloroformate at 18.6 ppm for 4 h, and an approximate LC_{50} of 85 ppm was reported (BASF 1990a).

8.7.3. Derivation of AEGL-3 Values

The experimental concentration of benzyl chloroformate causing no deaths in rats (18.6 ppm) after a 4-h exposure (BASF 1990a) was used as the point-of-departure for AEGL-3 values. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (18.6 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on benzyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (30 min and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for benzyl chloroformate are presented in Table 2-59; the calculations are presented in Appendix B.

TABLE 2-59 AEGL-3 Values for Benzyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm (26 mg/m^3)	3.7 ppm (26 mg/m^3)	2.9 ppm (20 mg/m^3)	1.9 ppm (13 mg/m^3)	0.93 ppm (6.5 mg/m^3)

8.8. Summary of AEGLs

8.8.1. AEGL Values and Toxicity End Points

AEGL values for benzyl chloroformate are presented in Table 2-60. Data were insufficient to derive AEGL-1 values for benzyl chloroformate, so no values are recommended. AEGL-2 values for benzyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values were based on a concentration causing no mortality in a 4-h rat study. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

8.8.2. Other Standards and Guidelines

No other exposure standards or guidelines for benzyl chloroformate were found.

8.8.3. Data Adequacy and Research Needs

No human toxicity data on benzyl chloroformate were found, and only two animal toxicity were available.

TABLE 2-60 AEGL Values for Benzyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)
AEGL-3 (lethal)	3.7 ppm (26 mg/m^3)	3.7 ppm (26 mg/m^3)	2.9 ppm (20 mg/m^3)	1.9 ppm (13 mg/m^3)	0.93 ppm (6.5 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

9. PHENYL CHLOROFORMATE

9.1. Summary

Data on phenyl chloroformate were insufficient to derive AEGL-1 values, so no values are recommended.

No appropriate acute inhalation data on phenyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approach is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on phenyl chloroformate provide evidence of a steep curve. Mortality rates in rats exposed to phenyl chloroformate for 4 h were 2/10 at 15.6 ppm, 7/10 at 44.5 ppm, and 9/10 at 74.9 ppm (Hofmann 1989; BASF 1990b); clinical signs resolved (were reversible) at 15.6 ppm (BASF 1990b).

A 4-h $BMCL_{05}$ of 3.6 ppm, calculated on the basis of lethality data from studies of rats (Hofmann 1989; BASF 1990b), was used as the lethality threshold point-of-departure for the AEGL-3 values for phenyl chloroformate. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (3.6 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate. The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on phenyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (30 min and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for phenyl chloroformate are presented in Table 2-61.

9.2. Chemical and Physical Properties

Phenyl chloroformate hydrolyzes in water to form phenol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of phenyl chloroformate are presented in Table 2-62.

TABLE 2-61 AEGL Values for Phenyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	0.24 ppm (1.5 mg/m³)	0.24 ppm (1.5 mg/m³)	0.19 ppm (1.2 mg/m³)	0.12 ppm (0.77 mg/m³)	0.06 ppm (0.38 mg/m³)	One-third the AEGL-3 values
AEGL-3 (lethal)	0.72 ppm (4.6 mg/m³)	0.72 ppm (4.6 mg/m³)	0.57 ppm (3.6 mg/m³)	0.36 ppm (2.3 mg/m³)	0.18 ppm (1.2 mg/m³)	4-h rat $BMCL_{05}$ for lethality (Hofmann 1989; BASF 1990b)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-62 Chemical and Physical Properties of Phenyl Chloroformate

Parameter	Value	Reference
Common name	Phenyl chloroformate	IPCS 2005c
Synonyms	Carbonochloridic acid phenyl ester; phenyl chlorocarbonate; phenoxycarbonyl chloride; formic acid, chloro-, phenyl ester	IPCS 2005c
CAS registry no.	1885-14-9	IPCS 2005c
Chemical formula	$C_7H_5ClO_2$	IPCS 2005c
Molecular weight	156.6	IPCS 2005c
Physical state	Colorless liquid	IPCS 2005c
Boiling point	188-189°C	IPCS 2005c
Flash point	69°C	IPCS 2005c
Vapor density	5.41 g/L (air = 1)	IPCS 2005c
Density/specific gravity	1.25 g/cm³	IPCS 2005c
Vapor pressure	0.68 mm Hg at 20°C	IPCS 2005c
Solubility	Decomposes in water	IPCS 2005c
Hydrolysis half-life	1.4 min at 19.6°C	Queen 1967
Conversion factors in air	1 mg/m³ = 0.16 ppm 1 ppm = 6.4 mg/m³	–

9.3. Human Toxicity Data

9.3.1. Acute Lethality

Information on death in humans after inhalation exposure to phenyl chloroformate was not available.

9.3.2. Nonlethal Toxicity

Information on the nonlethal toxicity of phenyl chloroformate in humans after inhalation exposure was not available.

9.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies on acute human exposure to phenyl chloroformate were not available.

9.3.4. Genotoxicity

No genotoxicity studies of acute human exposure to phenyl chloroformate were available.

9.3.5. Carcinogenicity

No carcinogenicity studies on human exposure to phenyl chloroformate were available.

9.3.6. Summary

No reports on the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of phenyl chloroformate were available.

9.4. Animal Toxicity Data

9.4.1. Acute Lethality

9.4.1.1. Rats

Groups of five male and five female SPF Wistar rats were exposed to phenyl chloroformate at 15.6, 74.9, or 159.3 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (BASF 1990b). The nose-only ex-

posures were performed in a 55-L glass and steel system; animals were restrained in tubes and their noses inserted into the chamber. Phenyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs during exposure included accelerated respiration and restlessness in the low-concentration group, irregular or intermittent respiration, eyelid closure, salivation, nasal discharge, escape attempts, and decreased pain reflex in the mid- and high-concentration animals. Clinical signs post-exposure included accelerated respiration, respiratory sounds, reddish ocular and nasal discharge, and aggressiveness in all exposure groups. In addition, squatting position, urine-stained fur, high-stepping gait, and deteriorated general state were observed in mid- and high-concentration animals, and piloerection was found only in high-concentration animals. All clinical signs in the low-concentration animals had resolved by day 3 post-exposure; clinical signs persisted through observation day 13 in the mid- and high-concentration animals. Body weight gain was decreased (compared with historical controls) in low-concentration males and females and in mid-concentration males during the first week after exposure; however, animals surviving to study termination returned to normal body weight. Body weight gain of mid-concentration females and high-concentration males and females was decreased during week 1 of the observation period; all animals in these groups died by week 2. No gross treatment-related effects were found at necropsy in low-concentration males and females surviving to study termination. One male rat in the mid-concentration group exhibited small atelectatic areas in the lung. Gross examination of animals that died during the study revealed pulmonary emphysema with hyperemia and pneumonia and necrotic foci and grey-brown lobular periphery of the liver. Four-hour LC_{50} values of 46.8, 15.8, and 28 ppm (95% CI: 16-48 ppm) were reported for male rats, female rats, male and female rats combined, respectively. $BMCL_{05}$ and BMC_{01} values were calculated (see Table 63); however, the validity of these values is questionable because study concentrations in the lower portion of the concentration-response curve were lacking. Mortality data from this study are summarized in Table 2-63.

TABLE 2-63 Mortality in Rats Exposed to Phenyl Chloroformate for 4 Hours

	Males	Females	Males and Females
15.6 ppm	0/5	2/5	2/10
74.9 ppm	4/5	5/5	9/10
159.3 ppm	5/5	5/5	10/10
LC_{50}	46.8 ppm	15.8 ppm	28 ppm
$BMCL_{05}$	7.45 ppm	0.49 ppm	3.2 ppm
BMC_{01}	45.8 ppm	8.99 ppm	41.5 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: BASF 1990b.

Groups of five male and five female SPF Wistar rats were exposed to phenyl chloroformate at 1.76, 44.5, 97, 156, or 311 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (Hofmann 1989). The nose-only exposures were performed in a 60-L glass and stainless steel exposure chamber operated under dynamic flow conditions. Phenyl chloroformate concentrations were measured every 60 min during exposure by gas chromatography. Clinical signs were observed in all treatment groups in a concentration-related manner and included irregular respiration, gasping, wheezing, staggered gait, squatting posture, ruffled fur, cyanosis, shivering, squinting, red ocular discharge, salivation, red nasal discharge, and sneezing. Additionally, foamy nasal discharge and corneal cloudiness were observed in the 156- and 311-ppm groups. Body weight gain was decreased in both sexes after exposure, but animals surviving to study termination regained initial body weight. Light beige-colored lungs with dark red foci were found at necropsy in animals surviving to study termination from the 44.5-ppm group. Gross examination of animals that died during the study revealed dark red colored lungs with red foci, foamy liquid in the lungs, dark colored liver and adrenal glands, and light-colored spleen. Four-hour LC_{50} values of 38.9 ppm and 43 ppm were calculated for males and females, respectively. $BMCL_{05}$ and BMC_{01} values were also calculated (see Table 2-64). Mortality results from this study are presented in Table 2-64.

Table 2-65 summarizes the mortality data from the BASF (1990b) and Hoechst (Hofmann 1989) studies. Because the test protocol (nose-only exposure) and mortality results are similar in the two studies, the datasets were combined to provide a more complete understanding of the concentration-response curve, especially at the lower-concentration portion of the curve. The LC_{50}, $BMCL_{05}$, and BMC_{01} values calculated on the basis of the combined data are presented in the table.

TABLE 2-64 Mortality in Rats Exposed to Phenyl Chloroformate for 4 Hours

	Males	Females	Males and Females
1.76 ppm	0/5	0/5	0/10
44.5 ppm	4/5	3/5	7/10
97 ppm	5/5	4/5	9/10
156 ppm	5/5	5/5	10/10
311 ppm	5/5	5/5	10/10
LC_{50}	38.9 ppm	43 ppm	39.6 ppm
$BMCL_{05}$	0.68 ppm	1.9 ppm	1.33 ppm
BMC_{01}	27 ppm	31 ppm	5.3 ppm must be an error correct value is 29 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Hofmann 1989.

TABLE 2-65 Mortality in Rats Exposed to Phenyl Chloroformate for 4 Hours

	Males	Females	Males and Females	Reference
1.76 ppm	0/5	0/5	0/10	Hofmann 1989
15.6 ppm	0/5	2/5	2/10	BASF 1990b
44.5 ppm	4/5	3/5	7/10	Hofmann 1989
74.9 ppm	4/5	5/5	9/10	BASF 1990b
97 ppm	5/5	4/5	9/10	Hofmann 1989
156 ppm	5/5	5/5	10/10	Hofmann 1989
159.3 ppm	5/5	5/5	10/10	BASF 1990b
311 ppm	5/5	5/5	10/10	Hofmann 1989
LC_{50}	37.6 ppm	24.2 ppm	30.0 ppm	
$BMCL_{05}$	6.3 ppm	0.82 ppm	3.6 ppm	
BMC_{01}	12.4 ppm	2.6 ppm	5.4 ppm	

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

Death occurred in 0/10 rats exposed to phenyl chloroformate at 200 ppm for 1 h (BASF 1970h). Clinical signs included mucous membrane irritation. No gross effects were found at necropsy. Smyth et al. (1969) reported that 3/6 rats died within 14 days after a 4-h exposure to phenyl chloroformate at 33 ppm. No clinical signs or additional details were provided.

Death occurred in 0/12, 4/6, 6/6, and 6/6 rats exposed to an "atmosphere enriched or saturated" with phenyl chloroformate vapor (20°C) for 3, 10, 30, or 60 min, respectively (BASF 1970h). Clinical signs included vigorous escape behavior, mucous membrane irritation, and altered respiration. Pulmonary edema was found at necropsy. The maximum exposure duration reported to result in no lethality in rats exposed to "concentrated vapor" of phenyl chloroformate was 15 min (Smyth et al. 1969). No other details of this study were available.

9.4.2. Nonlethal Toxicity

9.4.2.1. Mice

Following a 10-min fresh air control period, groups of four male Swiss-Webster mice were exposed head only to phenyl chloroformate aerosol at concentrations of 0, 4.5, 6.25, 12.5, 17.5, 25, 50, or 100 ppm for 30 min (Carpenter 1982a). The mice were then removed to fresh air for a 10-min recovery period, and respiratory rates were monitored continuously during both the exposure and recovery periods. Undiluted phenyl chloroformate was delivered to a Pitt No. 1 aerosol generator via a 2-cc syringe, driven by a pump at a

known rate. Aerosol was directed into a 9-L stainless steel chamber which was continuously evacuated at a rate of 20 L/min. An RD_{50} of 19.5 ppm was calculated. Results of this study are summarized in Table 2-66.

9.4.3. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of phenyl chloroformate was available.

9.4.4. Genotoxicity

No information on the genotoxicity of phenyl chloroformate was available.

9.4.5. Carcinogenicity

No information on the carcinogenicity of phenyl chloroformate was available.

9.4.6. Summary

Little animal data on phenyl chloroformate are available. Two 4-h inhalation studies with rats were available, and LC_{50} values of 28 ppm (BASF 1990b) and 39.6 ppm (Hofmann 1989) were estimated. These values are consistent with data reported by Smyth et al. (1969), in which 3/6 rats died after a 4-h exposure to phenyl chloroformate at 44 ppm. No mortality occurred in rats exposed at 200 ppm for 1 h (BASF 1970h). A 30-min RD_{50} of 19.5 ppm was reported for male Swiss-Webster mice (Carpenter 1982a). No animal data on the developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of phenyl chloroformate were available.

9.5. Data Analysis for AEGL-1

9.5.1. Human Data Relevant to AEGL-1

No human data on phenyl chloroformate consistent with the definition of AEGL-1 were available.

9.5.2. Animal Data Relevant to AEGL-1

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

TABLE 2-66 Effects in Male Swiss-Webster Mice Exposed to Phenyl Chloroformate for 30 Minutes

Concentration, ppm	Respiratory Rates, Control/Exposed	Decrease in Respiratory Rate, %	Mortality Within 24 h
4.5	285/240	16.1	0/4
6.25	250/180	26.0	0/4
12.5	265/145	45.3	0/4
17.5	265/140	47.2	0/4
25	250/90	64.0	0/4
50	200/70	65.0	0/4
100	245/50	79.6	0/4

Source: Carpenter 1982a.

9.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for phenyl chloroformate, so no values are recommended.

9.6. Data Analysis for AEGL-2

9.6.1. Human Data Relevant to AEGL-2

No human data on phenyl chloroformate consistent with the definition of AEGL-2 were available.

9.6.2. Animal Data Relevant to AEGL-2

No animal data on phenyl chloroformate consistent with the definition of AEGL-2 were available.

9.6.3. Derivation of AEGL-2 Values

No acute inhalation data on phenyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approach is used to estimate a threshold for effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on phenyl chloroformate provide evidence of a steep curve; mortality rates in rats exposed for 4 h were 2/10 at 15.6 ppm, 7/10 at 44.5 ppm, and 9/10 at 74.9 ppm (Hofmann 1989; BASF 1990b); clinical signs resolved (were reversible) at 15.6 ppm (BASF 1990b). AEGL-2 values for phenyl chloroformate are presented in Table 2-67.

TABLE 2-67 AEGL-2 Values for Phenyl Chloroformate

10 min	30 min	1 h	4 h	8 h
0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.06 ppm
(1.5 mg/m^3)	(1.5 mg/m^3)	(1.2 mg/m^3)	(0.77 mg/m^3)	(0.38 mg/m^3)

9.7. Data Analysis for AEGL-3

9.7.1. Human Data Relevant to AEGL-3

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

9.7.2. Animal Data Relevant to AEGL-3

Four-hour LC_{50} values of 28 ppm (BASF 1990b) and 39.6 ppm (Hofmann 1989) have been reported for male and female rats. When the data were combined, a 4-h LC_{50} value of 30.00 ppm and $BMCL_{05}$ value of 3.6 ppm were estimated.

9.7.3. Derivation of AEGL-3 Values

The 4-h rat $BMCL_{05}$ of 3.6 ppm was used as the point-of-departure for calculating AEGL-3 values for phenyl chloroformate. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (3.6 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on phenyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of

n = 3 when extrapolating from longer to shorter durations (30 min and 1 h) and n = 1 when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for phenyl chloroformate are presented in Table 2-68; the calculations are presented in Appendix B.

9.8. Summary of AEGLs

9.8.1. AEGL Values and Toxicity End Points

Data were insufficient to derive AEGL-1 values for phenyl chloroformate, so no values are recommended. AEGL-2 values for phenyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for phenyl chloroformate were based on a 4-h $BMCL_{05}$ value for lethality in rats. The AEGL values for phenyl chloroformate are presented in Table 2-69. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

9.8.2. Other Standards and Guidelines

No other exposure standards or guidelines for phenyl chloroformate were available.

TABLE 2-68 AEGL-3 Values for Phenyl Chloroformate

10 min	30 min	1 h	4 h	8 h
0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm
(4.6 mg/m^3)	(4.6 mg/m^3)	(3.6 mg/m^3)	(2.3 mg/m^3)	(1.2 mg/m^3)

TABLE 2-69 AEGL Values for Phenyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.06 ppm (0.38 mg/m^3)
AEGL-3 (lethal)	0.72 ppm (4.6 mg/m^3)	0.72 ppm (4.6 mg/m^3)	0.57 ppm (3.6 mg/m^3)	0.36 ppm (2.3 mg/m^3)	0.18 ppm (1.2 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

9.8.3. Data Quality and Research Needs

No human toxicity data on phenyl chloroformate were available. The only animal toxicity data were from acute lethality studies in rats and an RD_{50} study in male Swiss Webster mice.

10. 2-ETHYLHEXYL CHLOROFORMATE

10.1. Summary

Data on 2-ethylhexyl chloroformate were insufficient to derive AEGL-1 values, so no values are recommended.

No appropriate acute inhalation data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on 2-ethylhexyl chloroformate provide evidence of a steep curve; the mortality rate in rats exposed for 4 h was 0/20 at 22.8 ppm, 5/20 at 26.6 ppm, 9/20 at 34.3 ppm, and 20/20 at 46.9 ppm (BASF 1985).

A 4-h $BMCL_{05}$ of 18.1 ppm, calculated on the basis of lethality data from a study of male rats (BASF 1985), was used as the lethality threshold point-of-departure for deriving AEGL-3 values for 2-ethylhexyl chloroformate. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (18.1 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on 3-ethylhexyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (30 min and 1 h)

and n = 1 when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for 2-ethylhexyl chloroformate are presented in Table 2-70.

10.2. Chemical and Physical Properties

2-Ethylhexyl chloroformate hydrolyzes in water to form 2-ethyl-1-hexanol, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of 2-ethylhexyl chloroformate are presented in Table 2-71.

10.3. Human Toxicity Data

10.3.1. Acute Lethality

Information on death in humans after inhalation exposure to 2-ethylhexyl chloroformate was not available.

10.3.2. Nonlethal Toxicity

Information on the nonlethal toxicity of 2-ethylhexyl chloroformate in humans after inhalation exposure was not available.

10.3.4. Developmental and Reproductive Toxicity

Developmental and reproductive studies of acute human exposure to 2-ethylhexyl chloroformate were not available.

TABLE 2-70 AEGL Values for 2-Ethylhexyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR	Insufficient data
AEGL-2 (disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)	One-third the AEGL-3 values
AEGL-3 (lethal)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)	Lethality, 4-h rat BMCL$_{05}$ (BASF 1985)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-71 Chemical and Physical Properties of 2-Ethylhexyl Chloroformate

Parameter	Value	Reference
Common name	2-Ethylhexyl chloroformate	Kreutzberger 2001
Synonyms	Chloroformic acid 2-ethylhexyl ester; carbonochloridic acid, 2-ethylhexyl ester; 2-ethylhexyl chlorocarbonate; formic acid, chloro-, 2-ethylhexyl ester	Chemical Book 2016
CAS registry no.	24468-13-1	Kreutzberger 2001
Chemical formula	$C_9H_{17}ClO_2$	Kreutzberger 2001
Molecular weight	192.71	Kreutzberger 2001
Physical state	Clear, colorless liquid	RTECS 2005
Boiling point	208°C	Kreutzberger 2001
Flash point	NA	Kreutzberger 2001
Vapor density	>1 g/L (air = 1)	RTECS 2005
Density/specific gravity	0.9914 g/cm^3	Kreutzberger 2001
Solubility	Decomposes in water	RTECS 2005
Vapor pressure	1 mm Hg at 45°C	RTECS 2005
Conversion factors in air	1 mg/m^3 = 0.13 ppm 1 ppm = 7.9 mg/m^3	–

10.3.4. Genotoxicity

Genotoxicity studies of acute human exposure to 2-ethylhexyl chloroformate were not available.

10.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to 2-ethylhexyl chloroformate were not available.

10.3.6. Summary

No reports on the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of 2-ethylhexyl chloroformate in humans were available.

10.4. Animal Toxicity Data

10.4.1. Acute Lethality

10.4.1.1. Rats

Groups of 10 male and 10 female SPF Wistar rats were exposed to 2-ethylhexyl chloroformate at concentrations of 22.8, 26.6, 34.3, or 46.9 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (BASF 1985). The whole body exposures were performed in a 200-L glass and steel inhalation chamber, and 2-ethylhexyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs during exposure included closed palpebral fissure, red ocular and nasal discharge, irregular respiration, restlessness, squatting posture, and ruffled fur in the 26.6-, 34.3-, and 46.9-ppm groups. Clinical signs during the post-exposure observation period included irregular respiration, respiratory sounds, reddish nasal discharge, and staggering in the 46.9-ppm group. In addition, slight apathy was observed in the 34.3- and 46.9-ppm groups, and squatting posture and ruffled fur was observed in the 26.6-, 34.3-, and 46.9-ppm groups. No clinical signs were observed during or after exposure in the 22.8-ppm group. No gross treatment-related effects were found at necropsy in animals surviving to study termination. Gross examination of animals that died during the study revealed venous congestion and pulmonary emphysema with pneumonia. A 4-h LC_{50} value of 33.9 ppm was reported for male and female rats. Male rats appear to be more sensitive to 2-ethylhexyl chloroformate than female rats, both with regard to lethality incidence and time of death. $BMCL_{05}$ and BMC_{01} values were calculated and are presented in Table 2-72 (see Appendix A for the calculations), along with the mortality data from this study.

In a more recent acute lethality study, groups of five male and five female Crl:CD(SD)IGS BR rats were exposed (whole body) to 2-ethylhexyl chloroformate at concentrations of 23, 53, 96, 282, or 488 ppm (analytic concentrations) for 4 h (WIL Laboratories, Inc. 2002). Vapors were generated via evaporation of liquid flowing over glass beads and mixed with dilution air in a 130-L glass and steel inhalation chamber. Chamber concentrations were analyzed by gas chromatography. Mortality, clinical signs, and body weights were monitored for 14 days, and gross necropsy was performed on all animals. All rats died during exposure at the two highest concentrations; 7/10 and 9/10 died within the first day of exposure at 53 and 96 ppm, respectively. No deaths occurred at 23 ppm. Clinical signs observed during exposure included gasping at 282 and 488 ppm and increased respiration at 96 ppm. Immediately after exposure, increased respiration rate, clear discharge around the face, and yellow material around the urogenital area were observed in some animals in all exposure groups, along with red material around the nose in the 96-ppm group. These signs persisted during the post-exposure observation period; in addition, some animals exhibited decreased defecation and urination, hypoactivity, and

hypothermia. Rats exposed at 23 ppm appeared normal by day 3. Body weight losses were found up to 3 days after exposure in the 23-ppm group and survivors exposed at 53 and 96 ppm; the body weights of all surviving animals exceeded their pre-exposure measurements at 14 days post-exposure. Gross necropsy findings in animals that died during the study included dark red and/or mottled lungs and ocular opacity. In addition, females in the 23-ppm group had dark red (1/5) or mottled lungs (2/5) at scheduled termination. The investigators estimated LC_{50}s of 45 and 55 ppm for males and females, respectively, and a combined LC_{50} of 48 ppm. $BMCL_{05}$ and BMC_{01} values were calculated and are presented in Table 2-73 (see Appendix A for the calculations), along with the mortality data from this study.

Death occurred in 0/12, 3/6, 6/6, 3/3, and 6/6 rats exposed to an "atmosphere enriched or saturated" with 2-ethylhexyl chloroformate vapor (20°C) for 3 min, 10 min, 30 min, 1 h, and 2 h, respectively (BASF 1968d). The approximate concentration of 2-ethylhexyl chloroformate was 270 ppm, and the concentration of the contaminant, phosegene, was estimated to be 40 ppm. Clinical signs included mucous membrane irritation and difficulty breathing. Pulmonary edema was found at necropsy.

10.4.2. Nonlethal Toxicity

No information on the nonlethal toxicity of 2-ethylhexyl chloroformate was found.

TABLE 2-72 Mortality in Wistar Rats Exposed to 2-Ethylhexyl Chloroformate for 4 Hours

	Males	Time to Death	Females	Time to Death	Males and Females
22.8 ppm	0/10	–	0/10	–	0/20
26.6 ppm	4/10	2 on day of exposure 2 on day 1 post-exposure	1/10	Day 14 post-exposure	5/20
34.3 ppm	7/10	2 on day of exposure 5 on day 1 post-exposure	2/10	Day 1 post-exposure	9/20
46.9 ppm	10/10	8 on day of exposure 2 on day 1 post-exposure	10/10	3 on day of exposure 7 on day 1 post-exposure	20/20
LC_{50}	29.9 ppm		36.3 ppm		33.9 ppm
$BMCL_{05}$	18.1 ppm		26.0 ppm		20.1 ppm
BMC_{01}	19.7 ppm		31.9 ppm		21.1 ppm

Abbreviations: $BMCL_{01}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: BASF 1985.

TABLE 2-73 Mortality in Crl:CD(SD)IGS BR Rats Exposed to 2-Ethylhexyl Chloroformate for 4 Hours

Concentration	Males	Time to Death	Females	Time to Death	Combined Males and Females
23 ppm	0/5	–	0/5	–	0/10
53 ppm	4/5	3 during exposure 1 at day 1 of exposure	3/5	Day 1 of exposure	7/10
96 ppm	5/5	During exposure	4/5	1 during exposure 3 on day 1 of exposure	9/10
282 ppm	5/5	During exposure	5/5	During exposure	10/10
488 ppm	5/5	During exposure	5/5	During exposure	10/10
LC_{50} (95% CI)	45 ppm (35-57 ppm)		55 ppm (29-102 ppm)		48 ppm (33-70 ppm)
$BMCL_{05}$	14.6 ppm		7.9 ppm		13.7 ppm
BMC_{01}	36.1 ppm		17 ppm		18.7 ppm

Abbreviations: $BMCL_{01}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: WIL Laboratories, Inc. 2002.

10.4.3. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of 2-ethylhexyl chloroformate was found.

10.4.4. Genotoxicity

No information on the genotoxicity of 2-ethylhexyl chloroformate was found.

10.4.5. Carcinogenicity

No information on the carcinogenicity of 2-ethylhexyl chloroformate was found.

10.4.6. Summary

Only three mortality studies of 2-ethylhexyl chloroformate were available. One 4-h rat inhalation study reported an LC_{50} value of 33.9 ppm for male and female rats (BASF 1985). No animal data on the developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of 2-ethylhexyl chloroformate were available.

10.5. Data Analysis for AEGL-1

10.5.1. Human Data Relevant to AEGL-1

No human data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-1 were available.

10.5.2. Animal Data Relevant to AEGL-1

No animal data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-1 were available.

10.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for 2-ethylhexyl chloroformate, so no values are recommended.

10.6. Data Analysis for AEGL-2

10.6.1. Human Data Relevant to AEGL-2

No human data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-2 were available.

10.6.2. Animal Data Relevant to AEGL-2

No animal data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-2 were available.

10.6.3. Derivation of AEGL-2 Values

No acute inhalation data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on 2-ethylhexyl chloroformate provide evidence of a steep curve; mortality rates in rats exposed for 4 h were 0/20 at 22.8 ppm, 5/20 at 26.6 ppm, 9/20 at 34.3 ppm, and 20/20 at 46.9 ppm (BASF 1985). The AEGL-2 values for 2-ethylhexyl chloroformate are presented in Table 2-74.

TABLE 2-74 AEGL-2 Values for 2-Ethylhexyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm
(9.5 mg/m^3)	(9.5 mg/m^3)	(7.7 mg/m^3)	(4.7 mg/m^3)	(2.4 mg/m^3)

10.7. Data Analysis for AEGL-3

10.7.1. Human Data Relevant to AEGL-3

No human data on 2-ethylhexyl chloroformate consistent with the definition of AEGL-3 were available.

10.7.2. Animal Data Relevant to AEGL-3

Two lethality studies of rats exposed to 2-ethylhexyl chloroformate for 4 h were available (BASF 1985; WIL Laboratories, Inc. 2002). In the study with Wistar rats (BASF 1985), LC$_{50}$ values of 29.9, 36.3, and 33.9 ppm were calculated for males, females, and males and females combined, respectively. Corresponding BMCL$_{05}$ values of 18.1, 26.0, and 20.1 ppm were calculated. In the study with Crl:CD(SD)IGS BR rats (WIL Laboratories, Inc. 2002), LC$_{50}$ values were 45, 55, and 48 ppm for males, females, and males and females combined, respectively. Corresponding BMCL$_{05}$ values of 14.6, 7.9, and 13.7 ppm were calculated.

10.7.3. Derivation of AEGL-3 Values

The BASF (1985) study provides a more robust basis for the AEGL-3 values, because it tested lower concentrations of 2-ethylhexyl chloroformate, identified lower LC$_{50}$ values, and tested a larger number of animals then the WIL Laboratories, Inc. (2002) study. Thus, although the BMCL$_{05}$ values from the WIL Laboratories, Inc. (2002) study were lower than those from BASF (1985) study, the lower values appear to be due to uncertainty rather than greater vulnerability of the strain used in that study. Because the male rats appeared to be slightly more susceptible than females in the BASF (1985) study, the 4-h male rat BMCL$_{05}$ of 18.1 ppm was used as the point-of-departure for the AEGL-3 values. The effects of the chloroformates result from the direct-acting corrosive effects on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are

unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Thus, interspecies and intraspecies uncertainty factors of 3 would represent the potential for any toxicodynamic variability, resulting in a total uncertainty factor of 10 applied to the estimated threshold for lethality (3.6 ppm). Use of these factors is consistent with the ones applied in calculating AEGL-3 values for the structural analogs, methyl chloroformate (see Section 2.7.3), isopropyl chloroformate (see Section 5.7.3), and *n*-butyl chloroformate (see Section 6.7.3). The AEGL values for those analogs were considered protective when compared with chemical-specific, repeated-exposure data. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on phenyl chloroformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (30 min and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for 2-ethylhexyl chloroformate are presented in Table 2-75; the calculations are presented in Appendix B.

10.8. Summary of AEGLs

10.8.1. AEGL Values and Toxicity End Points

Data were insufficient to derive AEGL-1 values for 2-ethylhexyl chloroformate, so no values are recommended. AEGL-2 values for 2-ethylhexyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for 2-ethylhexyl chloroformate were based on a 4-h rat $BMCL_{05}$ value for lethality. The AEGL values for 2-ethylhexyl chloroformate are presented in Table 2-76. A derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

10.8.2. Comparison with Other Standards and Guidelines

No other exposure standards or guidelines for 2-ethylhexyl chloroformate were found.

10.8.3. Data Quality and Research Needs

No human toxicity data on 2-ethylhexyl chloroformate were available. The only animal toxicity data were from acute lethality studies in rats.

TABLE 2-75 AEGL-3 Values for 2-Ethylhexyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)

TABLE 2-76 AEGL Values for 2-Ethylhexyl Chloroformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)
AEGL-3 (lethal)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

11. ETHYL CHLOROTHIOFORMATE

11.1. Summary

Data on ethyl chlorothioformate were insufficient to derive AEGL-1 values, so no values are recommended.

No acute inhalation data on ethyl chlorothioformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on ethyl chlorothioformate provide evidence of a steep curve; the mortality rate in rats exposed for 4 h was 4/20 at 33 ppm, 14/20 at 59 ppm, and 20/20 at 65 ppm. Based on these results, the LC_{50} for a 4-h exposure to ethyl chlorothiochloroformate was calculated to be 45 ppm (Stauffer Chemical Company 1983).

An estimated 4-h lethality threshold based on taking 1/3 of the estimated 4-hr LC_{50} was 15 ppm in rats (Stauffer Chemical Company 1983) was used as the point-of-departure for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies uncertainty factor of 3 was applied because ethyl chlorothioformate and other chloroformates are respiratory irritants and pharmacodynamic variability between species is probably minimal (within a factor of 3). An intraspecies uncertainty factor of 3 was applied was used because the observed LC_{50}s for ethyl chlorothioformate and ethyl chloroformate were similar. Thus, the total uncertainty factor was 30. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on ethyl chlorothioformate were

insufficient for calculating an empirical value for the exponent n, so default values of n = 3 when extrapolating from longer to shorter durations (30 min and 1 h) and n = 1 when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for ethyl chlorothioformate are presented in Table 2-77.

11.2. Chemical and Physical Properties

Ethyl chlorothioformate hydrolyzes in water to form ethyl mercaptan, carbon dioxide, and hydrogen chloride. Selected chemical and physical properties of ethyl chlorothioformate are presented in Table 2-78.

11.3. Human Toxicity Data

11.3.1. Acute Lethality

No data on the lethal toxicity of ethyl chlorothioformate in humans were found.

11.3.2. Nonlethal Toxicity

No information about the nonlethal toxicity of ethyl chlorothioformate in humans was found.

TABLE 2-77 AEGL Values for Ethyl Chlorothioformate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]	Insufficient data
AEGL-2 (disabling)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.80 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)	One-third of the AEGL-3 values
AEGL-3 (lethal)	3.0 ppm (15 mg/m^3)	3.0 ppm (15 mg/m^3)	2.4 ppm (12 mg/m^3)	1.5 ppm (7.6 mg/m^3)	0.75 ppm (3.8 mg/m^3)	Estimated 4-h lethality threshold in rats (Stauffer Chemical Company 1983)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 2-78 Chemical and Physical Properties of Ethyl Chlorothioformate

Parameter	Value	Reference
Common name	Ethyl chlorothioformate	HSDB 2003b
Synonyms	Ethylthiol chloroformate; ethylthiocarbonyl chloride; formin acid, chlorothio-, S-ethyl ester	HSDB 2003b
CAS registry no.	2941-64-2	HSDB 2003b
Chemical formula	$C_3H_5ClO\text{-}S$	HSDB 2003b
Molecular weight	124.59	HSDB 2003b
Physical state	Amber liquid	Stauffer Chemical Company 1983
Freezing point	-60°C	Stauffer Chemical Company 1983
Boiling point	132°C	Stauffer Chemical Company 1983
Flash point	51.7°C	Stauffer Chemical Company 1983
Density/specific gravity	1.19 g/cm^3	Stauffer Chemical Company 1983
Solubility	Decomposes in water	Stauffer Chemical Company 1983
Vapor pressure	8.3 mm Hg at 21°C	Stauffer Chemical Company 1983
Hydrolysis half-life	4.3 min at 4.6°C	Queen et al. 1970
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ $1 \text{ ppm} = 5.1 \text{ mg/m}^3$	–

11.3.3. Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies of acute human exposure to ethyl chlorothioformate were available.

11.3.4. Genotoxicity

No genotoxicity studies of acute human exposure to ethyl chlorothioformate were available.

11.3.5. Carcinogenicity

No carcinogenicity studies of human exposure to ethyl chlorothioformate were available.

11.3.6. Summary

No reports on the lethal toxicity, nonlethal toxicity, developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity of ethyl chlorothioformate in humans were available.

11.4. Animal Toxicity Data

11.4.1. Acute Lethality

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to ethyl chlorothioformate at 263 ppm for 1 h (Stauffer Chemical Company 1982). Animals were exposed in 447-L stainless-steel and glass chambers. Ethyl chlorothioformate was aerosolized using a fritted bubbler and was delivered through 1-inch flexible stainless-steel tubing to the chamber inlet. Chamber concentrations were measured coulimetrically after 15, 30, and 45 min. Lacrimation, salivation, and closed eyes were observed in all rats within 15 min of exposure. Prostration and gasping were observed in a majority of rats within 30 min of exposure. All rats died within 24 h of exposure; findings at necropsy included red mottling of the lungs (20/20), frothiness of the trachea (17/20), moist, spongy lungs (8/20), and wetness around the nares (20/20).

In another study (Stauffer Chemical Company 1983), groups of 10 male and 10 female Sprague-Dawley rats were exposed to ethyl chlorothioformate at 0, 33, 59, 65, 69, or 124 ppm for 4 h, followed by a 14-day observation period. The exposure protocol was similar to that described in the Stauffer Chemical Company (1982) study, except that chamber concentrations were measured hourly during the 4-h exposure period. Lethargy, lacrimation, excessive saliva-tion, and breathing difficulty were observed in all treated animals. Clinical signs included rough coats, rhinorrhea, chromorhinorrhea, salivation, dyspnea, rales, dacryrrhea, chromodachrrhea, and paleness. Rats that survived became dehy-drated and some became emaciated as the 14-day observation period progressed. Treatment-related necropsy findings included discolored lungs, respiratory-tract necrosis, basal-cell hyperplasia, vascular congestion, and alveolar emphysema. Myocardial degeneration, nephrosis, hepatic necrosis, adrenal necrosis, splenic and lymphoid necrosis, and lymphoid-cell depletion also were found. Deaths occurring during or shortly after exposure were attributed to respiratory-tract corrosion, whereas deaths occurring later were attributed to a combination of local corrosive effects and systemic effects. LC_{50} values of 51 and 41 ppm were calculated for male and female rats, respectively; the LC_{50} was 45 ppm when the sexes were combined. Data from this study are presented in Table 2-79.

11.4.2. Nonlethal Toxicity

No data on the nonlethal toxicity of ethyl chlorothioformate were found.

11.4.3. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of ethyl chlorothioformate were found.

TABLE 2-79 Mortality in Rats Exposed to Ethyl Chlorothioformate for 4 Hours

	Males	Time to Death, Post-Exposure Day (no. rats)	Females	Time to Death, Post-Exposure Day (no. rats)	Males and Females
33 ppm	2/10	Day 1 (2)	2/10	Day 1 (1) Between days 7-14 (1)	4/20
59 ppm	6/10	Day 1 (5) Day 2 (1)	8/10	Day 1 (3) Day 2 (3) Day 3 (1) Between days 7-14 (1)	14/20
65 ppm	10/10	Day 1 (8) Day 2 (2)	10/10	Day 1 (6) Day 2 (2) Day 3 (2)	20/20
69 ppm	8/10	Day of exposure (1) Day 1 (7)	10/10	Day 1 (6) Day 2 (4)	18/20
124 ppm	10/10	Day of exposure (6) Day 1 (4)	10/10	Day of exposure (4) Day 1 (6)	20/20
LC_{50}	51 ppm		41 ppm		45 ppm

Source: Stauffer Chemical Company 1983.

11.4.4. Genotoxicity

Ethyl chlorothioformate was negative in a bacterial reverse-mutation assay in *S. typhimurium* strains TA97, TA98, TA1535, and TA1537 when tested both with and without metabolic activation (Zeiger et al. 1988).

11.4.5. Carcinogenicity

No information on the carcinogenicity of ethyl chlorothioformate was found.

11.4.6. Summary

Four-hour LC_{50} values of 51 ppm and 41 ppm were calculated for male and female rats, respectively; the LC_{50} value was 45 ppm when the sexes were combined. Signs of toxicity were consistent with severe respiratory-tract irritation and corrosion, and necropsy findings suggest that ethyl chlorothioformate may cause both portal-of-entry and systemic effects (Stauffer Chemical Company 1983). Ethyl chlorothioformate was negative in an Ames assay, and no animal data on the nonlethal toxicity, developmental toxicity, reproductive toxicity, or carcinogenicity of ethyl chlorothioformate were available.

11.5. Data Analysis for AEGL-1

11.5.1. Human Data Relevant to AEGL-1

No human data on ethyl chlorothioformate consistent with the definition of AEGL-1 were available.

11.5.2. Animal Data Relevant to AEGL-1

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

11.5.3. Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for ethyl chlorothioformate, so no values are recommended.

11.6. Data Analysis for AEGL-2

11.6.1. Human Data Relevant to AEGL-2

No human data on ethyl chlorothioformate consistent with the definition of AEGL-2 were available.

11.6.2. Animal Data Relevant to AEGL-2

No animal data on ethyl chlorothioformate consistent with the definition of AEGL-2 were available.

11.6.3. Derivation of AEGL-2 Values

No acute inhalation data on ethyl chlorothioformate consistent with the definition of AEGL-2 were available. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. That approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on ethyl chlorothioformate provide evidence of a steep curve; mortality rates in rats exposed for 4 h were 4/20 at 33 ppm, 14/20 at 59 ppm, and 20/20 at 65 ppm (Stauffer Chemical Company 1983). The AEGL-2 values for ethyl chlorothioformate are presented in Table 2-80.

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11.7. Data Analysis for AEGL-3

11.7.1. Human Data Relevant to AEGL-3

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

11.7.2. Animal Data Relevant to AEGL-3

The following 4-h LC_{50} values for ethyl chlorothioformate were estimated from lethality studies of rats (Stauffer Chemical Company 1983) 51 ppm for males, 41 ppm for females, and 45 ppm for males and females combined.

11.7.3. Derivation of AEGL-3 Values

A 4-h lethality threshold in rats of 15 ppm was estimated by dividing the LC_{50} of 45 ppm by 3 (Stauffer Chemical Company 1983). An interspecies uncertainty factor of 3 was applied because ethyl chlorothioformate and other chloroformates are respiratory irritants and pharmacodynamic variability between species is probably minimal (within a factor of 3). An intraspecies uncertainty factor of 3 (for a total uncertainty factor of 10) was used because the observed LC_{50}s for ethyl chlorothioformate and ethyl chloroformate were similar. Thus, the total uncertainty factor was 30. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on ethyl chlorothioformate were insufficient for calculating an empirical value for the exponent n, so default values of $n = 3$ when extrapolating from longer to shorter durations (30 min and 1 h) and $n = 1$ when extrapolating from shorter to longer durations (8 h) were used. The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value. The AEGL values for ethyl chlorothioformate are presented in Table 2-81; the calculations are presented in Appendix B.

TABLE 2-80 AEGL-2 Values for Ethyl Chlorothioformate

10 min	30 min	1 h	4 h	8 h
1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.80 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)

TABLE 2-81 AEGL-3 Values for Ethyl Chlorothioformate

10 min	30 min	1 h	4 h	8 h
3.0 ppm (15 mg/m^3)	3.0 ppm (15 mg/m^3)	2.4 ppm (12 mg/m^3)	1.5 ppm (7.6 mg/m^3)	0.75 ppm (3.8 mg/m^3)

11.8. Summary of AEGLs

11.8.1. AEGL Values and Toxicity End Points

Data were insufficient for deriving AEGL-1 values for ethyl chlorothioformate. AEGL-2 values were obtained by dividing the AEGL-3 values by 3, and the AEGL-3 values were based on an estimated 4-h lethality threshold in rats. The AEGL values for ethyl chlorothioformate are presented in Table 2-82; a derivation summary and category plot of the AEGL values and toxicity data are presented in Appendixes C and D, respectively.

11.8.2. Other Standards and Guidelines

No other exposure standards or guidelines for ethyl chlorothioformate were available.

11.8.3. Data Adequacy and Research Needs

No human toxicity data on ethyl chlorothioformate were available. The only animal toxicity data were from lethality studies in rats.

TABLE 2-82 AEGL Values for Ethyl Chlorothioformate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-2 (disabling)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.80 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)
AEGL-3 (lethal)	3.0 ppm (15 mg/m^3)	3.0 ppm (15 mg/m^3)	2.4 ppm (12 mg/m^3)	1.5 ppm (7.6 mg/m^3)	0.75 ppm (3.8 mg/m^3)

[a]Treatment of people exposed to chloroformates should consider that pulmonary edema frequently occurs, but its symptoms may not manifest for several hours after exposure and may be aggravated by physical exertion.
[b]NR, not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

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Appendix A

Biographical Information Committee on Acute Exposure Guidelines for Chloroformates

GEORGE RUSCH is a Senior Scientist at Risk Assessment and Toxicology Services. He is an expert on the toxicology of fluorocarbon refrigerants, foam blowing agents and solvents and he has worked with the U.S. Environmental Protection Agency (EPA) and the European Chemical Authority in the approval and registration of new chemical products. He previously served as the chair of the EPA's National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances and has served on the following National Research Council committees: the Committee on Toxicology; the Committee on Assessment of Fire Suppression Substitutes and Alternatives to Halon; and the Subcommittee on Iodotrifluoromethane: Toxicological Review. He has served on other advisory boards for the EPA and Department of Energy and he is the founding chair and current member of the American Industrial Hygiene Association's Emergency Response Planning Committee. He is currently an elected fellow of the Academy of Toxicological Sciences and a fellow of the American Industrial Hygiene Association. He received his PhD from Adelphi University.

RICHARD A. BECKER is a Senior Toxicologist at the American Chemistry Council (ACC). He leads ACC's Science and Research Division, and directs ACC's Long-Range Research Initiative, an innovative research program designed to modernize and improve chemical safety assessments. From 1999 to 2014 he served in ACC's Regulatory and Technical Affairs Department focusing on emerging health risk science issues, including advanced molecular screening methods in toxicity evaluation and risk assessment, human biomonitoring, sensitive subpopulations, endocrine screening and testing and alternative test methods. Previously, he held technical and scientific management positions in California state government. He received the Arnold Lehman Award from the Society of Toxicology in 2015 in recognition of his contributions to risk assessment and the regulation of chemicals. He is a diplomate of the American Board of Toxicology. Dr. Becker currently supports the Academies as a member of the Board on Environmental Studies and Toxicology. Dr. Becker received his PhD in pharmacology and toxicology from the University of California, Irvine.

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JACOB MCDONALD is Vice President of Applied Sciences at the Lovelace Respiratory Research Institute. He oversees contract research at the institute, and conducts research that bridges his education and experience in analytical chemistry, aerosol science, and toxicology. His work spans the study of complex mixtures, respiratory drug delivery, animal model development, and metabolism in mammals. He has more than 120 peer-reviewed publications and 2 book chapters. Dr. McDonald served on the National Research Council Committee to Review the Army's Enhanced Particulate Matter Surveillance Project Report and the Institute of Medicine Committee on the Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan. He earned a PhD in environmental chemistry and toxicology from the University of Nevada.

ROBERTA GRANT is a retired toxicologist at the Texas Commission on Environmental Quality where she managed staff conducting toxicological evaluations of air permit applications, monitoring projects, risk assessments, and toxicity assessments to develop acute and chronic inhalation toxicity factors. Dr. Grant has developed inhalation acute and chronic toxicity factors for several chemicals: 1,3-butadiene, three butene isomers, methacrolein, 4-vinylcyclohexene, crotonaldehyde, pentene isomers, crystalline silica, nickel compounds, and arsenic compounds. She has served on the Environmental Protection Agency's National Advisory Committee for Developing Acute Exposure Guideline Levels and on three Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panels. Dr. Grant served on the National Research Council Committee to Review California's Risk Assessment Process for Pesticides. Dr. Grant received a PhD in toxicology from the College of Pharmacy, The University of Texas at Austin.

NU-MAY RUBY REED is a retired toxicologist with the California Environmental Protection Agency (Cal/EPA) Department of Pesticide Regulation, where she led risk-assessment issues in the Health Assessment Section. Her research interests are in evaluating health risks and developing risk assessment guidelines for pesticides. She has been on several Cal/EPA working groups that initiate, research, and revise risk-assessment guidelines and policies. Dr. Reed represented her department in task forces on community concerns and emergency response, risk-management guidance, and public education. She taught health risk assessment at the University of California, Davis, for more than 15 years. Dr. Reed served on the National Research Council Subcommittee on Fluoride in Drinking Water, on the Standing Committee on Risk Analysis Issues and Reviews, and on the Committee for Acute Exposure Guideline Levels, and on numerous Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panels. She received her PhD from the University of California, Davis, and is a diplomate of the American Board of Toxicology.

Appendix B

Benchmark Concentration Calculations for Selected Chloroformates

Benchmark Concentration Calculation for Methyl Chloroformate

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 = Mean
Independent variable = Dose
Slope parameter is not restricted

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -20.4973
Slope = 5.16963

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept
Intercept	1

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

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Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	71.9357	0.449759
Slope	18	NA

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	5.00402	–	–	–
Fitted model	5.00722	0.00639048	3	0.9999
Reduced model	27.5256	45.0431	3	<0.0001

AIC: 12.0144.

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
35.0000	0.0000	0.000	0	10	1.008e-007
45.0000	0.0003	0.003	0	10	0.0564
57.0000	0.7993	7.993	8	10	0.005272
73.0000	1.0000	10.000	10	10	0.0007765

Chi-square = 0.00; DF = 3; P-value = 1.0000.

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

BMD = 49.6524
BMDL = 42.4113

13:37 09/27 2006
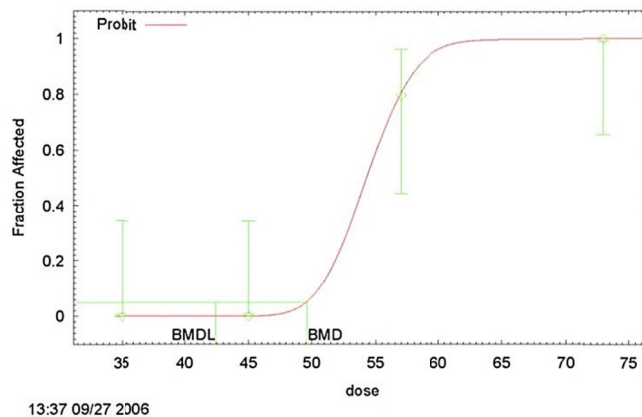
FIGURE B-1 Prohibit model with 0.95 confidence level.

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Benchmark Concentration Calculation for Allyl Chloroformate

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 = Mean
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
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 = -7.2918
Slope = 1.72308

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

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

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	-10.3866	2.68182
Slope	2.48392	0.621724

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	16.0896	–	–	–
Fitted model	17.3239	2.46858	4	0.6503
Reduced model	36.6519	41.1245	5	<0.0001

AIC: 38.6478.

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
33.7000	0.0495	0.495	0	10	0.7219
65.0000	0.4929	4.929	6	10	0.6774
77.7000	0.6648	6.648	7	10	0.236
134.5000	0.9632	9.632	9	10	1.06
175.7000	0.9929	9.929	10	10	0.2674
233.3000	0.9992	9.992	10	10	0.08938

Chi-square = 2.24; DF = 4; P-value = 0.6919.

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
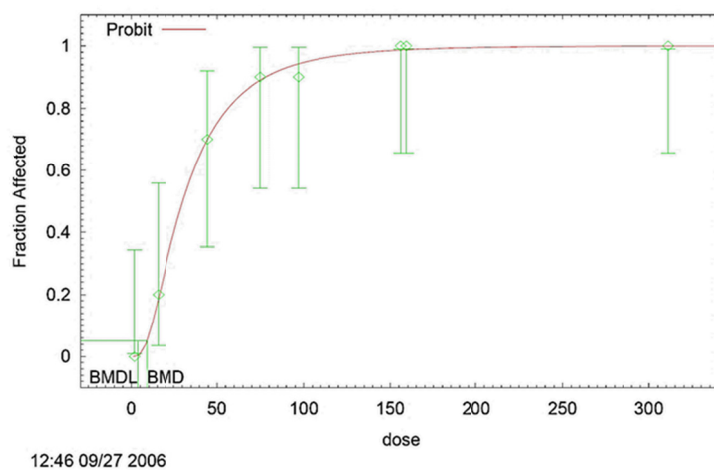BMD = 33.7621
BMDL = 21.098
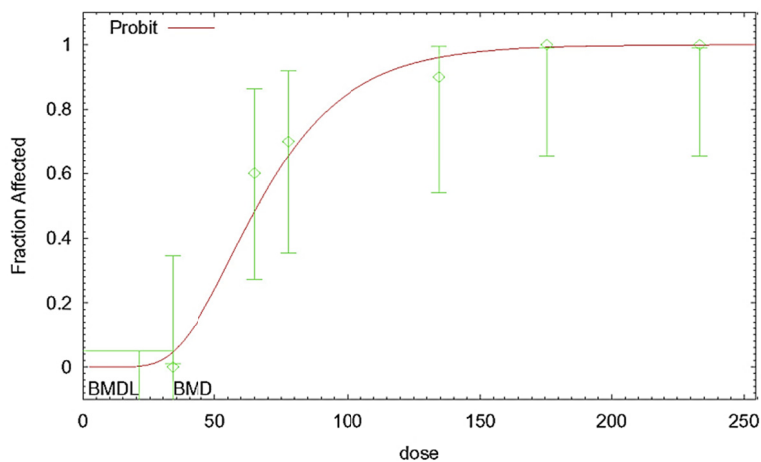
FIGURE B-2 Prohibit model with 0.95 confidence level.

Benchmark Concentration Calculation for Phenyl Chloroformate

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 = Mean
Independent variable = Dose
Slope parameter is not restricted

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 = -2.32244
Slope = 0.759796

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	0.98
Slope	–	1

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

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	4.60327	1.20324
Slope	1.35407	0.307109

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	17.6143	–	–	–
Fitted model	18.0291	0.829451	6	0.9913
Reduced model	47.9918	60.755	7	<0.0001

AIC: 40.0581.

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
1.7600	0.0001	0.001	0	10	0.02491
15.6000	0.1885	1.885	2	10	0.09264
44.5000	0.7040	7.040	7	10	0.02802
74.9000	0.8927	8.927	9	10	0.07446
97.0000	0.9442	9.442	9	10	0.6092
156.0000	0.9873	9.873	10	10	0.359
159.3000	0.9882	9.882	10	10	0.3459
311.0000	0.9992	9.992	10	10	0.08752

Chi-square = 0.64; DF = 6; P-value = 0.9956.

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 8.88924
BMDL = 3.57025

FIGURE B-3 Prohibit model with 0.95 confidence level.

Benchmark Concentration Calculation for 2-Ethylhexyl Chloroformate

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

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -15.0226
Slope = 4.37693

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

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

Parameter Estimates

Variable	Estimate	Standard Error
Background	0	NA
Intercept	18.7737	5.12639
Slope	5.52218	1.51755

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

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	12.8388	–	–	–
Fitted model	14.2231	2.76871	2	0.2505
Reduced model	27.6759	29.6742	3	<0.0001

AIC: 32.4462.

Goodness of Fit Scaled

Dose	Estimated Probability	Expected	Observed	Size	Residual
22.8000	0.0659	0.659	0	10	0.8398
26.6000	0.2559	2.559	4	10	1.044
34.3000	0.7728	7.728	7	10	-0.5491
46.9000	0.9934	9.934	10	10	0.2587

Chi-square = 2.16; DF = 2; P-value = 0.3390.

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
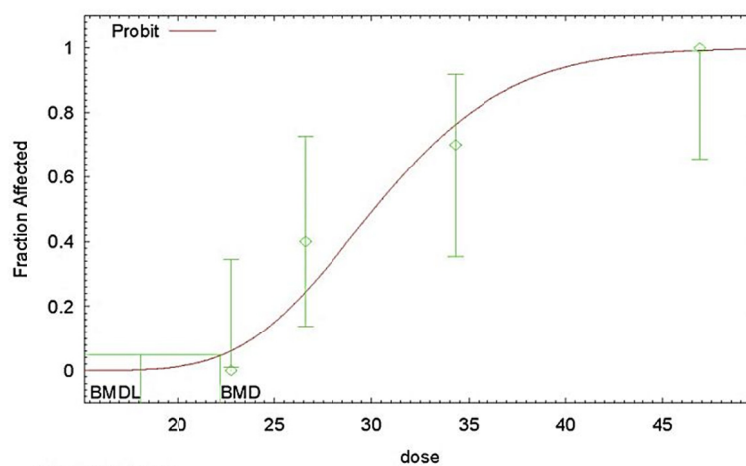Confidence level = 0.95
BMD = 22.2386
BMDL = 18.0971

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FIGURE B-4 Prohibit model with 0.95 confidence level.

Appendix C

Derivation of AEGL Values
for Selected Chloroformates

Methyl Chloroformate

Derivation of AEGL-1 Values for Methyl Chloroformate

Insufficient data were available on methyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Methyl Chloroformate

Insufficient data were available on methyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for methyl chloroformate by 3.

Calculations:

10-min AEGL-2:	12 ppm ÷ 3 = 4.0 ppm
30-min AEGL-2:	8.5 ppm ÷ 3 = 2.8 ppm
1-h AEGL-2:	6.7 ppm ÷ 3 = 2.2 ppm
4-h AEGL-2:	4.2 ppm ÷ 3 = 1.4 ppm
8-h AEGL-2:	2.1 ppm ÷ 3 = 0.70 ppm

Derivation of AEGL-3 Values for Methyl Chloroformate

Key study:	Hoechst. 1986. Chloroformic Acid Methyl Ester. Inhalation Toxicity in the Flow Through System in Male and Female SPF Wistar Rats. 4-hour LC_{50}. Hollander, H., Weigland, W, Mayer, D., Langer, K.H. Hoechst Pharmaceutical Research Toxicology. Report No. 86.0432. April 11, 1986.

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Toxicity end point:	Lethality threshold in rats (4-h $BMCL_{05}$ of 42.4 ppm)
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). $(42.4 \text{ ppm})^3 \times 4 \text{ h} = 304{,}900 \text{ ppm-h}$ $(42.4 \text{ ppm})^1 \times 4 \text{ h} = 170 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	$C^3 \times 0.167 \text{ h} = 304{,}900 \text{ ppm-h}$ $C^3 = 1{,}825{,}748 \text{ ppm}$ $C = 122 \text{ ppm}$ $122 \text{ ppm} \div 10 = 12 \text{ ppm}$
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 304{,}900 \text{ ppm-h}$ $C^3 = 609{,}800 \text{ ppm}$ $C = 84.8 \text{ ppm}$ $84.8 \text{ ppm} \div 10 = 8.5 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 304{,}900 \text{ ppm-h}$ $C^3 = 304{,}900 \text{ ppm}$ $C = 67.3 \text{ ppm}$ $67.3 \text{ ppm} \div 10 = 6.7 \text{ ppm}$
4-h AEGL-3:	$42.4 \text{ ppm} \div 10 = 4.2 \text{ ppm}$
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 170 \text{ ppm-h}$ $C^1 = 21.2 \text{ ppm}$ $C = 21.2 \text{ ppm}$ $21 \text{ ppm} \div 10 = 2.1 \text{ ppm}$

Ethyl Chloroformate

Derivation of AEGL-1 Values for Ethyl Chloroformate

Insufficient data were available on ethyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Ethyl Chloroformate

Insufficient data were available on ethyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for ethyl chloroformate by 3.

Calculations:

10-min AEGL-2:   8.8 ppm ÷ 3 = 2.9 ppm

30-min AEGL-2:   6.1 ppm ÷ 3 = 2.0 ppm

1-h AEGL-2:   4.8 ppm ÷ 3 = 1.6 ppm

4-h AEGL-2:   1.2 ppm ÷ 3 = 0.40 ppm

8-h AEGL-2:   0.60 ppm ÷ 3 = 0.20 ppm

Derivation of AEGL-3 Values for Ethyl Chloroformate

Key study:	Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-424.
Toxicity end point:	Lethality threshold; estimated LC_{01} ($LC_{50} \div 3$) from a 1-h exposure in male rats. LC_{50} = 145 ppm; 145 ppm ÷ 3 = 48.3 ppm (point of departure)
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). $(48.3\ \text{ppm})^3 \times 1\ \text{h} = 112{,}769\ \text{ppm-h}$ $(48.3\ \text{ppm})^1 \times 1\ \text{h} = 48.3\ \text{ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors

10-min AEGL-3: $C^3 \times 0.167$ h = 112,769 ppm-h
                        C^3 = 675,263 ppm
                        C = 87.7 ppm
                        87.7 ppm ÷ 10 = 8.8 ppm

30-min AEGL-3: $C^3 \times 0.5$ h = 112,769 ppm-h
                        C^3 = 225,538 ppm
                        C = 60.9 ppm
                        60.9 ppm ÷ 10 = 6.1 ppm

1-h AEGL-3:   48.3 ppm ÷ 10 = 4.8 ppm

4-h AEGL-3: $C^1 \times 4$ h = 48.3 ppm-h
                        C^1 = 12 ppm
                        C = 12 ppm
                        12 ppm ÷ 10 = 1.2 ppm

8-h AEGL-3: $C^1 \times 8$ h = 48.3 ppm-h
                        C^1 = 6.0 ppm
                        C = 6.0 ppm
                        6.0 ppm ÷ 10 = 0.60 ppm

Isopropyl Chloroformate

Derivation of AEGL-1 Values for Isopropyl Chloroformate

Insufficient data were available on isopropyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Isopropyl Chloroformate

Insufficient data were available on isopropyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for isopropyl chloroformate by 3.

Calculations:

10-min AEGL-2:   11 ppm ÷ 3 = 3.7 ppm

30-min AEGL-2:   11 ppm ÷ 3 = 3.7 ppm

1-h AEGL-2:   9.1 ppm ÷ 3 = 3.0 ppm

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4-h AEGL-2:   5.7 ppm ÷ 3 = 1.9 ppm

8-h AEGL-2:   3.8 ppm ÷ 3 = 1.3 ppm

Derivation of AEGL-3 Values for Isopropyl Chloroformate

Key study:	Collins, C.J., and B.G. Proctor. 1984. A 5-day Range-Finding Inhalation Toxicity Study of Isopropyl Chloroformate in the Albino Rat. Draft Report. Prepared by Bio-Research Laboratories, Ltd.: Quebec, Canada. Prepared for PPG Industries, Pittsburgh, PA.
Toxicity end point:	Concentration causing no mortality in male and female rats exposed for 6 h/day for 5 days (50 ppm)
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). $(50 \text{ ppm})^3 \times 6 \text{ h} = 750,000 \text{ ppm-h}$ $(50 \text{ ppm})^1 \times 6 \text{ h} = 300 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	11 ppm (set equal to 30-min AEGL-3 value, because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 750,000 \text{ ppm-h}$ $C^3 = 1,500,000 \text{ ppm}$ $C = 114 \text{ ppm}$ $114 \text{ ppm} \div 10 = 11 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 750,000 \text{ ppm-h}$ $C^3 = 750,000 \text{ ppm}$ $C = 90.9 \text{ ppm}$ $90.9 \text{ ppm} \div 10 = 9.1 \text{ ppm}$

4-h AEGL-3: $C^3 \times 4$ h = 750,000 ppm-h
                              $C^3 = 187,500$ ppm
                              C = 57.2 ppm
                              57.2 ppm ÷ 10 = 5.7 ppm

8-h AEGL-3: $C^1 \times 8$ h = 300 ppm-h
                              $C^1 = 37.5$ ppm
                              37.5 ppm ÷ 10 = 3.8 ppm

n-Propyl Chloroformate

Derivation of AEGL-1 Values for *n*-Propyl Chloroformate

Insufficient data were available on propyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for *n*-Propyl Chloroformate

AEGL-2 values for propyl chloroformate were set equal to AEGL-2 values for isopropyl chloroformate, because of the inadequate data on propyl chloroformate and the similar toxicity of the two chemicals.

Calculations:

10-min AEGL-2:   3.7 ppm

30-min AEGL-2:   3.7 ppm

1-h AEGL-2:   3.0 ppm

4-h AEGL-2:   1.9 ppm

8-h AEGL-2:   1.3 ppm

Derivation of AEGL-3 Values for *n*-Propyl Chloroformate

AEGL-3 values for *n*-propyl chloroformate were set equal to AEGL-3 values for isopropyl chloroformate, because of the inadequate data on *n*-propyl chloroformate and the similar toxicity of the two chemicals.

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Calculations:

10-min AEGL-3:   11 ppm

30-min AEGL-3:   11 ppm

1-h AEGL-3:   9.1 ppm

4-h AEGL-3:   5.7 ppm

8-h AEGL-3:   3.8 ppm

Allyl Chloroformate

Derivation of AEGL-1 Values for Allyl Chloroformate

Insufficient data were available on allyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Allyl Chloroformate

Insufficient data were available on allyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for allyl chloroformate by 3.

Calculations:

10-min AEGL-2:   3.8 ppm ÷ 3 = 1.3 ppm

30-min AEGL-2:   2.6 ppm ÷ 3 = 0.87 ppm

1-h AEGL-2:   2.1 ppm ÷ 3 = 0.70 ppm

4-h AEGL-2:   0.53 ppm ÷ 3 = 0.18 ppm

8-h AEGL-2:   0.26 ppm ÷ 3 = 0.09 ppm

Derivation of AEGL-3 Values for Allyl Chloroformate

Key study: Stillmeadow Inc. 1987. Rat Acute Inhalation
                        Toxicity: Allyl Chloroformate. Stillmeadow, Inc.
                        Biological Testing Laboratory: Houston, TX.
                        Project No. 4438-86. Report Submitted to PPG

Industries, Inc.: Chicago, IL. February 19, 1987. OTS0536028.

Toxicity end point:	Lethality threshold (1-h rat $BMCL_{05}$ = 21 ppm)
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). $(21 \text{ ppm})^3 \times 1 \text{ h} = 9{,}261 \text{ ppm-h}$ $(21 \text{ ppm})^1 \times 1 \text{ h} = 21 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	$C^3 \times 0.167 \text{ h} = 9{,}261 \text{ ppm-h}$ $C^3 = 55{,}455 \text{ ppm}$ C = 38 ppm 38 ppm ÷ 10 = 3.8 ppm
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 9{,}261 \text{ ppm-h}$ $C^3 = 18{,}522 \text{ ppm}$ C = 26.4 ppm 26.4 ppm ÷ 10 = 2.6 ppm
1-h AEGL-3:	21 ppm ÷ 10 = 2.1 ppm
4-h AEGL-3:	$C^1 \times 4 \text{ h} = 21 \text{ ppm-h}$ $C^1 = 5.25 \text{ ppm}$ C = 5.25 ppm 5.25 ppm ÷ 10 = 0.53 ppm
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 21 \text{ ppm-h}$ $C^1 = 2.63 \text{ ppm}$ C = 2.63 ppm 2.63 ppm ÷ 10 = 0.26 ppm

n-Butyl Chloroformate, Isobutyl Chloroformate, and *sec*-Butyl Chloroformate

Data were insufficient to derive AEGL values for isobutyl or *sec*-butyl chloroformate. Because these two compounds are structural analogs of *n*-butyl

chloroformate and because they appear to have similar toxicity, the AEGL values for *n*-butyl chloroformate were adopted for these chemicals. The section below shows how the values for *n*-butyl chloroformate were derived.

Derivation of AEGL-1 Values for *n*-Butyl Chloroformate

Insufficient data were available on *n*-butyl chloroformate to derive AEGL-1 values, so no values are recommended. No values are also recommended for isobutyl chloroformate or *sec*-butyl chloroformate.

Derivation of AEGL-2 Values for *n*-Butyl Chloroformate

Insufficient data were available on *n*-butyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for *n*-butyl chloroformate by 3. The values were also applied to isobutyl chloroformate and *sec*-butyl chloroformate.

Calculations:

10-min AEGL-2:	12 ppm ÷ 3 = 4.0 ppm
30-min AEGL-2:	8.4 ppm ÷ 3 = 2.8 ppm
1-h AEGL-2:	6.7 ppm ÷ 3 = 2.2 ppm
4-h AEGL-2:	1.7 ppm ÷ 3 = 0.57 ppm
8-h AEGL-2:	0.83 ppm ÷ 3 = 0.28 ppm

Derivation of AEGL-3 Values for *n*-Butyl Chloroformate

Key study:	BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. *n*-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung. Unpublished Report No. XIX 352
Toxicity end point:	Estimated 1-h lethality threshold in rats (66.7 ppm) 4/10 rats died after exposure at 200 ppm for 1 h; lethality threshold was estimated by taking one-third of that concentration (200 ppm ÷ 3 = 66.7 ppm).

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).
	$(66.7 \text{ ppm})^3 \times 1 \text{ h} = 296{,}741 \text{ ppm-h}$
	$(66.7 \text{ ppm})^1 \times 1 \text{ h} = 66.7 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences
	3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	$C^3 \times 0.167 \text{ h} = 296{,}741 \text{ ppm-h}$
	$C^3 = 1{,}776{,}892 \text{ ppm}$
	$C = 121 \text{ ppm}$
	$121 \text{ ppm} \div 10 = 12 \text{ ppm}$
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 296{,}741 \text{ ppm-h}$
	$C^3 = 593{,}482 \text{ ppm}$
	$C = 84.0 \text{ ppm}$
	$84.0 \text{ ppm} \div 10 = 8.4 \text{ ppm}$
1-h AEGL-3:	$66.7 \text{ ppm} \div 10 = 6.7 \text{ ppm}$
4-h AEGL-3:	$C^1 \times 4 \text{ h} = 66.7 \text{ ppm-h}$
	$C^1 = 16.8 \text{ ppm}$
	$C = 16.8 \text{ ppm}$
	$16.8 \text{ ppm} \div 10 = 1.7 \text{ ppm}$
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 66.7 \text{ ppm-h}$
	$C^1 = 8.34 \text{ ppm}$
	$C = 8.34 \text{ ppm}$
	$8.34 \text{ ppm} \div 10 = 0.83 \text{ ppm}$

AEGL-3 values for *n*-butyl chloroformate were also applied to isobutyl chloroformate and *sec*-butyl chloroformate.

Benzyl Chloroformate

Derivation of AEGL-1 Values for Benzyl Chloroformate

Insufficient data were available on benzyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Benzyl Chloroformate

Insufficient data were available on benzyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for benzyl chloroformate by 3.

Calculations:

10-min AEGL-2:   3.7 ppm ÷ 3 = 1.2 ppm

30-min AEGL-2:   3.7 ppm ÷ 3 = 1.2 ppm

1-h AEGL-2:   2.9 ppm ÷ 3 = 0.97 ppm

4-h AEGL-2:   1.9 ppm ÷ 3 = 0.63 ppm

8-h AEGL-2:   0.93 ppm ÷ 3 = 0.31 ppm

Derivation of AEGL-3 Values for Benzyl Chloroformate

Key study:	BASF. 1990. Study on the Acute Inhalation Toxicity LC_{50} of Benzyl Chloroformate as a Vapor in Rats, 4-Hour Exposure. Project No. 13I0674/887075. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology: Ludwigshafen, Germany. February 15, 1990.
Toxicity end point:	Concentration causing no mortality in 4-h rat study (18.6 ppm)
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). $(18.6 \text{ ppm})^3 \times 4 \text{ h} = 25,739 \text{ ppm-h}$ $(18.6 \text{ ppm})^1 \times 4 \text{ h} = 74.4 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors

10-min AEGL-3:   3.7 ppm (set equal to 30-min AEGL-3 value, because of the uncertainty associated with extrapolating a 4-h point-of-departure to a 10-min value)

30-min AEGL-3:

$$C^3 \times 0.5\ h = 25,739\ \text{ppm-h}$$
$$C^3 = 51,478\ \text{ppm}$$
$$C = 37.2\ \text{ppm}$$
$$37.2\ \text{ppm} \div 10 = 3.7\ \text{ppm}$$

1-h AEGL-3:

$$C^3 \times 1\ h = 25,739\ \text{ppm-h}$$
$$C^3 = 25,739\ \text{ppm}$$
$$C = 29.5\ \text{ppm}$$
$$29\ \text{ppm} \div 10 = 2.9\ \text{ppm}$$

4-h AEGL-3: $18.6\ \text{ppm} \div 10 = 1.9\ \text{ppm}$

8-h AEGL-3:

$$C^1 \times 8\ h = 74.4\ \text{ppm-h}$$
$$C^1 = 9.3\ \text{ppm}$$
$$C = 9.3\ \text{ppm}$$
$$9.3\ \text{ppm} \div 10 = 0.93\ \text{ppm}$$

Phenyl Chloroformate

Derivation of AEGL-1 Values for Phenyl Chloroformate

Insufficient data were available on phenyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Phenyl Chloroformate

Insufficient data were available on phenyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for phenyl chloroformate by 3.

Calculations:

10-min AEGL-2: $0.72\ \text{ppm} \div 3 = 0.24\ \text{ppm}$

30-min AEGL-2: $0.72\ \text{ppm} \div 3 = 0.24\ \text{ppm}$

1-h AEGL-2: $0.57\ \text{ppm} \div 3 = 0.19\ \text{ppm}$

4-h AEGL-2:	0.36 ppm ÷ 3 = 0.12 ppm
8-h AEGL-2:	0.18 ppm ÷ 3 = 0.06 ppm

Derivation of AEGL-3 Values for Phenyl Chloroformate

Key studies:	BASF. 1990. Study on the Acute Inhalation Toxicity LC_{50} of Phenyl Chloroformate as a Vapor in Rats, 4-Hour Exposure. Project No. 13I0675/887076. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology: Ludwigshafen, Germany. January 18, 1990.
	Hoechst. 1989. Chloroformic Acid Phenyl Ester. Aerosol Inhalation Toxicity in Male and Female SPF Wistar Rats. 4-Hour LC_{50}. Hofmann, T. Hoechst Pharmaceutical Research Toxicology. Report No. 89.0761. April 26, 1989.
Toxicity end point:	Lethality threshold (4-h rat $BMCL_{05}$ = 3.6 ppm)
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). $(3.6 \text{ ppm})^3 \times 4 \text{ h} = 186.7$ ppm-h $(3.6 \text{ ppm})^1 \times 4 \text{ h} = 14.4$ ppm-h
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	0.72 ppm (set equal to 30-min AEGL-3 value, because of the uncertainty associated with extrapolating a 4-h point-of-departure to a 10-min value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 186.7$ ppm-h $C^3 = 373.4$ ppm C = 7.2 ppm 7.2 ppm ÷ 10 = 0.72 ppm

1-h AEGL-3: $C^3 \times 1\ h = 186.7$ ppm-h
                               $C^3 = 186.7$ ppm
                               $C = 5.7$ ppm
                               5.7 ppm $\div 10 = 0.57$ ppm

4-h AEGL-3: 3.6 ppm $\div 10 = 0.36$ ppm

8-h AEGL-3: $C^1 \times 8\ h = 14.4$ ppm-h
                               $C^1 = 1.8$ ppm
                               $C = 1.8$ ppm
                               1.8 ppm $\div 10 = 0.18$ ppm

2-Ethylhexyl Chloroformate

Derivation of AEGL-1 Values for 2-Ethylhexyl Chloroformate

Insufficient data were available on 2-ethylhexyl chloroformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for 2-Ethylhexyl Chloroformate

Insufficient data were available on 2-ethylhexyl chloroformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for 2-ethylhexyl chloroformate by 3.

Calculations:

10-min AEGL-2: 3.6 ppm $\div 3 = 1.2$ ppm

30-min AEGL-2: 3.6 ppm $\div 3 = 1.2$ ppm

1-h AEGL-2: 2.9 ppm $\div 3 = 0.97$ ppm

4-h AEGL-2: 1.8 ppm $\div 3 = 0.60$ ppm

8-h AEGL-2: 0.91 ppm $\div 3 = 0.30$ ppm

Derivation of AEGL-3 Values for 2-Ethylhexyl Chloroformate

Key study: BASF. 1985. Acute Inhalation Toxicity LC_{50}
                               for a 4-Hour Exposure (Rats), Vapor Test of
                               2-Ethylhexyl Chloroformate. Unpublished report,
                               BASF Aktiengesellschaft, Experimental Toxicology

	and Ecology: Ludwigshafen, Germany. February 8, 1985.
Toxicity end point:	Lethality threshold (4-h rat $BMCL_{05}$ [18.1 ppm])
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). $(18.1 \text{ ppm})^3 \times 4 \text{ h} = 23,719 \text{ ppm-h}$ $(18.1 \text{ ppm})^1 \times 4 \text{ h} = 72.4 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	3.6 ppm (set equal to 30-min AEGL-3 value, because of the uncertainty associated with extrapolating a 4-h point-of-departure to a 10-min value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 23,719 \text{ ppm-h}$ $C^3 = 47,438 \text{ ppm}$ $C = 36.2 \text{ ppm}$ $36.2 \text{ ppm} \div 10 = 3.6 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 23,719 \text{ ppm-h}$ $C^3 = 23,719 \text{ ppm}$ $C = 28.7 \text{ ppm}$ $28.7 \text{ ppm} \div 10 = 2.9 \text{ ppm}$
4-h AEGL-3:	$18.6 \text{ ppm} \div 10 = 1.8 \text{ ppm}$
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 72.4 \text{ ppm-h}$ $C^1 = 9.1 \text{ ppm}$ $C = 9.1 \text{ ppm}$ $9.1 \text{ ppm} \div 10 = 0.91 \text{ ppm}$

Ethyl Chlorothioformate

Derivation of AEGL-1 Values for Ethyl Chlorothioformate

Insufficient data were available on ethyl chlorothioformate to derive AEGL-1 values, so no values are recommended.

Derivation of AEGL-2 Values for Ethyl Chlorothioformate

Insufficient data were available on ethyl chlorothioformate to derive AEGL-2 values. In the absence of relevant data, AEGL-2 values were estimated by dividing the AEGL-3 values for ethyl chlorothioformate by 3.

Calculations:

10-min AEGL-2:	3.0 ppm ÷ 3 = 1.0 ppm
30-min AEGL-2:	3.0 ppm ÷ 3 = 1.0 ppm
1-h AEGL-2:	2.4 ppm ÷ 3 = 0.80 ppm
4-h AEGL-2:	1.5 ppm ÷ 3 = 0.50 ppm
8-h AEGL-2:	0.75 ppm ÷ 3 = 0.25 ppm

Derivation of AEGL-3 Values for Ethyl Chlorothioformate

Key study:	Stauffer Chemical Company. 1983. Acute Inhalation Toxicity of Ethyl Chlorothioformate in Rats (T-10710). Environmental Health Center Inhalation Facility. Stauffer Chemical Company: Farmington, CT. OTS0538464.
Toxicity end point:	Estimated 4-h lethality threshold of 15 ppm in rats (LC_{50} = 45 ppm; 45 ppm ÷ 3)
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). $(15 \text{ ppm})^3 \times 4 \text{ h} = 13,500 \text{ ppm-h}$ $(15 \text{ ppm})^1 \times 4 \text{ h} = 60 \text{ ppm-h}$

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Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	Point of departure ÷ product of the uncertainty factors
10-min AEGL-3:	3.0 ppm (set equal to 30-min AEGL-3 value, because of the uncertainty associated with extrapolating a 4-h point-of-departure to a 10-min value)
30-min AEGL-3:	$C^3 \times 0.5$ h = 13,500 ppm-h C^3 = 27,000 ppm C = 30 ppm 30 ppm ÷ 10 = 3.0 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 13,500 ppm-h C^3 = 13,500 ppm C = 23.8 ppm 23.8 ppm ÷ 10 = 2.4 ppm
4-h AEGL-3:	15 ppm ÷ 10 = 1.5 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 60 ppm-h C^1 = 7.5 ppm C = 7.5 ppm 7.5 ÷ 10 = 0.75 ppm

Appendix D

Acute Exposure Guideline Levels for Selected Chloroformates

DERIVATION SUMMARY METHYL CHLOROFORMATE

AEGL-1 Values for Methyl Chloroformate

The data on methyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Methyl Chloroformate

10 min	30 min	1 h	4 h	8 h
4.0 ppm	2.8 ppm	2.2 ppm	1.4 ppm	0.70 ppm

Data adequacy: In the absence of specific data on methyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). The values are supported by the results of repeated-exposure studies. No deaths occurred in rats repeatedly exposed to methyl chloroformate at 3.1 ppm and only histopathologic changes in the nasal turbinates and lesions of the larynx were found. Larynx lesions were the only finding in rats exposed at 1.01 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1993).

AEGL-3 Values for Methyl Chloroformate

10 min	30 min	1 h	4 h	8 h
12 ppm	8.5 ppm	6.7 ppm	4.2 ppm	2.1 ppm

Key reference: Hoechst. 1986. Chloroformic Acid Methyl Ester. Inhalation Toxicity in the Flow Through System in Male and Female SPF Wistar Rats. 4-hour LC_{50}. Hollander, H., Weigland, W, Mayer, D., Langer, K.H. Hoechst Pharmaceutical Research Toxicology. Report No. 86.0432. April 11, 1986.

Test species/Strain/Sex/Number: Rats; Wistar; 5/sex/group

Exposure route/Concentrations/Durations: Inhalation; 35, 45, 57, or 73 ppm for 4 h

End point/Concentration/Rationale: Lethality; 4-h $BMCL_{05}$ = 42.4 ppm, estimated threshold for death in rats

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Effects:
LC_{50} (males) = 51 ppm; LC_{50} (females) = 53 ppm
$BMCL_{05}$ (males and females) = 42.4 ppm
BMC_{01} (males and females) = 47.8 ppm

Concentration	Male mortality	Female mortality
35 ppm	0/5	0/5
45 ppm	0/5	0/5
57 ppm	5/5	3/5
73 ppm	5/5	5/5

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary congestion, pulmonary edema, and increased lung weights) in short-term repeated-exposure studies of rats exposed to methyl chloroformate (Gage 1970; HRC 1992; BASF 1993, 1999). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

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). Time scaling from 4 h to 10 min is supported by a 1-h LC_{50} study (Industrial Bio-Test Laboratories, Inc. 1975); using a $BMCL_{05}$ from this study would result in a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from the study by Holendar (1986).

Data adequacy: Acute lethality studies in rats had consistent results that were relevant for calculating AEGL-3 values. The AEGL-3 values are supported by the results of repeated-exposure studies. No deaths occurred in rats exposed to methyl chloroformate at 7.8 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1999), and no deaths occurred until week 4 in rats exposed at 8.8 ppm for 6 h/day, 5 days/week for 4 weeks (BASF 1993).

DERIVATION SUMMARY FOR ETHYL CHLOROFORMATE

AEGL-1 Values for Ethyl Chloroformate

The data on ethyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Ethyl Chloroformate

10 min	30 min	1 h	4 h	8 h
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm

Data adequacy: In the absence of specific data on ethyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on ethyl chloroformate provide evidence of a steep curve. Fisher et al. (1981b) report a 1-h rat LC_{50} of 189-200 ppm, and that rats exposed at 47 ppm for 1 h were clinically normal and had no mortality.

AEGL-3 Values for Ethyl Chloroformate

10 min	30 min	1 h	4 h	8 h
8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm

Key reference: Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-424.

Test species/Strain/Sex/Number: Rat, Sprague-Dawley rats, males

Exposure route/Concentrations/Durations: Inhalation for 1 h

End point/Concentration/Rationale: Lethality; LC_{01} was estimated taking one-third of the LC_{50} (145 ppm ÷ 3 = 48.3 ppm)

Effects: Male rat LC_{50} = 145 ppm; female rat LC_{50} = 170 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of respiratory effects (e.g., lung congestion, edema, and emphysema) in lethality studies of rats (BASF 1970a,b; Gage, 1970; WARF Institute, Inc. 1978; Fisher et al. 1981). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Furthermore, interspecies and intraspecies uncertainty factors of 3 were also used in determining the AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate, and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data on these analogs.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

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).

Data adequacy: Two acute lethality studies in rats had consistent results and were adequate for deriving AEGL-3 values.

DERIVATION SUMMARY FOR ISOPROPYL CHLOROFORMATE

AEGL-1 Values for Isopropyl Chloroformate

The data on isopropyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Isopropyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm	3.7 ppm	3.0 ppm	1.9 ppm	1.3 ppm

Data adequacy: No appropriate data on isopropyl chloroformate were available to derive AEGL-2 values. Thus, the AEGL-2 values were calculated by taking one-third of the AEGL-3 values. This approached is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). The values are supported by the study by Gage (1970), which reported only nasal irritation in rats exposed to isopropyl chloroformate at 20 ppm for 6 h/day for 20 days.

AEGL-3 Values for Isopropyl Chloroformate

10 min	30 min	1 h	4 h	8 h
11 ppm	11 ppm	9.1 ppm	5.7 ppm	3.8 ppm

Key reference: Collins, C.J., and B.G. Proctor. 1984. A 5-day Range-Finding Inhalation Toxicity Study of Isopropyl Chloroformate in the Albino Rat. Draft Report. Prepared by Bio-Research Laboratories, Ltd.: Quebec, Canada. Prepared for PPG Industries, Pittsburgh, PA.

Test species/Strain/Sex/Number: Rats; 4 males and 4 females/group

Exposure route/Concentrations/Durations: Inhalation; 25, 50, and 100 ppm (measured concentrations) for 6 h/day for 5 days

End point/Concentration/Rationale: Lethality threshold (42 ppm)

Effects: No deaths at 22 or 42 ppm; 3/4 males and 3/4 females died in the 86-ppm group.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) in short-term repeated exposure rat studies with isopropyl chloroformate (Gage 1970; Collins and Proctor 1984). Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). On the basis of these considerations, factors of 3 would represent the potential for any toxicodynamic variability.

(Continued)

AEGL-3 Continued (*Isopropyl Chloroformate*)

Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data
Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 6-h repeated exposure to a 10-min value.
Data adequacy: The acute toxicity studies on isopropyl chloroformate are sparse, but are supported by a repeated-exposure study.

DERIVATION SUMMARY FOR *N*-PROPYL CHLOROFORMATE

AEGL-1 Values for *n*-Propyl Chloroformate

The data on *n*-propyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for *n*-Propyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm	3.7 ppm	3.0 ppm	1.9 ppm	1.3 ppm

Data adequacy: Sparse data set on *n*-propyl chloroformate. Chemical-specific data were insufficient to derive AEGL-2 values because of uncertainties in the quality of the available data. However, *n*-propyl chloroformate is a structural analog of isopropyl chloroformate, and available data suggest that *n*-propyl chloroformate and isopropyl chloroformate have similar toxicity. Thus, the AEGL-2 values for isopropyl chloroformate were adopted as the AEGL-2 values for *n*-propyl chloroformate.

AEGL-3 Values for *n*-Propyl Chloroformate

10 min	30 min	1 h	4 h	8 h
11 ppm	11 ppm	9.1 ppm	5.7 ppm	3.8 ppm

Data adequacy: Sparse data set on *n*-propyl chloroformate. Chemical-specific data were insufficient to derive AEGL-3 values because of uncertainties in the quality of the available data. However, *n*-propyl chloroformate is a structural analog of isopropyl chloroformate, and available data suggest that *n*-propyl chloroformate and isopropyl chloroformate have similar toxicity. Thus, the AEGL-3 values for isopropyl chloroformate were adopted as the AEGL-3 values for *n*-propyl chloroformate.

DERIVATION SUMMARY FOR ALLYL CHLOROFORMATE

AEGL-1 Values for Allyl Chloroformate

The data on allyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Allyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm
(6.4 mg/m^3)	(4.3 mg/m^3)	(3.4 mg/m^3)	(0.88 mg/m^3)	(0.44 mg/m^3)

Data adequacy: In the absence of specific data on allyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on allyl chloroformate provide evidence of a steep curve. The incidence of mortality in rats exposed to ally chloroformate for 1 h was 0/10 at 33.7 ppm, 6/10 at 65 ppm, and 10/10 at 175.7 ppm (Stillmeadow Inc. 1987).

AEGL-3 Values for Allyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm

Key reference: Stillmeadow Inc. 1987. Rat Acute Inhalation Toxicity: Allyl Chloroformate. Stillmeadow, Inc. Biological Testing Laboratory: Houston, TX. Project No. 4438-86. Report Submitted to PPG Industries, Inc., Chicago, IL. February 19, 1987. OTS0536028.

Test species/Strain/Sex/Number: Rat; Sprague Dawley; 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 33.7, 65.0, 77.7, 134.5, 175.7, and 233.3 ppm for 1 h

End point/Concentration/Rationale: Lethality threshold; 1-h $BMCL_{05}$ = 21 ppm

Effects: Mortality rates were 0/10 at 33.7 ppm; 6/10 at 65.0 ppm; 7/10 at 77.7 ppm; 9/10 at 134.5 ppm; 10/10 at 175.7 ppm; and 10/10 at 233.3 ppm. The data were used to calculate the following: LC_{50} = 65.1 ppm; $BMCL_{05}$ = 21 ppm; and BMC_{01} = 25.7 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). On the basis of these considerations, factors of 3 would represent the potential for any toxicodynamic variability. Furthermore, interspecies and intraspecies uncertainty factors of 3 were also used in determining the AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate, and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data on these analogs.

(Continued)

AEGL-3 Continued (*Allyl Chloroformate*)

Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data
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).
Data adequacy: Only one study of allyl chloroformate was available.

DERIVATION SUMMARY FOR *N*-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, AND *SEC*-BUTYL CHLOROFORMATE

AEGL-1 Values for *n*-Butyl, Isobutyl, and *sec*-Butyl Chloroformate

The data on *n*-butyl, isobutyl, and *sec*-butyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for *n*-Butyl, Isobutyl, and *sec*-Butyl Chloroformate

10 min	30 min	1 h	4 h	8 h
4.0 ppm	2.8 ppm	2.2 ppm	0.57 ppm	0.28 ppm

Data adequacy: Data on *n*-butyl, isobutyl, and *sec*-butyl chloroformate were inadequate for deriving AEGL-2 values.

For *n*-butyl chloroformate, AEGL-2 values were estimated by dividing the AEGL-3 values by 3. The values are supported by results of repeated-exposure studies by HRC (1990), which found no effects in rats exposed to *n*-butyl chloroformate at 1.8 ppm for 6 h/day, 5 days/week for 4 weeks, or at 2.9 ppm for 6 h/day for 5 days.

Because isobutyl and *sec*-butyl chloroformate are structural analogs to *n*-butyl chloroformate, the AEGL-2 values for *n*-butyl chloroformate were adopted for them. Additionally, mouse RD_{50} data suggest that two chemicals have similar toxicity; the RD_{50} values from studies in male Swiss-Webster mice were 97 ppm for isobutyl chloroformate and 117 ppm for *sec*-butyl chloroformate (Carpenter 1982d).

AEGL-3 Values for *n*-Butyl, Isobutyl, and *sec*-Butyl Chloroformate

10 min	30 min	1 h	4 h	8 h
12 ppm	8.4 ppm	6.7 ppm	1.7 ppm	0.83 ppm

Key reference: BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. *N*-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung. Unpublished Report No. XIX 352.
Test species/Strain/Sex/Number: Rat; Sprague Dawley; 5 males and 5 females per group
Exposure route/Concentrations/Durations: Inhalation; *n*-butyl chloroformate at 200 ppm for 1 h

End point/Concentration/Rationale: Threshold for death was estimated by dividing 200 ppm by 3 (66.7 ppm)
Effects: 4/10 rats died
Uncertainty factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 Intraspecies: 3 The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). On the basis of these considerations, factors of 3 would represent the potential for any toxicodynamic variability.
Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data
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).
Data adequacy: Data on *n*-butyl chloroformate were sparse. Values are supported by results from repeated-exposure studies conducted by HRC (1990); no rats died when exposed to *n*-butyl chloroformate 5.1 ppm for 6 h/day, 5 days/week for 4 weeks or at 28.4 ppm for 6 h/day for 5 days. Even less data were available on isobutyl and *sec*-butyl chloroformate. Because the two compounds are structural analogs of *n*-butyl chloroformate, the AEGL-3 values for *n*-butyl chloroformate were adopted for isobutyl chloroformate and *sec*-butyl chloroformate. Additionally, mouse RD_{50} data suggest that two chemicals have similar toxicity; the RD_{50} values from studies in male Swiss-Webster mice were 97 ppm for isobutyl chloroformate and 117 ppm for *sec*-butyl chloroformate (Carpenter 1982d).

DERIVATION SUMMARY BENZYL CHLOROFORMATE

AEGL-1 Values for Benzyl Chloroformate

The data on benzyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Benzyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.2 ppm	1.2 ppm	0.97 ppm	0.63 ppm	0.31 ppm

Data adequacy: In the absence of specific data on benzyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). Lethality data on benzyl chloroformate provide evidence of a steep curve. Mortality rates in rats exposed to benzyl chloroformate for 4 h were 0/10 at 18.6 ppm and 5/10 at 84.6 ppm (BASF 1990); clinical signs in surviving rats resolved (were reversible).

AEGL-3 Values for Benzyl Chloroformate

10 min	30 min	1 h	4 h	8 h
3.7 ppm	3.7 ppm	2.9 ppm	1.9 ppm	0.93 ppm

Key reference: BASF. 1990. Study on the Acute Inhalation Toxicity LC_{50} of Benzyl Chloroformate as a Vapor in Rats, 4-Hour Exposure. Project No. 13I0674/887075. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology: Ludwigshafen, Germany. February 15, 1990.

Test species/Strain/Sex/Number: Rat; Sprague Dawley; 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 18.6 or 84.6 ppm for 4 h

End point/Concentration/Rationale: No deaths occurred at 18.6 ppm

Effects: No deaths at 18.6 ppm; 5/10 rats died at 84.6 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Furthermore, interspecies and intraspecies uncertainty factors of 3 were also used in determining the AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate, and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data on these analogs.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value.

Data adequacy: Sparse data set.

DERIVATION SUMMARY PHENYL CHLOROFORMATE

AEGL-1 Values for Phenyl Chloroformate

The data on phenyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Phenyl Chloroformate

10 min	30 min	1 h	4 h	8 h
0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.06 ppm

Data adequacy: In the absence of specific data on phenyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). This approach is justified based on the steep concentration curve with regard to lethality; mortality rates in rats exposed to phenyl chloroformate for 4 h were 2/10 at 15.6 ppm, 7/10 at 44.5 ppm, and 9/10 at 74.9 ppm (Hoechst 1989; BASF 1990b); clinical signs resolved (were reversible) at 15.6 ppm (BASF 1990b).

AEGL-3 Values for Phenyl Chloroformate

10 min	30 min	1 h	4 h	8 h
0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm

Key references:
BASF. 1990. Study on the Acute Inhalation Toxicity LC_{50} of Phenyl Chloroformate as a Vapor in Rats, 4-Hour Exposure. Project No. 13I0675/887076. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology: Ludwigshafen, Germany. January 18, 1990.

Hoechst. 1989. Chloroformic Acid Phenyl Ester. Aerosol Inhalation Toxicity in Male and Female SPF Wistar Rats. 4-Hour LC_{50}. Hofmann, T. Hoechst Pharmaceutical Research Toxicology. Report No. 89.0761. April 26, 1989.

Test species/Strain/Sex/Number: Rat; Sprague Dawley; 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 1.76, 15.6, 44.5, 74.9, 97,156, 159.2, and 311 ppm for 4 h

End point/Concentration/Rationale: Lethality threshold, $BMCL_{05}$ =3.6 ppm

(Continued)

AEGL-3 Continued (*Phenyl Chloroformate*)

Effects:	
Concentration	Mortality
1.76 ppm	0/10
15.6 ppm	2/10
44.5 ppm	7/10
74.9 ppm	9/10
97 ppm	9/10
156 ppm	10/10
159.3 ppm	10/10
311 ppm	10/10

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Furthermore, interspecies and intraspecies uncertainty factors of 3 were also used in determining the AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate, and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data on these analogs.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; default values of $n = 3$ for extrapolating to shorter durations and $n = 1$ for extrapolating to longer durations (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value.

Data adequacy: Sparse data set.

Derivation Summary 2-Ethylhexyl Chloroformate

AEGL-1 Values for 2-Ethylhexyl Chloroformate

      The data on 2-ethylhexyl chloroformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for 2-Ethylhexyl Chloroformate

10 min	30 min	1 h	4 h	8 h
1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm

Data adequacy: In the absence of specific data on 2-ethylhexyl chloroformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). This approach is justified based on the steep concentration curve with regard to lethality; mortality rates in rats exposed to 2-ethylhexyl chloroformate for 4 h were 0/20 at 22.8 ppm, 5/20 at 26.6 ppm, 9/20 at 34.3 ppm, and 20/20 at 46.9 ppm (BASF 1985).

AEGL-3 Values for 2-Ethylhexyl Chloroformate

10 min	30 min	1 h	4	8 h
3.6 ppm	3.6 ppm	2.9 ppm	1.8 ppm	0.91 ppm

Key reference: BASF. 1985. Acute Inhalation Toxicity LC_{50} for a 4-Hour Exposure (Rats), Vapor Test of 2-Ethylhexyl Chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology: Ludwigshafen, Germany. February 8, 1985.

Test species/Strain/Sex/Number: Rats; Wistar; 10 males and 10 females per group

Exposure route/Concentrations/Durations: Inhalation; 22.8, 26.6, 34.3, and 46.9 ppm for 4 h

End point/Concentration/Rationale: Lethality threshold, $BMCL_{05}$ = 18.1 ppm

Effects:

Concentration	Male Mortality	Female Mortality	Male and Female Mortality
22.8 ppm	0/10	0/10	0/20
26.6 ppm	4/10	1/10	5/20
34.3 ppm	7/10	2/10	9/20
46.9 ppm	10/10	10/10	20/20

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The effects of the chloroformates result from the direct-acting corrosive effects of the chemicals on the airways, in the absence of other systemic effects. Supporting information for this mode of action comes from observations of nasal irritation and respiratory effects (pulmonary inflammation, pulmonary edema, and emphysema) observed in humans and animals for several chloroformates evaluated in this report. Interspecies and intraspecies uncertainty factors of 3 are often used for respiratory irritants because pharmacodynamic variability is probably minimal (within a factor of 3) for irritants and because metabolic (pharmacokinetic) differences among species and individuals are unlikely to play a major role in direct-acting irritation or corrosion at the portal-of-entry (respiratory tract). Furthermore, interspecies and intraspecies uncertainty factors of 3 were also used in determining the AEGL-3 values for the structural analogs, methyl chloroformate, isopropyl chloroformate, and *n*-butyl chloroformate, and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data on these analogs.

(Continued)

AEGL-3 Continued (*2-Ethylhexyl Chloroformate*)

Modifying factor: Not applicable
Animal-to-human dosimetric adjustment: Insufficient data
Time scaling: $C^n \times t = k$; default values of $n = 3$ for extrapolating to shorter durations and $n = 1$ for extrapolating to longer durations (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value.
Data adequacy: Sparse data set.

Derivation Summary Ethyl Chlorothioformate

AEGL-1 Values for Ethyl Chlorothioformate

The data on ethyl chlorothioformate were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Ethyl Chlorothioformate

10 min	30 min	1 h	4 h	8 h
1.0 ppm	1.0 ppm	0.80 ppm	0.50 ppm	0.25 ppm

Data adequacy: In the absence of specific data on ethyl chlorothioformate to derive AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. This calculation is used to estimate a threshold for irreversible effects if a chemical has a steep concentration-response curve (NRC 2001). This approach is justified based on the steep concentration curve with regard to lethality; mortality rates in rats exposed to ethyl chlorothioformate for 4 h were 4/20 at 33 ppm, 14/20 at 59 ppm, and 20/20 at 65 ppm (Stauffer Chemical Company 1983).

AEGL-3 Values for Ethyl Chlorothioformate

10 min	30 min	1 h	4 h	8 h
3.0 ppm	3.0 ppm	2.4 ppm	1.5 ppm	0.75 ppm

Key reference: Stauffer Chemical Company. 1983. Acute Inhalation Toxicity of Ethyl Chlorothioformate in Rats (T-10710). Environmental Health Center Inhalation Facility. Stauffer Chemical Company: Farmington, CT. OTS0538464.
Test species/Strain/Sex/Number: Rat; Sprague Dawley; 10 males and 10 females per group
Exposure route/Concentrations/Durations: Inhalation; 0, 33, 59, 65, 69, or 124 ppm for 4 h (estimated lethality threshold of 1/3 the 4-hour rat LC_{50} of 45 ppm ($1/3 \times 45$ ppm = 15 ppm) is the point-of-departure for AEGL-3)
End point/Concentration/Rationale: 4-h lethality threshold estimated by dividing the LC_{50} of 45 ppm by 3, for a point-of-departure of 15 ppm.
Effects: $LC_{50} = 51$ ppm (males); 41 ppm (females); 45 ppm (males and females)

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because ethyl chlorothioformate and other chloroformates are respiratory irritants and pharmacodynamic variability between species is probably minimal (within a factor of 3).
Intraspecies: 3, because the observed LC_{50}s for ethyl chlorothioformate and ethyl chloroformate were similar
Modifying factor: No applicable
Animal-to-human dosimetric adjustment: Insufficient data
Time scaling: $C^n \times t = k$; default values of $n = 3$ for extrapolating to shorter durations and $n = 1$ for extrapolating to longer durations (NRC 2001). The 30-min AEGL-3 value was adopted for the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value.
Data adequacy: Database included only lethality studies in rats.

Appendix E

Category Plots for Selected Chloroformates
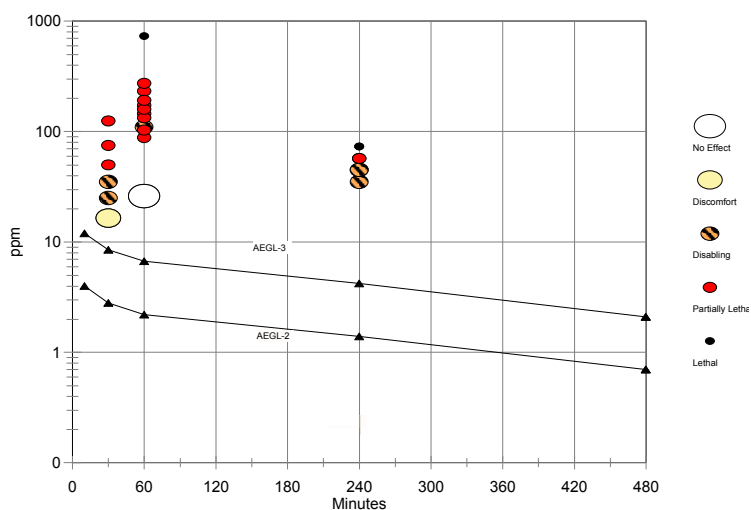
FIGURE E-1 Category plot of toxicity data and AEGL values for methyl chloroformate.
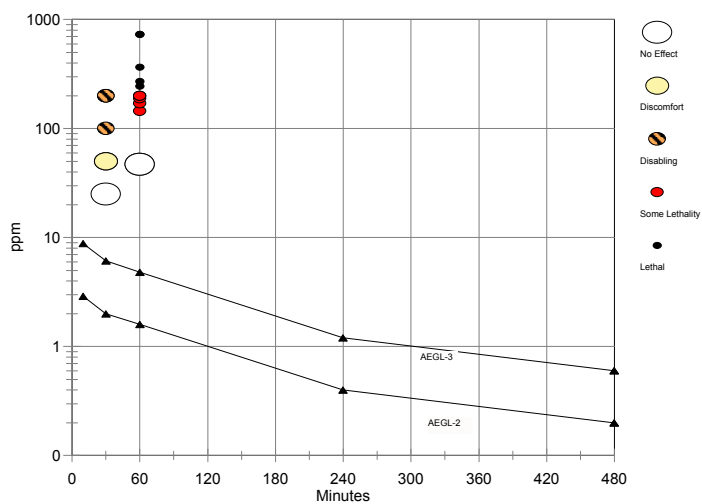
FIGURE E-2 Category plot of toxicity data and AEGL values for ethyl chloroformate.

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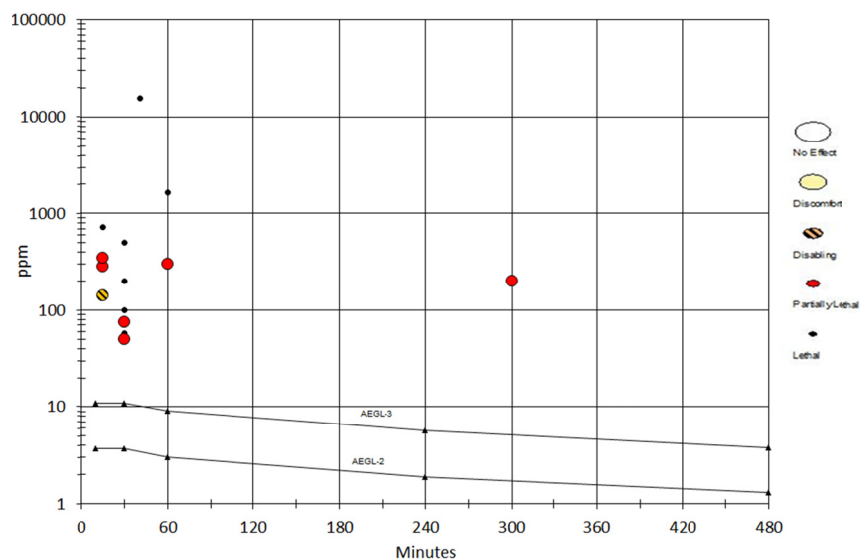
FIGURE E-3 Category plot of toxicity data and AEGL values for isopropyl chloroformate.
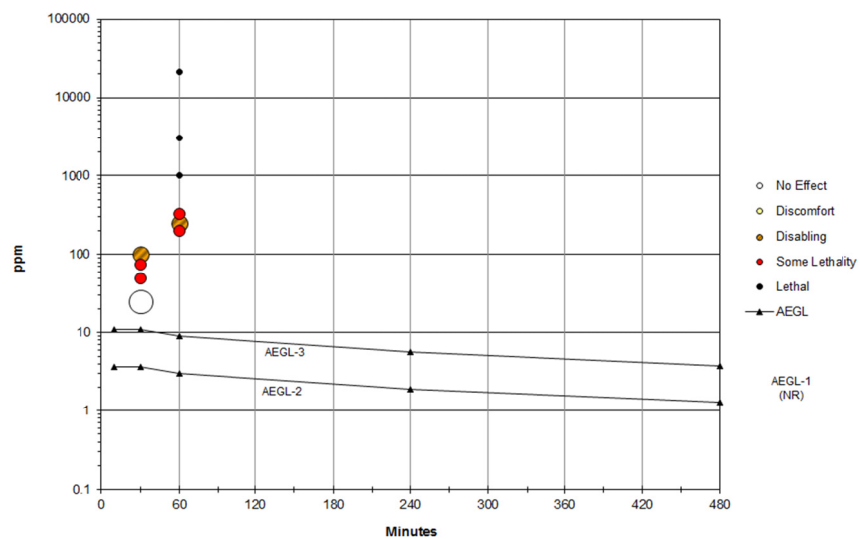
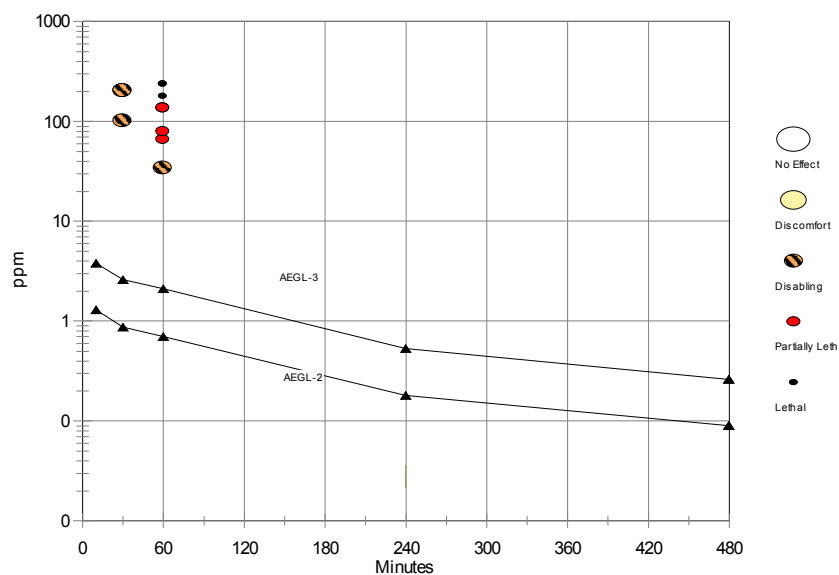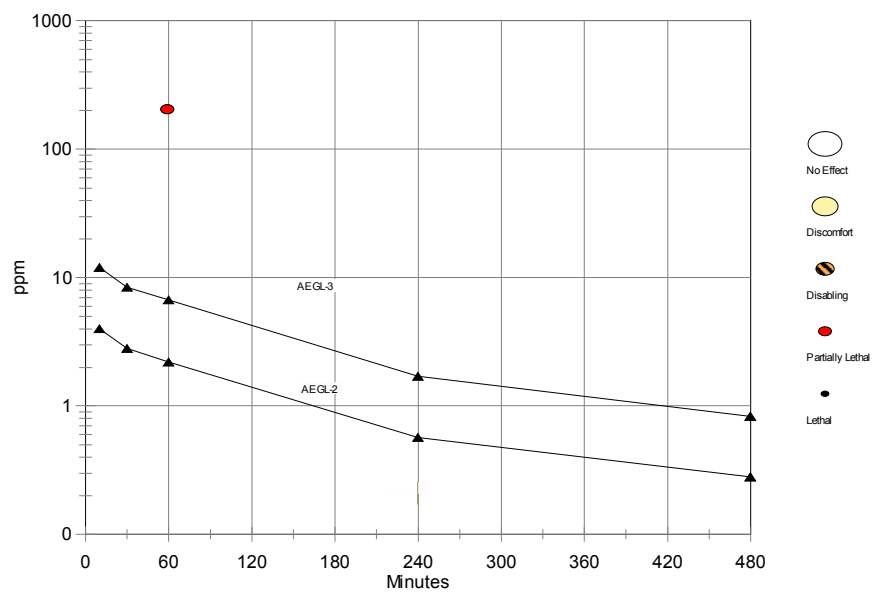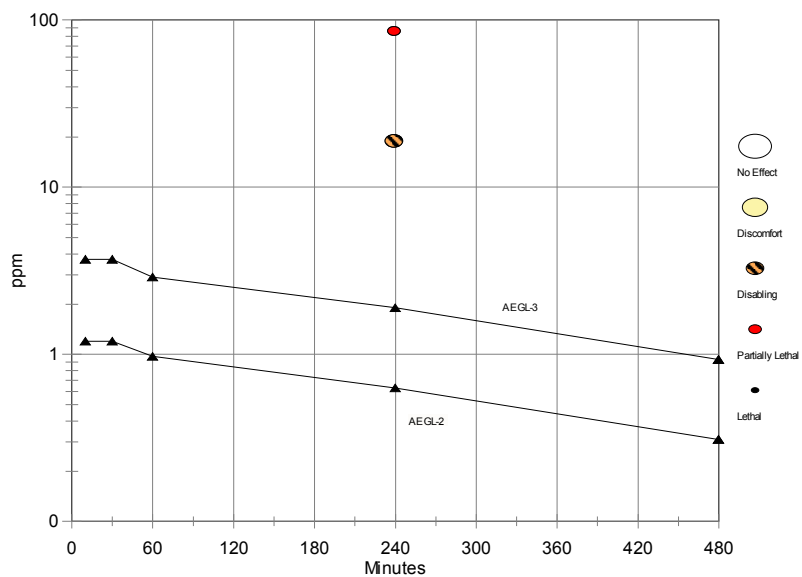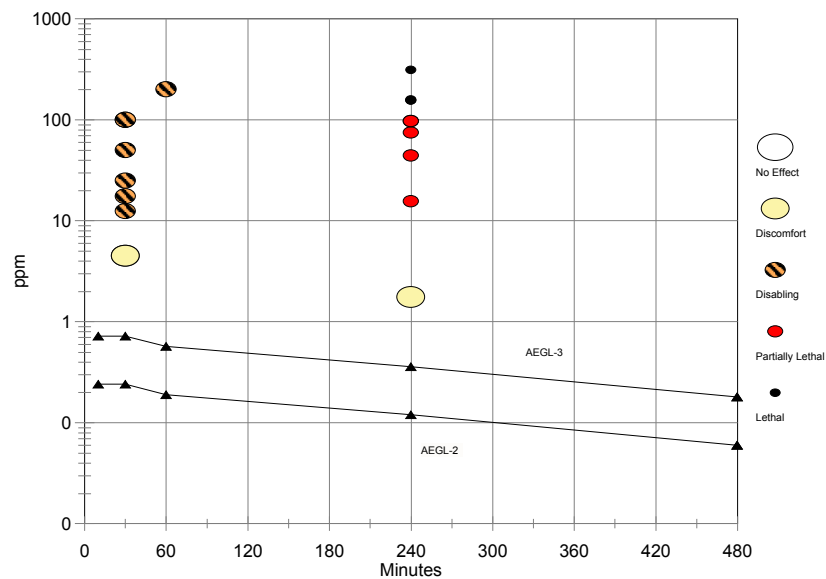**FIGURE E-4** Category plot of toxicity data and AEGL values for *n*-propyl chloroformate.

FIGURE E-5 Category plot of toxicity data and AEGL values for allyl chloroformate.

TABLE E-6 Category plot of toxicity data and AEGL values for *n*-butyl, isobutyl, and *sec*-butyl chloroformate.

FIGURE E-7 Category plot of toxicity data and AEGL values for benzyl chloroformate.

FIGURE E-8 Category plot of toxicity data and AEGL values for phenyl chloroformate.
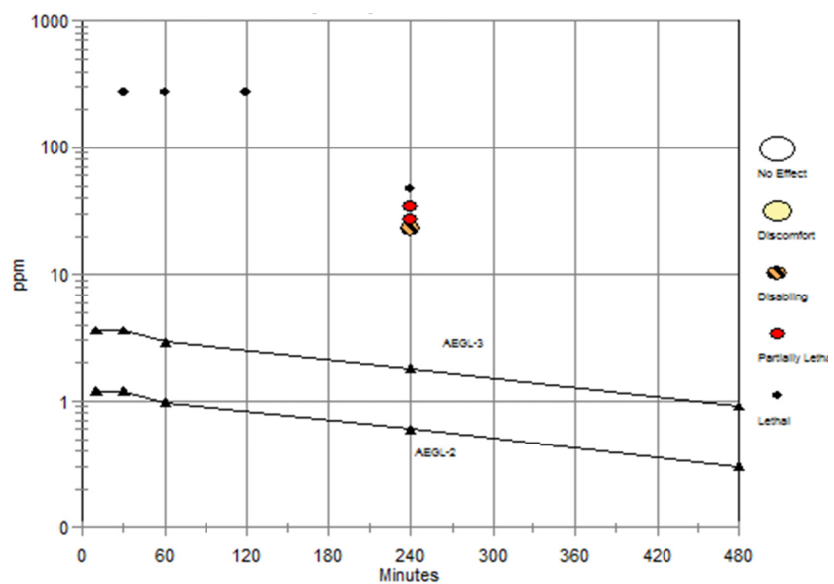
FIGURE E-9 Category plot of toxicity data and AEGL values for 2-ethylhexyl chloroformate.
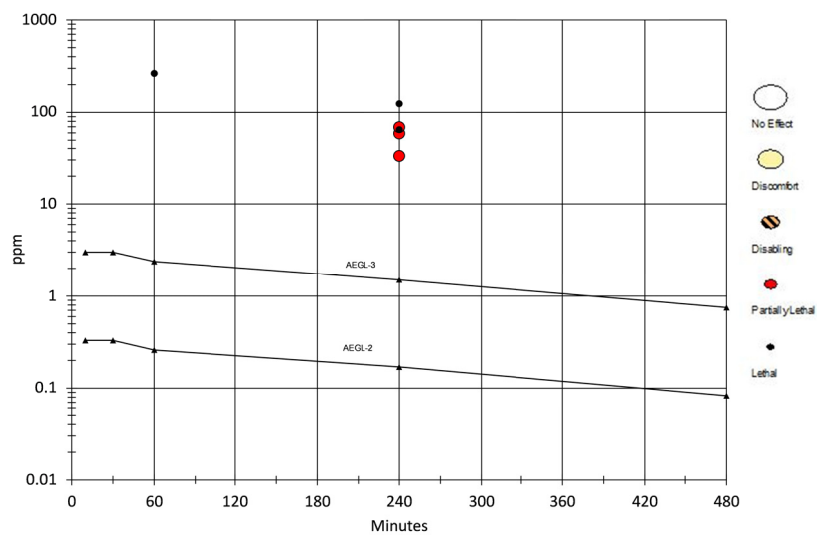

FIGURE E-10 Category plot of toxicity data and AEGL values for ethyl chlorothioformate.