INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROFORMATES

Methyl Chloroformate C₂H₃ClO₂ (CAS Reg. No. 79-22-1)

Ethyl Chloroformate C₃H₅ClO₂ (CAS Reg. No. 541-41-3)

Propyl Chloroformate C₄H₇ClO₂ (CAS Reg. No. 109-61-5)

Isopropyl Chloroformate C₄H₇ClO₂ (CAS Reg. No. 108-23-6)

Allyl Chloroformate C₄H₅ClO₂ (CAS Reg. No. 2937-50-0)

n-Butyl Chloroformate C₅H₉ClO₂ (CAS Reg. No. 592-34-7)

Isobutyl Chloroformate C₅H₁₀ClO₂ (CAS Reg. No. 543-27-1)

sec-Butyl Chloroformate C₅H₉ClO₂ (CAS Reg. No. 17462-58-7)

Benzyl Chloroformate C₈H₇ClO₂ (CAS Reg. No. 501-53-1)

Phenyl Chloroformate C₇H₅ClO₂ (CAS Reg. No. 1885-14-9)

2-Ethylhexyl Chloroformate C₉H₁₇ClO₂ (CAS Reg. No. 24468-13-1)

Ethyl Chlorothioformate C₃H₅ClO-S (CAS Reg. No. 2941-64-2)

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

PREFACE

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

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

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

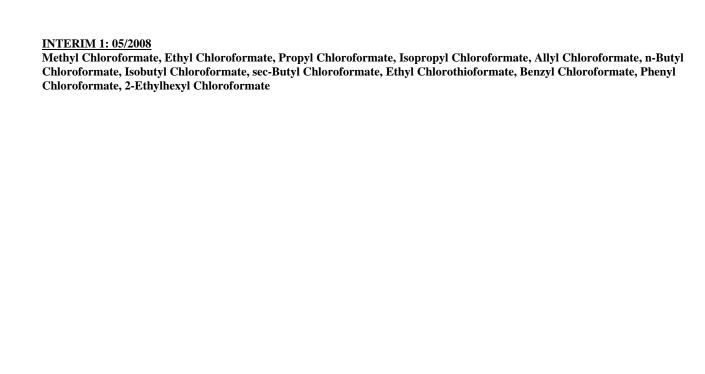
AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

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

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

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

I.1 General Chemical and Physical Properties

Chloroformates are generally clear, colorless liquids with relatively low freezing points and relatively high boiling points (>100EC). They are soluble in organic solvents, and hydrolyze in water. Lower chloroformates (such as methyl and ethyl chloroformate) hydrolyze rapidly in water at room temperature, and the higher and aromatic chloroformates hydrolyze more slowly at room temperature (Kreutzberger, 2003).

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> primary alkyl> secondary alkyl> tertiary alkyl (Kreutzberger, 2003).

Available physicochemical properties of the title chloroformates are presented in Tables I-1 through I-12.

TABLE I-1. Chemical and Physical Data for Methyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Methyl Chloroformate	HSDB, 2005a
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, 2005a
CAS Registry No.	79-22-1	HSDB, 2005a
Chemical Formula	C ₂ H ₃ ClO ₂	HSDB, 2005a
Molecular Weight	94.5	HSDB, 2005a
Physical State	Colorless liquid	HSDB, 2005a
Vapor Pressure	108.5 mm Hg at 25EC	HSDB, 2005a
Vapor Density	3.26 g/L (air = 1)	HSDB, 2005a
Density/Specific Gravity	1.223 g/cm ³	HSDB, 2005a
Melting/Boiling/Flash Point	-61EC/71.0EC/12.2EC	HSDB, 2005a
Solubility	slightly soluble (hydrolyzes) in water; Soluble in chloroform, benzene, alcohol, ether	HSDB, 2005a
Conversion factors in air	$1 \text{ mg/m}^3 = 0.26 \text{ ppm}$ $1 \text{ ppm} = 3.9 \text{ mg/m}^3$	

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

TABLE I-2. Chemical and Physical Data for Ethyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Ethyl Chloroformate	HSDB, 2005b
Synonyms	Ethyl chlorocarbonate	HSDB, 2005b
CAS Registry No.	541-41-3	HSDB, 2005b
Chemical Formula	C ₃ H ₅ ClO ₂	HSDB, 2005b
Molecular Weight	108.53	HSDB, 2005b
Physical State	Water-white liquid	HSDB, 2005b
Vapor Pressure	22.4 mm Hg at 25EC	HSDB, 2005b
Vapor Density	3.7 g/L (air = 1)	HSDB, 2005b
Density/Specific Gravity	1.403 g/cm ³	HSDB, 2005b
Melting/Boiling/Flash Point	-80.6EC/95EC/27.8EC	HSDB, 2005b
Solubility	Gradually decomposes in water	HSDB, 2005b
Conversion factors in air	1 mg/m ³ = 0.23 ppm 1 ppm = 4.4 mg/m ³	

TABLE I-3. Chemical and Physical Data for Propyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Propyl Chloroformate	HSDB, 2005c
Synonyms	Carbonochloridic acid, propyl ester; Formic acid, chloro-, propyl ester; Propyl chlorocarbonate; N-Propyl chloroformate	HSDB, 2005c
CAS Registry No.	109-61-5	HSDB, 2005c
Chemical Formula	C ₄ H ₇ ClO ₂	HSDB, 2005c
Molecular Weight	122.55	HSDB, 2005c
Physical State	Colorless liquid	HSDB, 2005c
Vapor Pressure	20 mm Hg at 25EC	HSDB, 2005c
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005c
Density/Specific Gravity	1.09 g/cm ³	HSDB, 2005c
Boiling/Flash Point	112.4EC/34.4EC	HSDB, 2005c
Solubility	Miscible in chloroform, benzene, ether	HSDB, 2005c
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ $1 \text{ ppm} = 5.0 \text{ mg/m}^3$	

TABLE I-4. Chemical and Physical Data for Isopropyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Isopropyl Chloroformate	HSDB, 2005d

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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, 2005d
CAS Registry No.	108-23-6	HSDB, 2005d
Chemical Formula	C ₄ H ₇ ClO ₂	HSDB, 2005d
Molecular Weight	122.55	HSDB, 2005d
Physical State	Colorless liquid	HSDB, 2005d
Vapor Pressure	100 mm Hg at 47EC	HSDB, 2005d
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005d
Density/Specific Gravity	1.08 g/cm ³	HSDB, 2005d
Boiling/Flash Point	104.6EC/27.8EC	HSDB, 2005d
Solubility	Soluble in ether; hydrolyzes in water	HSDB, 2005d
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ $1 \text{ ppm} = 5.0 \text{ mg/m}^3$	

TABLE I-5. Chemical and Physical Data for Allyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Allyl Chloroformate	HSDB, 2005e
Synonyms	Chloroformic acid, allyl ester; Allyl Chlorocarbonate	HSDB, 2005e
CAS Registry No.	2937-50-0	HSDB, 2005e
Chemical Formula	C ₄ H ₅ ClO ₂	HSDB, 2005e
Molecular Weight	120.54	HSDB, 2005e
Physical State	Colorless liquid	HSDB, 2005e
Vapor Pressure	20 mm Hg at 25EC	HSDB, 2005e
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005e
Density/Specific Gravity	1.14 g/cm ³	HSDB, 2005e
Boiling/Flash Point	110EC/31.1EC	HSDB, 2005e
Solubility	Hydrolyzes in water	HSDB, 2005e
Conversion factors in air	1 mg/m ³ = 0.20 ppm 1 ppm = 4.9 mg/m ³	

TABLE I-6. Chemical and Physical Data for n-Butyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	n-butyl Chloroformate	Kreutzberger, 2003
Synonyms	Butyl chlorocarbonate; Butoxycarbonyl chloride; Chloroformic acid, butyl ester	BG Chemie, 2005

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

CAS Registry No.	592-34-7	Kreutzberger, 2003
Chemical Formula	C ₅ H ₉ ClO ₂	Kreutzberger, 2003
Molecular Weight	136.58	Kreutzberger, 2003
Physical State	liquid	BG Chemie, 2005
Vapor Pressure	7 hPa at 20EC	BG Chemie, 2005
Vapor Density	-	-
Density/Specific Gravity	1.06 g/cm ³	Kreutzberger, 2003
Solubility	Poorly soluble (hydrolyzes) in water; Miscible in ether; soluble in acetone and ethanol	BG Chemie, 2005
Boiling/Flash Point	77.6EC/46.0EC	Kreutzberger, 2003
Conversion factors in air	$1 \text{ mg/m}^3 = 0.18 \text{ ppm}$ $1 \text{ ppm} = 5.6 \text{ mg/m}^3$	

TABLE I-7. Chemical and Physical Data for Isobutyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	Isobutyl Chloroformate	Kreutzberger, 2003
Synonyms	Carbonochloridic acid, 2-methylpropyl ester; Isobutyl chlorocarbonate	O'Neil et al., 2001
CAS Registry No.	543-27-1	O'Neil et al., 2001
Chemical Formula	$C_5H_{10}ClO_2$	O'Neil et al., 2001
Molecular Weight	136.58	O'Neil et al., 2001
Physical State	Clear liquid	O'Neil et al., 2001
Vapor Pressure	-	-
Vapor Density	-	-
Density/Specific Gravity	1.04 g/cm ³	O'Neil et al., 2001
Boiling/Flash Point	130EC/39.4EC	O'Neil et al., 2001
Solubility	Miscible in chloroform, benzene, ether; Gradually decomposes in water	O'Neil et al., 2001
Conversion factors in air	$1 \text{ mg/m}^3 = 0.18 \text{ ppm}$ $1 \text{ ppm} = 5.6 \text{ mg/m}^3$	

TABLE I-8. Chemical and Physical Data for sec-Butyl Chloroformate		
Characteristic/Property	Data	Reference
Common Name	sec-Butyl Chloroformate	Kreutzberger, 2003
Synonyms	Carbonochloridic acid, 1-methylpropyl ester	NLM, 2005
CAS Registry No.	17462-58-7	NLM, 2005
Chemical Formula	C ₅ H ₉ ClO ₂	Kreutzberger, 2003

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Molecular Weight	136.58 Kreutzberger, 2003		
Physical State	Colorless liquid	Kreutzberger, 2003	
Vapor Pressure	-	-	
Vapor Density	-	-	
Density/Specific Gravity	1.049 g/cm ³	Kreutzberger, 2003	
Boiling/Flash Point	NA/35.6EC	Kreutzberger, 2003	
Solubility	-	-	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.18 \text{ ppm}$ $1 \text{ ppm} = 5.6 \text{ mg/m}^3$		

TABLE I-9. Chemical and Physical Data for Benzyl Chloroformate Characteristic/Property Reference **Data** Benzyl Chloroformate Common Name Kreutzberger, 2003 Carbonochloridic acid phenyl methyl O'Neil et al., 2001 Synonyms ester; Carbobenzoxy chlorode; Chloroformic acid benzyl ester; Benzyl carbonyl chloride CAS Registry No. 501-53-1 O'Neil et al., 2001 Chemical Formula C₈H₇ClO₂ O'Neil et al., 2001 170.60 Molecular Weight O'Neil et al., 2001 Physical State Clear to pale yellow liquid HSDB, 2006 IPCS, 1999 Vapor Pressure 0.009 kPa at 85-87EC Vapor Density 1 g/L (air = 1)IPCS, 1999 Density/Specific Gravity 1.22 g/cm³ Kreutzberger, 2003 103EC/80EC Boiling/Flash Point O'Neil et al., 2001 Solubility Decomposes in water O'Neil et al., 2001 Conversion factors in air $1 \text{ mg/m}^3 = 0.14 \text{ ppm}$ 1 ppm = 7.0 mg/m^3

TABLE I-10. Chemical and Physical Data for Phenyl Chloroformate					
Characteristic/Property	Data	Reference			
Common Name	Phenyl Chloroformate Kreutzberger, 200				
Synonyms	Carbonochloridic acid phenyl ester; Phenyl chlorocarbonate; Phenoxycarbonyl chloride; Formic acid, chloro-, phenyl ester	IPCS, 2005			
CAS Registry No.	1885-14-9	IPCS, 2005			
Chemical Formula	C ₇ H ₅ ClO ₂	IPCS, 2005			
		IPCS, 2005			
		IPCS, 2005			

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Vapor Pressure	90 Pa at 20EC	IPCS, 2005	
Vapor Density	5.41 g/L (air = 1)	IPCS, 2005	
Density/Specific Gravity	1.25 g/cm ³	Kreutzberger, 2003	
Boiling/Flash Point	188-189EC/69EC	IPCS, 2005	
Solubility	Decomposes in water	IPCS, 2005	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.16 \text{ ppm}$ $1 \text{ ppm} = 6.4 \text{ mg/m}^3$		

TABLE I-11. Chemical and Physical Data for 2-Ethylhexyl Chloroformate					
Characteristic/Property	Data	Reference			
Common Name	2-Ethylhexyl Chloroformate	Kreutzberger, 2003			
Synonyms	Chloroformic acid 2-ethylhexyl ester; Carbonochloridic acid, 2-ethylhexyl ester; 2-Ethylhexyl chlorocarbonate; Formic acid, chloro-, 2-ethylhexyl ester	RTECS, 2005			
CAS Registry No.	24468-13-1	RTECS, 2005			
Chemical Formula	C ₉ H ₁₇ ClO ₂	RTECS, 2005			
Molecular Weight	192.71	RTECS, 2005			
Physical State	Clear, colorless liquid	RTECS, 2005			
Vapor Pressure	1 mm Hg at 45EC	RTECS, 2005			
Vapor Density	>1 g/L (air = 1)	RTECS, 2005			
Density/Specific Gravity	0.9914 g/cm ³	Kreutzberger, 2003			
Boiling/Flash Point	208EC/NA	Kreutzberger, 2003			
Solubility	Decomposes in water	RTECS, 2005			
Conversion factors in air $ 1 \text{ mg/m}^3 = 0.13 \text{ ppm} $ $ 1 \text{ ppm} = 7.9 \text{ mg/m}^3 $					

TABLE I-12. Chemical and Physical Data for Ethyl Chlorothioformate					
Characteristic/Property	Data	Reference			
Common Name	Ethyl Chlorothioformate	HSDB, 2005f			
Synonyms	Ethylthiol chloroformate; Ethylthiocarbonyl chloride; Formin acid, chlorothio-, S-ethyl ester	HSDB, 2005f			
CAS Registry No.	2941-64-2	HSDB, 2005f			
Chemical Formula	C ₃ H ₅ ClO-S	HSDB, 2005f			
Molecular Weight	124.59	HSDB, 2005f			
Physical State	Amber liquid	Stauffer Chemical Company, 1983			
Vapor Pressure	8.3 mm Hg at 21EC	Stauffer Chemical Company, 1983			

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Vapor Density	-	-	
Density/Specific Gravity	1.19 g/cm ³	Stauffer Chemical Company, 1983	
Freezing/Boiling/Flash Point	-60EC/132EC/51.7EC	Stauffer Chemical Company, 1983	
Solubility	decomposes in water	Stauffer Chemical Company, 1983	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ $1 \text{ ppm} = 5.1 \text{ mg/m}^3$		

I.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, 2003).

Chloroformates are used as intermediates in the synthesis of pesticides, herbicides, perfumes, pharmaceuticals, foods, polymers, and dyes. Chloroformates 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, 2003).

I.3 Absorption, Metabolism, Disposition and Excretion

Information concerning the metabolism and disposition of chloroformates was not located in the available literature.

I.4 Mechanism of Toxicity

Chloroformates hydrolyze in water or moist air to produce the parent hydroxy compound, hydrogen chloride, carbon dioxide, and a carbonate. They are direct-acting contact irritants, and are corrosive to the eyes, skin, gastrointestinal and respiratory tracts. Inhalation may result in coughing, labored breathing, sore throat, unconsciousness, convulsions, and death. Lung edema frequently occurs, and symptoms of this edema may not manifest for several hours after exposure and may be aggravated by physical exertion. Ingestion may result in a burning sensation of the digestive tract, nausea, vomiting, and abdominal pain (Kreutzberger, 2003).

I.5 Concurrent Exposure Issues

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

I.6 Species Sensitivity

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

No rigorous comparative information concerning species differences and acute chloroformate toxicity were located. However, given their highly-reactive nature and the fact that chloroformates are direct-acting irritants, little interspecies variability would be expected. Limited RD_{50} data for methyl, ethyl, propyl, isopropyl, isoobutyl, sec-butyl, and phenyl chloroformates seem to suggest that the mouse may be more sensitive than the rat. However, this is likely an artifact of the RD_{50} procedure stressing the mice (restrained with collar), and is not likely indicative of an increased sensitivity to chloroformates.

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I.7 Temporal Extrapolation

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). Thus, exponential scaling ($C^n x t = k$) will be used to derive exposure duration-specific AEGL values for the chloroformates.

Empirical data were not available for derivation of the exponent "n" for any of the title chloroformates. In the absence of chemical specific data, an n of 3 will be applied to extrapolate to shorter time periods, and an n of 1 will be applied to extrapolate to longer time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl
Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl
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CHAPTER II. METHYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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SUMMARY: Methyl Chloroformate

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

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for methyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat LC_{50} : 51-53 ppm, 0% mortality in rats exposed to 45 ppm and 80% mortality in rats exposed to 57 ppm for 4 hours (Hoechst, 1986); 1-hour rat LC_{50} : 100 ppm; rats exposed to 26 ppm for 1-hr were clinically normal and had no mortality (Fisher et al., 1981)).

The calculated 4-hr BMCL $_{05}$ value in rats (42.4 ppm) (Hoechst, 1986) was used as the point-of-departure for methyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 each were applied because methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by c^n x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-min, 30-min and 1-hr) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC $_{50}$ study (Bio-Test, 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 Hoechst (1986).

The AEGL values are listed in the table below.

	Summary of AEGL Values For Methyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	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)	1/3 the AEGL-3 values (Hoechst, 1986)	
AEGL-3 (Lethality)	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 (BMCL ₀₅) in the rat after a 4-hour exposure (Hoechst,1986)	

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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II.1. HUMAN TOXICITY DATA

II.1.1 Acute Lethality

No data concerning human lethality from methyl chloroformate exposure were located in the available literature.

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II.1.2 Non-lethal Toxicity

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II.1.2.1 Case Reports

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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 eye 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 lobes. The next day (about 24 hours later), a followup 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 37.2EC. The worker was kept for observation over night, with an oxygen supply, a bronchodilator (Brondilat) and 40 mg Urbason i.v. During the night the symptoms receded and the worker slept well to the early morning hours. At that time, the cough resumed and auscultation showed slight dry rales in the right lower lung lobe. The worker was sent home following administration of Omnicillin and Codipront. Examination on 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 with a morning cough still present, and drug treatment was discontinued.

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In another report, a 46-year-old male worker was exposed to methyl chloroformate in the process of repairing a methyl chloroformate pipeline (Penkovitch and Anikin, 1988). The liquid soaked his clothes 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 minutes. Methyl chloroformate concentrations were not reported. He returned to his home and reported no abnormal symptoms for 4-5 hours. 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 hours after the accident.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

He presented with pulmonary edema which resolved within 24 hours after treatment with Prednisolone and Lasix.

II.1.3 Developmental/Reproductive Toxicity

Developmental or reproductive studies regarding acute human exposure to methyl chloroformate were not available.

II.1.4 Genotoxicity

Genotoxic studies regarding acute human exposure to methyl chloroformate were not available.

II.1.5 Carcinogenicity

Carcinogenicity studies regarding human exposure to methyl chloroformate were not available.

II.1.6 Summary

Case reports of methylchloroformate toxicity exist; however, details of exposure concentration and duration are unreported. 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 hours (Schuckmann, 1972) and 22 hours (Penkovitch and Anikin, 1988). No data concerning lethality, developmental/reproductive toxicity, genotoxicity, and carcinogenicity in humans from methyl chloroformate exposure were located in the available literature.

II.2 ANIMAL TOXICITY DATA

32 II.2.1 Lethality33 II.2.1.1 Rats

233, or 274 ppm (nominal concentrations) methyl chloroformate vapor for 1 hour, followed by a 14-day observation period (Bio-Test Laboratories, Inc., 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-hour LC_{50} was determined to be 163 ppm, and the calculated BMCL $_{05}$ is 74 ppm. Males appear 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 sacrificed on day 14 post-exposure and in rats that died

Groups of five male and five female Charles River albino rats were exposed to 0, 145, 173,

parenchyma was observed in animals sacrificed on day 14 during the experiment. Data are summarized in Table II-1.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

TABLE II-1*. Mortality of Rats Exposed to Methyl Chloroformate for 1-hour				
Concentration (ppm)	Male	Female		
0	0/5	0/5		
145	4/5	0/5		
173	5/5	2/5		
233	5/5	4/5		
274	5/5	1/5		
BMCL ₀₅	74 ppm			
LC ₅₀		163 ppm		

^{*}Bio Test Laboratories, Inc. (1975)

In another study, groups of ten male Sprague Dawley rats were exposed to 735, 2947, 9610, or 66,235 ppm (nominal concentrations) methyl chloroformate for 1 hour (WARF Institute, Inc., 1972). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air flow was utilized. 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 hours of exposure. Data are summarized in Table II-2.

TABLE II-2*. Mortality of Rats Exposed to Methyl Chloroformate for 1-hour				
Concentration (ppm) Results				
735	735 10/10 dead at 20 minutes into exposure			
2,947	9/10 dead at end of 1-hour exposure; 1/10 dead 2 minutes post-exposure			
9,610	5/10 dead at end of 1-hour exposure; 5/10 dead 10 minutes post-exposure			
66,235	All 10 animals survived the 1 hour exposure. 7/10 dead 3 hours post-exposure; 3/10 dead within 18 hours post-exposure			

^{*}WARF Institute, Inc. (1972)

Groups of five male and five female Fischer 344 rats (main group) were exposed to 0, 26, 110, 133, 159, or 192 ppm methyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber (Fisher et al., 1981). Methyl chloroformate chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. In addition 10, 10, and 20 rats/sex (satellite rats) were concurrently exposed to 26, 110, or 133 ppm methyl chloroformate, respectively. One satellite rat/sex/concentration and 2 rats/sex at the lower three concentrations of the main group were sacrificed at 4 and 24 hours and 9 or 10 days post-exposure. All other surviving animals were sacrificed 14 days post-exposure. The LC₅₀ values were 100 ppm for female rats, and between 92 and 123 ppm for male rats at 14 days post-exposure. Respiratory distress occurred in all main group rats at 110, 133, 159, and 192 ppm during the first 24 hours following exposure. The respiratory distress resolved within 24 hours in the 110 ppm group;

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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 lung lesions were observed in rats 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 to 26 ppm. Lesions in satellite rats exposed to 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. By day 9 or 10, the nasal turbinate effects had resolved, but regeneration was incomplete and purulent rhinitis persisted. Other respiratory tract and lung lesions seen at 4 and 24 hours had 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 receiving 26 ppm.

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

Groups of five male and five female SPF Wistar rats were exposed to 35, 45, 57, or 73 ppm (analytical concentrations) methyl chloroformate for 4-hours followed by a 14-day observation period (Hoechst, 1986). The whole body exposures were performed in a 2.25 m³ exposure chamber operated under dynamic flow conditions. Methyl chloroformate concentrations were measured every 15 minutes during exposure using a single beam photometer, and were analytically measured every 120 minutes using gas chromatography. Clinical signs noted in all treatmentgroups 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/crackling breathing sounds, sneezing, and piloerection. Body weight gain was decreased in both sexes after exposures, but animals surviving to study termination regained initial body weight. There were no gross treatment-related effects noted 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 tract. Histopathological examination showed increased permeability in the alveolar septa and corresponding damage to bronchial epithelium; this effect was noted in all treatment groups. Four hour LC₅₀ values of 51 ppm and 53 ppm were calculated for males and females, respectively. A combined male and female BMCL₀₅ value of 42.4 ppm and combined male and female BMC₀₁ value of 47.8 ppm were calculated. Mortality data are summarized in Table II-3.

TABLE II-3*. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours						
Concentration (ppm)	Concentration (ppm) Male Female					
35 0/5 0/5						

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

45	0/5	0/5		
57	5/5	3/5		
73	5/5	5/5		
LC ₅₀	51 ppm	53 ppm		
BMCL_{05}	42.4 ppm			
BMC_{01}	47.8 ppm			

^{*}Hoechst, 1986

Groups of ten male and ten female Sprague-Dawley rats were exposed to 16, 65, 96, or 127 ppm (nominal concentrations) methyl chloroformate for 4-hours, followed by a 14-day observation period (BASF, 1980). Analytical concentrations are reported as 1.5, 13.7, 33.6, and 31.0 ppm for the 16, 65, 96, and 127 ppm groups, respectively. Whole body exposures were conducted in a glass-steel inhalation chamber with a volume of 200 L. Analytical concentrations were measured via 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 had 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_{05} value of 15 ppm was also calculated. It should be noted that the LC_{50} values calculated from this study appear to be inconsistent with the other available data (see

TABLE II-4*. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours					
Nominal Concentration (ppm)	Analytical Concentration (ppm)	Male	Female		
16	1.5	0/10	0/10		
65	13.7	5/10	3/10		
96	33.6	10/10	7/10		
127	31.0	10/10	10/10		
LC ₅₀		13 ppm	18 ppm		
		15 ppm			

*BASF, 1980

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

Death occurred in 11/12, 5/6, and 6/6 rats exposed to an "atmosphere enriched or saturated" with methyl chloroformate vapor at 20EC for 3, 10, and 30 minutes, respectively (BASF, 1978).

Table II-6). Data are summarized in Table II-4.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Clinical signs included vigorous escape behavior, extremely severe mucous membrane irritation, corneal opacity, dyspnea, and convulsions. Lung edema and emphysema and bilateral dilation of the heart were noted at necropsy.

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

 The following oral LD_{50} values were reported for rats: 190 mg/kg for male Sprague-Dawley (Vernot et al., 1977); 110 mg/kg for female Sprague-Dawley (Vernot et al., 1977); 313 mg/kg for male and female Sprague-Dawley rats combined (BASF, 1981b), and 220 mg/kg (WARF, 1972). A dermal LD_{50} value of 894 mg/kg was reported for male and female Sprague-Dawley rats combined (BASF, 1981c). In another study, a dermal LD_{50} of >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; this study is described in Section II.2.2.

II.2.1.2 Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 16.5, 25, 35, 50, 75, or 125 ppm methyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted methyl chloroformate was delivered to a Pitt #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 20 L/min. An RD $_{50}$ of 52.4 ppm was calculated. Results are summarized in Table II-5.

TABLE II-5. Exposure of Male Swiss-Webster Mice to Methyl Chloroformate for 30 minutes*						
Concentration (ppm)	Respiratory rates(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 hr.)			
75	275/100	63.6	1/4 (<6 hr.)			
125	250/50	80	4/4 (<5 hr.)			
125	280/50	82.1	3/4 (<20 hr.)			

.*Carpenter, 1982

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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

II.2.2. Repeated-Exposure

In an inhalation range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to 0, 1.9, 6.2, or 19.5 ppm methyl chloroformate 6 hours/day for 5 days (HRC, 1992). No treatment-related effects were noted 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 to 19.5 ppm. Animals were necropsied three 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 noted 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. Lung weight was increased in all high-concentration females; organ weights were not examined in males due to experimental error during necropsy. Inflammatory and erosive mucous membrane lesions were noted in the nose, larynx, and trachea, and bronchiolitis and pneumonia were noted in high-concentration rats. Focal epithelial hyperplasia of the nasal mucosa was noted in the 6.2 and 19.5 ppm groups. Comparison of histological findings in a satellite group examined immediately after three days of exposure suggested that regeneration and repair of epithelial lesions had occurred in animals examined three days post-exposure.

In a repeated-exposure study, groups of five male and five female Sprague-Dawley rats were exposed to 0, 0.13, 0.38, 1.01, 3.1, or 8.8 ppm methyl chloroformate 6 hours/day, 5 days/week for 4 weeks (BASF, 1993). Mortality was observed 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 animals. Increased packed cell volume, increased hemoglobin concentration, increased red cell count, increased neutrophil count, increased total protein, decreased albumin, increased globulin, decreased albumin/globulin ratio, and increased cholesterol were observed at 8.8 ppm as well. In addition, uncollapsed lungs, lung congestion, enlarged tracheobronchial and medistinal lymph nodes, and increased lung weight were observed at necropsy in rats exposed to 8.8 ppm. Histopathological lesions of the nasal turbinates were observed at 3.1 and 8.8 ppm, while lesions were observed in the larynx of animals exposed to 1.01, 3.1, and 8.8 ppm methyl chloroformate.

 Groups of ten male and ten female Wistar rats were exposed to 0, 0.40, 2.15, 3.98, or 7.83 ppm methyl chloroformate 6 hours/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, 1999). In addition to observation for clinical signs and complete necropsy, cell proliferation measurements were performed in four female rats per group. 5-Bromo-2'-deoxyuridine (BrdU) was administered to these females via subcutaneously implanted minipumps. Pumps remained in the animals for 8 hours or 3 days for evaluation of cell proliferation in 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 noted only in high-

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

concentration animals and included rubbing of snout, sneezing, nasal crusts in the animals that subsequently died, as well as abnormal respiration, and general morbidity. Decreased body weight and body weight gain were noted in males in the 3.98 and 7.83 ppm groups sacrificed 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 sacrificed after three exposures, exhibited increased lung weight. Concentration and duration-related histological effects were limited 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 were noted at 2.15, 3.98, and 7.83 ppm. Focal epithelial hyperplasia and squamous cell metaplasia and hyperplasia of the trachea and lungs were noted at 3.98 and 7.83 ppm. No histopathology was noted 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 involved respiratory and transitional cell epithelium of the nose and in the ciliated and squamous epithelium of the larynx. No cell proliferation was noted at 0.40 ppm.

Groups of four male and four female Alderly Park SPF rats were exposed to 1 ppm (fifteen 6-hour exposures, 5 ppm (fifteen 6-hr exposures), or 20 ppm (fifteen 6-hr exposures) methyl chloroformate vapor in isopropanol (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 noted at 5 ppm, and nasal irritation, respiratory difficulty, weight loss, lethargy, and poor condition were observed at 20 ppm. Distended lungs and lung hemorrhage, and kidney congestion were noted at autopsy in the 20 ppm group. No further details were provided.

II.2.3. Developmental/Reproductive Toxicity

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

II.2.4. Genotoxicity

Methyl chloroformate was negative in *Salmonella typhimuium* strains TA 98, TA 100, TA1535, and TA 1537 in the presence and absence of S9 mix (BASF, 1988; Miltenburger, 1985; Hoechst, 1977). Methyl chloroformate induced chromosome aberrations in Chinese hamster V79 cells in the presence of S-9 mix; no increase in aberrations was noted in the absence of S-9 mix (Miltenburger, 1986).

II.2.5 Carcinogenicity

Animal carcinogenicity data were not located.

II.2.6 Summary

Animal toxicity data include both acute and repeated-exposure inhalation studies. Rat 1-hr LC_{50} values were relatively consistent between studies as follows: 163 ppm for male and female

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Charles River rats (Bio-Test Laboratories, Inc., 1975), 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), and 88 ppm and 103 ppm for male and female Sprague Dawley rats, respectively (Vernot et al., 1977). Rat 4-hr LC₅₀ values were reported to be 51-53 ppm (Hoechst, 1986) and 15 ppm (BASF, 1980); 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, hematological effects consistent with decreased oxygen availability (assumed secondary to pulmonary congestion and edema), and bronchiolitis, fibrosis, and pulmonary edema. A 30-min RD₅₀ of 47.2 ppm (nominal concentration) methyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). Methyl chloroformate did not induce mutations in an Ames bacterial reverse mutation assay ((BASF, 1988; Miltenburger, 1985; Hoechst, 1977) but did induce chromosomal aberrations in Chinese hamster V79 cells in the presence of S9 (Miltenburger, 1986). No data concerning developmental/reproductive toxicity or carcinogenicity of methyl chloroformate were located in the available literature. Animal data are summarized in Table II-6.

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Table II-6. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate						
Species	Concentration (ppm)	Exposure Duration	Effect	Reference		
		1	Acute Exposure			
Rat	37,500	3 minutes	12/12 dead	BASF, 1978		
Rat	735 (nominal)	20 minutes	10/10 dead	WARF Institute, Inc., 1972		
Rat	26	1 hour	No effects	Fisher et al., 1981		
Rat	74 (nominal)	1 hour	BMCL ₀₅	Bio-Test Labs, Inc., 1975		
Rat-male	88	1 hour	LC ₅₀	Vernot et al., 1977		
Rat-male	92-123	1 hour LC ₅₀ Fisher et al., 19		Fisher et al., 1981		
Rat-female	100	1 hour	LC ₅₀	Fisher et al., 1981		
Rat-female	Rat-female 103 1 hour LC ₅₀ Ven		Vernot et al., 1977			
Rat	163 (nominal)	1 hour	LC ₅₀	Bio-Test Labs Inc., 1975		
Rat	2974 (nominal)	1 hour	10/10 dead	WARF Institute, Inc., 1972		
Rat	15	4 hours	LC ₅₀	BASF, 1980		
Rat	42.4 ppm	4 hours	BMCL ₀₅	Hoechst, 1986		
Rat-male	51	4 hours	LC ₅₀	Hoechst, 1986		
Rat-female	53	4 hours	LC ₅₀	Hoechst, 1986		
Mouse	52.4	30 minutes	RD ₅₀	Carpenter, 1982		
	•	Re	epeated Exposure	<u>.</u>		
Rat	0.40	6 hr/day, 3 days	No effects	BASF, 1999		
Rat	2.15	6 hr/day, 3 days	Histopathology	BASF, 1999		

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	Rat	3.98	6 hr/day, 3 days	Histopathology, decreased body weight	BASF, 1999
2	Rat	7.83	6 hr/day, 3 days	Clinical signs, histopathology, decreased body weight	BASF, 1999
3	Rat	1.9	6 hr/day, 5 days	No effects	HRC, 1992
4	Rat	6.2	6 hr/day, 5 days	Clinical signs consistent with irritation, focal epithelia hyperplasia; petechial lung bleeding	HRC, 1992
5	Rat	19.5	6 hr/day, 5 days	Clinical signs consistent with irritation, focal epithelia hyperplasia; inflammatory and erosive mucous membrane changes, petechial lung bleeding, increased lung weight; pneumonia	HRC, 1992
6	Rat	0.40	6 hr/day, 5 days/week, 2 weeks	No effects	BASF, 1999
7	Rat	2.15	6 hr/day, 5 days/week, 2 weeks	Histopathology	BASF, 1999
8	Rat	3.98	6 hr/day, 5 days/week, 2 weeks	Histopathology, cell proliferation	BASF, 1999
9	Rat	7.83	6 hr/day, 5 days/week, 2 weeks	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF, 1999
10	Rat	1	6 hr, 15 exposures	No effects	Gage, 1970
11	Rat	5	6 hr, 15 exposures	Nasal irritation, lethargy	Gage, 1970
12	Rat	20	6 hr, 15 exposures	Nasal irritation, respiratory difficulty, lethargy, lung pathology, kidney congestion	Gage, 1970
13	Rat	0.13	6 hr/day, 5 days/week, 4 weeks	No effects	BASF, 1993
14	Rat	0.38	6 hr/day, 5 days/week, 4 weeks	No effects	BASF, 1993
15	Rat	0.40	6 hr/day, 5 days/week, 4 weeks	No effects	BASF, 1999
16	Rat	1.01	6 hr/day, 5 days/week, 4 weeks	larynx lesions	BASF, 1993
17	Rat	2.15	6 hr/day, 5 days/week, 4 weeks	Histopathology, cell proliferation	BASF, 1999
18	Rat	3.1	6 hr/day, 5 days/week, 4 weeks	Nasal turbinate histopathology; larynx lesions	BASF, 1993
19	Rat	3.98	6 hr/day, 5 days/week, 4 weeks	Histopathology, cell proliferation	BASF, 1999
20	Rat	7.83	6 hr/day, 5 days/week, 4 weeks	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF, 1999

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Rat	8.8	6 hr/day, 5 days/week, 4 weeks	3/10 deaths in final week of exposure; clinical signs; decreased BW; hematological effects; lung congestion; increased lung weight; nasal turbinate histopathology; larynx lesions	BASF, 1993
Rat	0.40	6 hr/day, 5 days/week, 13 weeks	No effects	BASF, 1999
Rat	2.15	6 hr/day, 5 days/week, 13 weeks	Histopathology, cell proliferation	BASF, 1999
Rat	3.98	6 hr/day, 5 days/week, 13 weeks	Histopathology, cell proliferation, decreased body weight	BASF, 1999
Rat	7.83	6 hr/day, 5 days/week, 13 weeks	4/10 deaths-males (occurred after 24, 32, 36, or 41 exposures), clinical signs, histopathology, cell proliferation, increased lung weight, decreased body weight	BASF, 1999

II.3. DATA ANALYSIS AND AEGL-1

II.3.1 Human Data Relevant to AEGL-1

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

II.3.2 Animal Data Relevant to AEGL-1

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

II.3.3 Derivation of AEGL-1

Data were insufficient for derivation of AEGL-1 values for methyl chloroformate. Therefore, AEGL-1 values are not recommended (Table II-7).

TABLE II-7. AEGL-1 Values for Methyl Chloroformate						
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-1 NR NR NR NR						

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

II.4. DATA ANALYSIS AND AEGL-2

II.4.1 Human Data Relevant to AEGL-2

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Case-reports describing human poisonings with methyl chloroformate leading to effects consistent with the definition of AEGL-2 exist. However, due to the lack of reliable concentration and duration information, these data are not appropriate for derivation of AEGL-2 values.

II.4.2 Animal Data Relevant to AEGL-2

No acute animal data consistent with the definition of AEGL-2 were located.

II.4.3 Derivation of AEGL-2

 No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for methyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat LC₅₀: 51-53 ppm, 0% mortality in rats exposed to 45 ppm and 80% mortality in rats exposed to 57 ppm for 4 hours (Hoechst, 1986); 1-hour rat LC₅₀: 100 ppm; rats exposed to 26 ppm for 1-hr were clinically normal and had no mortality (Fisher et al., 1981). The AEGL-2 values for methyl chloroformate are presented in Table II-8, and the calculations for these AEGL-2 values are presented in Appendix II-A.

TABLE II-8. AEGL-2 Values for Methyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
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/m³)	0.70 ppm (2.7 mg/m ³)	

These values are considered protective because rats showed no deaths and only nasal turbinate histopathology and larynx lesions when repeatedly exposed to 3.1 ppm, and showed only larynx lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

II.5. DATA ANALYSIS AND AEGL-3 II.5.1 Human Data Relevant to AEGL-3

Human lethality data were anecdotal and lacked reliable concentration and time information. Thus, those reports were not appropriate for establishing the AEGL-3 values.

II.5.2 Animal Data Relevant to AEGL-3

Rat 1-hr LC_{50} values were as follows: 163 ppm for male and female Charles River rats (Bio-Test Laboratories, In., 1975), 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), 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 26 ppm methyl chloroformate for 1 hour resulted in no deaths (Fisher et al., 1981). Four hour LC_{50} values of 51 ppm and 53 ppm were calculated for male and female Wistar rats, respectively; a combined

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

male and female BMCL $_{05}$ value of 42.4 ppm and combined male and female BMC $_{01}$ value of 47.8 ppm were also calculated (Hoechst, 1986).

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II.5.3 Derivation of AEGL-3

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The calculated 4-hr BMCL₀₅ value in rats (42.4 ppm) (Hoechst, 1986) will be used as the pointof-departure for methyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 each will be applied because methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t =$ k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10min, 30-min and 1-hr) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC₅₀ study (Bio-Test, 1975); utilizing the BMCL₀₅ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986). The AEGL-3 values for methyl chloroformate are presented in Table II-9, and the calculations for these AEGL-3 values are presented in Appendix II-A.

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TABLE II-9. AEGL-3 Values for Methyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
AEGL-3	12 ppm (47 mg/m³)	8.5 ppm (33 mg/m³)	6.7 ppm (26 mg/m ³)	4.2 ppm (16 mg/m³)	2.1 ppm (8.2 mg/m ³)	

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These values are considered protective because rats showed no deaths when exposed to 7.8 ppm 6 hours/day, 5 days/week for 4 weeks (BASF,1999), and showed no deaths until week 4 when exposed to 8.8 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks) (BASF, 1993).

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II.6. SUMMARY OF AEGLSII.6.1 AEGL Values and Toxicity Endpoints

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38 39 The derived AEGL values for various levels of effects and durations of exposure are summarized in Table II-9. 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-hour lethality threshold in rats.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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TABLE II-10. Summary of AEGL Values For Methyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.0 ppm (16 mg/m³)	2.8 ppm (11 mg/m³)	2.2 ppm (8.6 mg/m ³)	1.4 ppm (5.5 mg/m ³)	0.70 ppm (2.7 mg/m³)
AEGL-3 (Lethality)	12 ppm (47 mg/m³)	8.5 ppm (33 mg/m³)	6.7 ppm (26 mg/m³)	4.2 ppm (16 mg/m³)	2.1 ppm (8.2 mg/m ³)

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

II.6.2 Other Exposure Criteria

No extant standards and guidelines exposure have been established for methyl chloroformate.

II.6.3 Data Adequacy and Research Needs

Human data are limited to 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 derived AEGL values.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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APPENDIX II-A: Time Scaling Calculations for Methyl Chloroformate

6

1	DERIVATION OF AEGL-1 VALUES FOR METHYL CHLOROFORMATE
2	
3	Data are insufficient for derivation of AEGL-1 values; therefore, AEGL-1 values are Not
4	Recommended.
5	

1 2 3	DERIVATION OF AEGL-2	VALUES FOR METHYL CHLOROFORMATE
4 5	Key study: Hoechst, 1986	
6	rey study. Hocenst, 1900	
7	Toxicity Endpoint: 1/3 of the AEGL-3 va	alues
8		
9		
10		
11		
12		
13	<u>10-min AEGL-2</u> :	$12 \text{ ppm} \div 3 = 4.0 \text{ ppm}$
14	20 min AECL 2.	9.5
15 16	30-min AEGL-2:	$8.5 \text{ ppm} \div 3 = 2.8 \text{ ppm}$
17	<u>1-hr AEGL-2</u> :	$6.7 \text{ ppm} \div 3 = 2.2 \text{ ppm}$
18	<u>1-III /ALGL-2</u> .	0.7 ppm : 3 = 2.2 ppm
19	4-hr AEGL-2:	$4.2 \text{ ppm } \div 3 = 1.4 \text{ ppm}$
20	·	TI TI
21	8-hr AEGL-2:	$2.1 \text{ ppm} \div 3 = 0.70 \text{ ppm}$
22		

1	DERIVATION OF AEGL-3	VALUES FOR METHYL CHLOROFORMATE			
2 3 4	Key study: Hoechst, 1986				
5 6	Toxicity Endpoint: Calculated BMCL ₀₅	(42.4 ppm) from a 4-hour exposure in rats.			
7 8 9 10 11	Scaling:	10-min, 30-min, and 1-hour $C^3 \times t = k$ $(42.4 \text{ ppm})^3 \times 4 \text{ hr} = 304900 \text{ ppm}^{\text{th}}$			
12 13 14 15		$\frac{8-\text{hours}}{\text{C}^{1} \times t = k}$ $(42.4 \text{ ppm})^{1} \times 4 \text{ hr} = 170 \text{ ppm}^{1}\text{hr}$			
16 17 18 19	Uncertainty Factors:	3 for interspecies variability 3 for intraspecies variability			
20 21 22 23	10-min AEGL-3	$C^3 \times 0.167 \text{ hr} = 304900 \text{ ppm}^{1}\text{hr}$ $C^3 = 1825748 \text{ ppm}$ C = 122 ppm 10-min AEGL-3 = 122/10 = 12 ppm			
24 25 26 27 28 29	30-min AEGL-3	$C^3 \times 0.5 \text{ hr} = 304900 \text{ ppm}^{\dagger} \text{hr}$ $C^3 = 609800 \text{ ppm}$ $C = 84.8 \text{ ppm}$ $30\text{-min AEGL-3} = 84.8/10 = 8.5 \text{ ppm}$			
30 31 32 33 34 35 36	1-hr AEGL-3	C^3 x 1 hr = 304900 ppm hr C^3 = 304900 ppm C = 67.3 ppm 1-hr AEGL-3 = 67.3/10 = 6.7 ppm			
37 38	4-hr AEGL-3	4-hr AEGL-3 = $42.4/10 = 4.2 \text{ ppm}$			
39 40 41 42 43	8-hr AEGL-3	C^{1} x 8 hr = 170 ppm hr C^{1} = 21.2 ppm C = 21.2 ppm 8-hr AEGL-3 = 21/10 = 2.1 ppm			

1	APPENDIX II-B:
2	
3	Derivation Summary for Methyl Chloroformate

1

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

ACUTE EXPOSURE GUIDELINES FOR METHYL CHLOROFORMATE DERIVATION SUMMARY

DERIVATION SUMMARY				
	AEGL-1	VALUES FOR MI	ETHYL CHLOROFOR	MATE
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Strain	/Number: NA			
Exposure Route/Co	oncentrations/Dura	ations: NA		
Effects: NA				
Endpoint/Concentra	ation/Rationale: N	ÍΑ		
Uncertainty Factors/Rationale: $Interspecies = NA \\ Intraspecies = NA \\ (Alarie method requires no additional UF)$				
Modifying Factor: 1		101)		
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data quality and research needs: Data were insufficient for derivation of AEGL-1 values. AEGL-1 values are recommended.				

1	AEGL-2 VALUES FOR METHYL CHLOROFORMATE				
2	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
3	4.0 ppm	2.8 ppm	2.2 ppm	1.4 ppm	0.70 ppm
4 5 6 7	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., and Langer, K.H. Hoechst Pharmaceutical Research Toxicology. Report No. 86.0432. April 11, 1986.				
8	Test Species/Strain/Nu	mber: See AEGL-3 De	erivation summary tab	le	
9	Exposure Route/Conce	entrations/Durations: S	ee AEGL-3 Derivation	n summary table	
10	Effects: See AEGL-3 I	Derivation summary ta	ble		
11 12 13 14 15	Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. Approach is justified based on the steep concentration curve with regard to lethality (4-hour rat LC ₅₀ : 51-53 ppm, 0% mortality in rats exposed to 45 ppm and 80% mortality in rats exposed to 57 ppm for 4 hours (Hoechst, 1986); 1-hour rat LC ₅₀ : 100 ppm; rats exposed to 26 ppm for 1-hr were clinically normal and had no mortality (Fisher et al., 1981))				
16	Uncertainty Factors/Ra	ationale: See AEGL-3	Derivation summary ta	able	
17	Modifying Factor: NA	1			
18	Animal to Human Dos	imetric Adjustment: N	A		
19	Time Scaling: See AEGL-3 Derivation summary table				
20 21 22 23	Data quality and research needs: See AEGL-3 Derivation summary table. These values are considered protective because no rats died and only nasal turbinate histopathology and larynx lesions when repeatedly exposed to 3.1 ppm, and showed only larynx lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).				
24					

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

	AEGL-3 VALUES	FOR METHYL C	HLOROFORMAT	E
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
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., and 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: Rats/Inhalation/4 hours

Endpoint/Concentration/Rationale: Calculated BMCL₀₅ in rats after a 4 hr-exposure/ 42.4 ppm/Estimated threshold for death for 1 hour exposure in rats

Effects:

Male rat $LC_{50} = 51$ ppm; female rat $LC_{50} = 53$ ppm

Male and Female BMCL₀₅ = 42.4

Male and Female BMC₀₁ = 47.8

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:

Interspecies = 3:

Intraspecies = 3:

Methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals.

Total UF = 10.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (10-min, 30-min and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC₅₀ study (Bio-Test, 1975); utilizing the BMCL₀₅ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986).

Data Quality and Research Needs: Many rat acute lethality studies exist with consistent results. Appropriate endpoint for AEGL-3. These values are considered protective because no rats died when exposed to 7.8 ppm 6 hours/day, 5 days/week for 4 weeks (BASF, 1999), and no rats died until week 4 when exposed to 8.8 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks) (BASF, 1993).

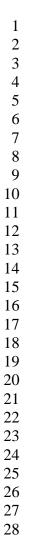
1 2

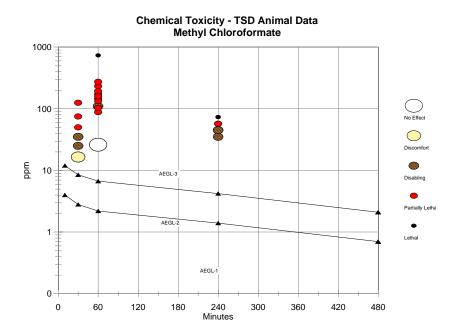
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

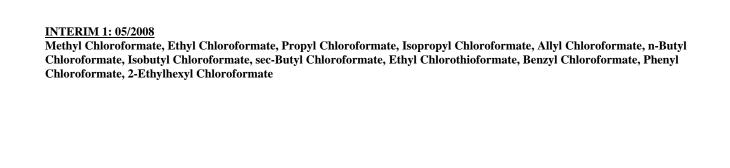
APPENDIX II-C:

Category Plot for Methyl Chloroformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate







APPENDIX II-D:

Benchmark Concentration Calculation for Methyl Chloroformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

```
1
       BMDS MODEL RUN
 2
 3
         The form of the probability function is:
 4
             P[response] = Background
 5
6
7
8
                + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
         where CumNorm(.) is the cumulative normal distribution function
         Dependent variable = Mean
        Independent variable = Dose
 9
        Slope parameter is not restricted
10
11
         Total number of observations = 4
12
         Total number of records with missing values = 0
13
        Maximum number of iterations = 250
14
         Relative Function Convergence has been set to: 1e-008
15
        Parameter Convergence has been set to: 1e-008
16
17
         User has chosen the log transformed model
18
19
                 Default Initial (and Specified) Parameter Values
20
                   background =
                                       0
21
                    intercept = -20.4973
22
                      slope =
                                 5.16963
23
24
             Asymptotic Correlation Matrix of Parameter Estimates
25
             ( *** The model parameter(s) -background -slope
26
                 have been estimated at a boundary point, or have been specified by the user,
27
                 and do not appear in the correlation matrix )
28
29
               intercept
30
       intercept
                       1
31
32
                      Parameter Estimates
33
34
                                         Std. Err.
           Variable
                          Estimate
35
          background
                                          NA
36
          intercept
                          -71.9357
                                         0.449759
37
             slope
                             18
                                        NA
38
39
       NA - Indicates that this parameter has hit a bound
40
          implied by some inequality constraint and thus
          has no standard error.
41
42
43
                     Analysis of Deviance Table
44
45
           Model
                     Log(likelihood) Deviance Test DF
                                                         P-value
46
          Full model
                         -5.00402
47
        Fitted model
                         -5.00722 0.00639048
                                                   3
                                                          0.9999
48
        Reduced model
                           -27.5256
                                        45.0431
                                                   3
                                                          <.0001
49
50
             AIC:
                       12.0144
51
52
53
```

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

12 13 14

21

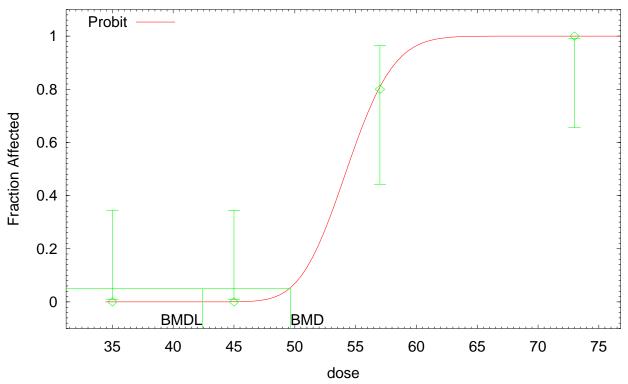
Goodness of Fit

			Scaled	l	
Dose	EstProb.	Expected	Observed	Size	Residual
35.0000	0.0000	0.000	0	10 -1.0	08e-007
45.0000	0.0003	0.003	0	10 -0	0.0564
57.0000	0.7993	7.993	8	10 0.0	005272
73.0000	1.0000	10.000	10	10 0.	.0007765
Chi-sanar	e = 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

Probit Model with 0.95 Confidence Level



13:37 09/27 2006

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate			
CHAPTER III. ETHYL CHLOROFORMATE			

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: ETHYL CHLOROFORMATE

Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate. Therefore, AEGL-1 values are not recommended.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for ethyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat LC_{50} : 189-200 ppm; rats exposed to 47 ppm for 1-hr were clinically normal and had no mortality; Fisher et al., 1981).

One-third of the most conservative 1-hr LC₅₀ value in rats (145 ppm x $\frac{1}{3}$ =48 ppm) (Vernot et al., 1977) was used as the point-of-departure for ethyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and intraspecies uncertainty factors of 3 each were applied because ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentrationexposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemicalspecific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

The calculated values are listed in the table below.

	Summary of AEGL Values For Ethyl Chloroformate						
Classification 10-Minute		30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data	
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)	1/3 the AEGL-3 values (Vernot et al., 1977)	
AEGL-3 (Lethality)	8.8 ppm (39 mg/m ³)	6.1 ppm (27 mg/m ³)	4.8 ppm (21 mg/m³)	1.2 ppm (5.3 mg/m ³)	0.60 ppm (2.6 mg/m ³)	Estimated lethality threshold in the rat after a 1-hour exposure (Vernot et al., 1977)	

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

10

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

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. Journal Hazardous Materials 13:301-309.

Vernot, E.H., MacEwen, J.D., Haun, C.C., 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.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

III.1. HUMAN TOXICITY DATA

III.1.1 Acute Lethality

Information concerning death in humans following inhalation exposure to ethyl chloroformate is not available.

III.1.2 Non-lethal Toxicity

III.1.2.1 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). Because of the nature of ethyl chloroformate, the worker was wearing a polyvinyl chloride apron, safety shoes, long gloves and a full face fresh air mask, and this protective clothing limited the exposure to an area on his right thigh. He showered in a domestic shower, and developed ocular irritation and cough, presumably because the warmth/humidity of the shower room produced ethyl chloroformate fumes from the discarded clothing. Symptoms then subsided until 3.5 hours after the incident when he experienced chest tightness and difficulty breathing. He was slightly cyanotic and had audible crepitations at the base of his right lung; a reddened area was visible on the right thigh. He was then hospitalized and subsequently developed pulmonary edema. He received medical treatment and symptoms resolved over the next few days, with no long-term effects.

III.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to ethyl chloroformate were not available.

III.1.4 Genotoxicity

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

III.1.5 Carcinogenicity

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

III.1.6 Summary

 Data concerning human exposure to ethyl chloroformate are limited to one occupational case report lacking exposure concentration and duration information. This report suggests that ethyl chloroformate is a respiratory tract irritant and is capable of inducing delayed pulmonary edema. No reports regarding developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

III.2. ANIMAL TOXICITY DATA

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

III.2.1 Acute Lethality III.2.1.1 Rats

Groups of ten male Sprague Dawley rats were exposed to 365 or 730 ppm (nominal concentrations) ethyl chloroformate for 1 hour (WARF Institute, Inc, 1978). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air flow was utilized. 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 one minute, and throughout the 1-hour exposure period, animals in both groups had closed eyes and were gasping. Animals in the 730 ppm group were in a semi-conscious state from 10-minutes into the exposure through the end of the exposure period; all animals in the 730 ppm group died between one and two hours post-exposure. All animals in the 365 ppm group died within 24-hours post-exposure. Hemorrhage in all lung lobes and hemorrhage in the trachea were noted during gross necropsy.

Groups of five male and five female Fischer 344 rats were exposed to 0, 47, 153, 180, 245, or 270 ppm ethyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber, followed by a 14-day observation period (Fisher et al., 1981). Ethyl chloroformate chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. The LC₅₀ values were 189 (164-216) ppm for male rats, and 200 (173-232) ppm for female rats at 14 days post-exposure. Controls and rats in the 47 ppm group were clinically normal and showed no treatment-related effects at necropsy. Body weight gain was decreased for 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 prior to scheduled sacrifice. Average relative lung weight of animals in the 245 and 270 ppm groups was approximately three-times greater than that of controls, and corroborating lesions indicative of acute alveolar hemorrhage were noted. Relative lung weight was also increased (magnitude not specified) in the 153 and 180 ppm groups. Red lung coloration was noted 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 a 1-hour LC_{50} of 145 (140-150) ppm for male Sprague-Dawley rats and a value of 170 (150-180) ppm for female Sprague-Dawley rats. Experiments were performed in bell jars using groups of five rats per exposure level and concentrations were analytically determined. No further experimental details were available.

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

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

Groups of four male and four female Alderly Park SPF rats were exposed to 1 ppm (twenty 6-hour exposures), 5 ppm (twenty 6-hr exposures), or 20 ppm (ten 6-hr exposures) ethyl chloroformate vapor

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

in isopropanol (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, 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 lung hemorrhage were noted at autopsy in the 20 ppm group. No further details were provided.

The following oral LD_{50} values were reported for male rats: 470 mg/kg (Vernot et al., 1977) and 411 mg/kg (WARF Institute, Inc., 1978). An oral LD_{50} value of 614 mg/kg was reported for female Wistar rats (Hoechst, 1975); an oral LD_{50} of 244 mg/kg was reported for an unspecified sex and strain of rat (BASF, 1970c). A dermal LD_{50} value of >2 mL/kg was reported for male rats (WARF Institute, Inc., 1978), and a dermal LD_{50} value of 7120 mg/kg was reported for New Zealand white rabbits (Vernot et al., 1977).

III.2.1.2 Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 25, 50, 100, or 200 ppm ethyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted ethyl chloroformate was delivered to a Pitt #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 RD₅₀ of 77.5± 5.4 ppm was calculated. Results are summarized in Table III-1.

TABLE III-1. Exposure of Male Swiss-Webster Mice to Ethyl Chloroformate for 30 minutes*						
Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs			
25	285/255	11	0/4			
50	280/235	52	0/4			
100	260/120	54	3/4			
200	215/55	74	4/4			

III.2.2 Developmental/Reproductive Toxicity

 Studies concerning the developmental/reproductive toxicity of ethyl chloroformate were not located.

III.2.3 Genotoxicity

Ethyl chloroformate was negative in a preincubation test both with and without metabolic activation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 (BASF, 1988).

III.2.4 Carcinogenicity

^{*}Carpenter, 1982

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Groups of 50 male Sprague-Dawley rats were administered 1.5, 3.0, or 6.0 ppm ethyl chloroformate by inhalation 6 hours/day, 5 days/week for a total of 30 exposures (Sellakumar et al., 1987). There was no treatment-related effect on life span. A single (1/50) 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.

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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 to 50 mice received dermal applications of 3.0, 4.3, or 5.5 mg ethyl chloroformate in acetone three times/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 dose 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 noted in 6/50 animals (4 papillomas, 2 squamous cell carcinomas), suggesting that ethyl chloroformate may be active as a tumor promoter. In a subcutaneous injection study, mice were injected in the left flank once weekly with 0.3 or 1.1 mg ethyl chloroformate in 0.1 mL tricaprylin for 18-22 months. Tumor incidence was 1/50 for the 0.3 mg group (squamous cell carcinoma) and 0/50 in the 1.1 mg group.

III.2.5 Summary

Animal toxicity data for ethyl chloroformate are limited. Rat 1-hr LC₅₀ values were relatively consistent between studies as follows: 189 ppm and 200 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), 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 RD₅₀ of 77.5 ppm (nominal concentration) ethyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). No data concerning developmental/reproductive toxicity were located in the available literature. Ethyl chloroformate was negative in the Ames assay. Carcinogenicity data (Van Duuren et al., 1987) suggest that ethyl chloroformate may be a tumor promoter by the dermal route. Animal data are summarized in Table III-2.

	Table III-2. Summary of Acute Inhalation Data of Animals Exposed to Ethyl Chloroformate						
Species	Concentration (ppm)	Exposure Duration	Effect	Reference			
Rat	47	1 hour	No effects	Fisher et al., 1981			
Rat-male	145	1 hour	LC ₅₀	Vernot et al., 1977			
Rat-female	170	1 hour	LC ₅₀	Vernot et al., 1977			
Rat-male	189	1 hour	LC ₅₀	Fisher et al., 1981			
Rat-female	200	1 hour	LC ₅₀	Fisher et al., 1981			
Rat	245	1 hour	10/10 dead	Fisher et al., 1981			
Rat	270	1 hour	10/10 dead	Fisher et al., 1981			

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Rat	365 (nominal)	1 hour	10/10 dead	WARF Institute, Inc., 1978
Rat	730 (nominal)	1 hour	10/10 dead	WARF Institute, Inc, 1978
Mouse	77.5 (nominal)	30 minutes	RD ₅₀	Carpenter, 1982

III.3. DATA ANALYSIS AND AEGL-1

III.3.1 Human Data Relevant to AEGL-1

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

III.3.2 Animal Data Relevant to AEGL-1

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

III.3.3 Derivation of AEGL-1

Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate. Therefore, AEGL-1 values are not recommended (Table III-3).

TABLE III-3. AEGL-1 Values for Ethyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

III.4. DATA ANALYSIS AND AEGL-2

III.4.1 Human Data Relevant to AEGL-2

No human data with quantified concentration and duration parameters consistent with the definition of AEGL-2 were available.

III.4.2 Animal Data Relevant to AEGL-2

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

III.4.3 Derivation of AEGL-2

 No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for ethyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

with regard to lethality (1-hour rat LC_{50} : 189-200 ppm; rats exposed to 47 ppm for 1-hr were clinically normal and had no mortality; Fisher et al., 1981). The AEGL-2 values for ethyl chloroformate are presented in Table III-4, and the calculations for these AEGL-2 values are presented in Appendix III-A.

8-Hour

0.20 ppm

 (0.88 mg/m^3)

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 TABLE III-4. AEGL-2 Values for Ethyl Chloroformate

 Classification
 10-Minute
 30-Minute
 1-Hour
 4-Hour

 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)

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III.5. DATA ANALYSIS AND AEGL-3 III.5.1 Human Data Relevant to AEGL-3

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

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III.5.2 Animal Data Relevant to AEGL-3

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19 20 Rat 1-hr LC₅₀ values were as follows: 189 ppm and 200 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), 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 47 ppm methyl chloroformate for 1 hour resulted in no deaths (Fisher et al., 1981).

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III.5.3 Derivation of AEGL-3

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One-third of the most conservative 1-hr LC₅₀ value in rats (145 ppm x $\frac{1}{3}$ =48 ppm) (Vernot et al., 1977) will be used as the point-of-departure for ethyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and intraspecies uncertainty factors of 3 each will be applied because ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n=1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for ethyl chloroformate are presented in Table III-5, and the calculations for these AEGL-3 values are presented in Appendix III-A.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

	TABLE III-5. AEGL-3 Values for Ethyl Chloroformate				
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	8.8 ppm (39 mg/m ³)	6.1 ppm (27 mg/m ³)	4.8 ppm (21 mg/m³)	1.2 ppm (5.3 mg/m ³)	0.60 ppm (2.6 mg/m ³)

III.6. SUMMARY OF AEGLS

III.6.1 AEGL Values and Toxicity Endpoints

The derived AEGL values are summarized in Table III-6. Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on an estimated 1-hour lethality threshold in rats.

TABLE III-6. Summary of AEGL Values for Ethyl Chloroformate					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
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/m³)	1.2 ppm (5.3 mg/m ³)	0.60 ppm (2.6 mg/m^3)

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

III.6.2 Comparison with Other Standards and Guidelines

The Dutch MAC for ethyl chloroformate is 1 ppm [MAC (Maximaal Aanvaarde Concentratie) (Maximal Accepted Concentration)], is defined analogous to the ACGIH-TLV-TWA (SDU Uitgevers, 2000).

No other extant standards were located for ethyl chloroformate.

III.6.3 Data Quality and Research Needs

Animal data are limited to acute rat inhalation studies and a mouse RD_{50} study. The consistency observed in the rat LC_{50} studies adds to confidence in the derived AEGL values.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2

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INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 APPENDIX III-A:
2
3 Derivation of AEGL Values for Ethyl Chloroformate

1 2

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR ETHYL CHLOROFORMATE

3 Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate.

1	De	erivation of AEGL-2 Values for Ethyl Chloroformate
2		
3		
4	Key study: Vernot et al.	, 1977
5		
6	Toxicity Endpoint: 1/3 of	the AEGL-3 values
7		
8		
9		
10		
11		
12	<u>10-min AEGL-2</u> :	$8.8 \text{ ppm} \div 3 = 2.9 \text{ ppm}$
13		
14	30-min AEGL-2:	$6.1 \text{ ppm} \div 3 = 2.0 \text{ ppm}$
15		
16	<u>1-hr AEGL-2</u> :	$4.8 \text{ ppm} \div 3 = 1.6 \text{ ppm}$
17		
18	<u>4-hr AEGL-2</u> :	1.2 ppm $\div 3 = 0.40$ ppm
19		
20	8-hr AEGL-2:	$0.60 \text{ ppm} \div 3 = 0.20 \text{ ppm}$
21		

```
DERIVATION OF AEGL-3 VALUES FOR ETHYL CHLOROFORMATE
 1
 2
 3
        Key study: Vernot et al., 1977
 4
 5
        Toxicity Endpoint: Estimated LC_{01} (1/3 the LC_{50}) from a 1-hour exposure in male rats.
 6
 7
        LC50 = 145 \text{ ppm}; \frac{1}{3} \times 145 \text{ ppm} = 48.3 \text{ ppm} (point of departure)
 8
 9
        Scaling:
                      10-minutes and 30-minutes
10
                      \mathbf{C}^3 \times t = k
                      (48.3 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 112769 \text{ ppm}^{\text{th}} \text{r}
11
12
13
14
                 4-hours and 8-hours
                 \mathbf{C}^1 \times t = k
15
                 (48.3 \text{ ppm})^1 \text{ x } 1 \text{ hr} = 48.3 \text{ ppm}^{\text{th}} r
16
17
18
        Uncertainty Factors:
19
             3 for interspecies variability
20
             3 for intraspecies variability
21
22
        10-min AEGL-3
             C^3 \times 0.167 \text{ hr} = 112769 \text{ ppm}^{\text{th}} \text{r}
23
             C^3 = 675263 \text{ ppm}
24
25
             C = 87.7 \text{ ppm}
26
             10-min AEGL-3 = 87.7/10 = 8.8 ppm
27
28
        30-min AEGL-3
             C^3 \times 0.5 \text{ hr} = 112769 \text{ ppm}^{\text{h}}\text{r}
29
30
             C^3 = 225538 \text{ ppm}
31
             C = 60.9 \text{ ppm}
32
             30-min AEGL-3 = 60.9/10 = 6.1 ppm
33
34
        1-hr AEGL-3
             1-hr AEGL-3 = 48.3/10 = 4.8 ppm
35
36
37
        4-hr AEGL-3
            C^1 \times 4 \text{ hr} = 48.3 \text{ ppm}^{\text{th}} \text{r}
38
             C^1 = 12 \text{ ppm}
39
40
             C = 12 ppm
41
             4-hr AEGL-3 = 12/10 = 1.2 ppm
42
43
        8-hr AEGL-3
            C^1 \times 8 \text{ hr} = 48.3 \text{ ppm}^{\text{th}} \text{r}
44
45
             C^1 = 6.0 \text{ ppm}
```

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 C = 6.0 ppm2 8-hr AEGL-3 = 6.0/10 = 0.60 ppm3

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

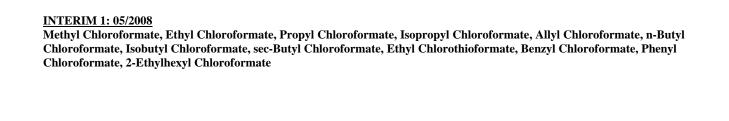
1 APPENDIX III- B: 2 3 Derivation Summary for Ethyl Chloroformate

AEGL-1 VALUES FOR ETHYL CHLOROFORMATE							
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
NR	NR	NR	NR	NR			
deference: NA							
est Species/Strair	n/Number: NA						
xposure Route/Co	oncentrations/Dura	tions: NA					
ffects: NA							
Endpoint/Concentration/Rationale: NA							
Incertainty Factors/Rationale: Interspecies = NA Intraspecies = NA Alarie method requires no additional UF)							
Iodifying Factor: NA							
Animal to Human Dosimetric Adjustment: NA							
Time Scaling: NA							
Pata quality and re ecommended.	esearch needs: Data	were insufficient fo	or derivation of AEGL-1	values. AEGL-1 v			

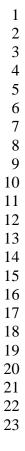
AEGL-2 VALUES FOR ETHYL CHLOROFORMATE							
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm			
corrosi	Key Reference: Vernot, E.H., MacEwen, J.D., Haun, C.C., and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-424.						
Test Species/Strain/Number: See AEGL-3 Derivation summary table							
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table							
Effects: See AEGL-3 Derivation summary table							
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat LC ₅₀ : 189-200 ppm; rats exposed to 47 ppm for 1-hr were clinically normal and had no mortality; Fisher et al., 1981).							
Uncertainty Factors/Ra	ationale: See AEGL-3	Derivation summary t	able				
Modifying Factor: NA							
Animal to Human Dosimetric Adjustment: NA							
Time Scaling: See AEGL-3 Derivation summary table							

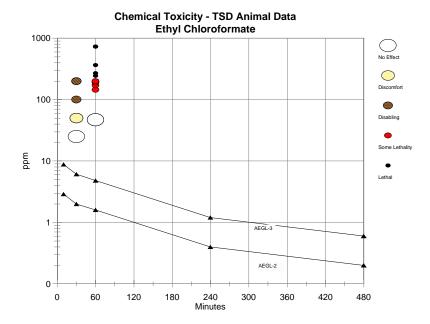
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR ETHYL CHLOROFORMATE							
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm			
Key Reference: Vernot, E.H., MacEwen, J.D., Haun, C.C., 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	x/Number: Sprague-Da	awley rats/ males					
Exposure Route/Conce				= 48.3 ppm)			
Endpoint/Concentration/Rationale: Estimated LC_{01} in rats after a 1 hr-exposure/ 48.3 ppm/Estimated threshold for death for 1 hour exposure in rats							
Effects: Male rat $LC_{50} = 145$ ppm; female rat $LC_{50} = 170$ ppm							
Uncertainty Factors/Rationale: Interspecies = 3: Intraspecies = 3: Ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the issues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, nter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and noutyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Fotal UF = 10.							
Modifying Factor: NA							
Animal to Human Dosimetric Adjustment: Insufficient data							
Time Scaling: $c^n x t = k$, where $n=3$ when extrapolating to shorter time points (10-minutes and 30-minutes) and $= 1$ when extrapolating to longer time points (4-hours and 8-hours).							
Data Quality and Resea	arch Needs: Two rat ac	cute lethality studies	with consistent resu	ılts. Appropriate endp			



1 APPENDIX III-C: 2 3 CATEGORY PLOT FOR ETHYL CHLOROFORMATE





INTERIM 1: 05/2008 Methyl Chloroformate, Ethy	l Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-But
Chloroformate, Isobutyl Chl Chloroformate, 2-Ethylhexyl	oroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate
	CHAPTER IV: PROPYL CHLOROFORMATE

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: PROPYL CHLOROFORMATE

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Data were insufficient for derivation of AEGL-1 values for propyl chloroformate. Therefore, AEGL-1 values are not recommended.

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No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for propyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 333 ppm; 10/10 at 1000 ppm; Bio-Test, 1970).

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The calculated 1-hour rat BMCL₀₅ of 216 ppm (Bio-Test Laboratories, Inc., 1970) was used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because propyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. A modifying factor of 2 was also applied because the key study reported nominal, not analytical, concentrations and there are no confirmatory studies. Thus, the total uncertainty/modifying factor is 20. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n=1when extrapolating to longer time points (4-hours and 8-hours).

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The calculated values are listed in the table below.

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	Summary of AEGL Values For Propyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data
AEGL-2 (Disabling)	6.7 ppm (34 mg/m³)	4.7 ppm (24 mg/m ³)	3.7 ppm (19 mg/m ³)	0.90 ppm (4.5 mg/m ³)	0.47 ppm (2.4 mg/m ³)	1/3 the AEGL-3 values (Bio-Test Laboratories, Inc, 1970)
AEGL-3 (Lethality)	20 ppm (100 mg/m ³)	14 ppm (70 mg/m³)	11 ppm (55 mg/m ³)	2.7 ppm (14 mg/m ³)	1.4 ppm (7.0 mg/m ³)	1-hour rat BMCL ₀₅ (Bio-Test Laboratories, Inc., 1970)

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NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2

- 41 is without adverse effects.
- 42 References 43 Bio-Test Labo
 - Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG Industries, Inc. IBT

- No. A8345.
- 2 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline
- 3 Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
- 5 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and
- 6 systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 IV.1. HUMAN TOXICITY DATA

IV.1.1 Acute Lethality

No information regarding human lethality from propyl chloroformate exposure was located.

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IV.1.2 Non-lethal Toxicity

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> No information regarding non-lethal human toxicity from propyl chloroformate exposure was located.

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IV.1.3 Developmental/Reproductive Toxicity

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Developmental/reproductive studies regarding acute human exposure to propyl chloroformate were not available.

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IV.1.4 Genotoxicity

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

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IV.1.5 Carcinogenicity

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Carcinogenicity studies regarding human exposure to propyl chloroformate were not available.

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IV.1.6 Summary

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Data concerning human exposure to propyl chloroformate are not available.

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IV.2. ANIMAL TOXICITY DATA

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IV.2.1 Acute Lethality

IV.2.1.1 Rats

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Groups of five male and five female young adult Charles River albino rats (avg. wt. 320 g) were exposed to nominal concentrations of 249, 333, 1000, 3077, or 21,538 ppm propyl chloroformate vapor for one hour (Bio-Test Laboratories, Inc., 1970). Vapor was generated by bubbling clean, dry air through undiluted 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 exhausted at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the propyl

- 41 chloroformate vaporized by the total volume of air used during each inhalation exposure. No adverse
- 42 effects were observed in the 249 ppm group during exposure. Bloody nasal discharge and dyspnea
- 43 were observed in the 333 ppm group toward the end of the exposure period, while hyperactivity, clear nasal discharge, dyspnea, and salivation were observed in the 1000, 3077, and 21,538 ppm groups. 44
- 45 No adverse effects on body weight were observed in any animals that survived the 14-day observation

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

period; however, necropsy revealed slight to moderate hyperemia in these animals. In animals that did not survive the 14-day observation period, necropsy revealed moderate to severe lung hyperemia. A 1-hour LC_{50} of 410 ppm, $BMCL_{05}$ of 216 ppm, and BMC_{01} of 229 ppm were calculated. Data are summarized in Table IV-1.

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TABLE IV-1. Exposure of Albino Rats to Propyl Chloroformate 1 hour*						
Nominal Concentration (ppm)	Mortality	Time of Death Post-Exposure	Observations at Necropsy	Observations During Exposure		
249	0/10	NA	Slight to moderate lung hyperemia	NA		
333	2/10	Within 60 min.	Slight to moderate lung hyperemia in survivors; Moderate to severe lung hyperemia in decedents	Bloody nasal discharge; dyspnea		
1000	10/10	Within 60 min.	Moderate to severe lung hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation		
3077	10/10	Within 60 min.	Moderate to severe lung hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation		
21,538	10/10	Within 30 min.	Moderate to severe lung hyperemia	Hyperactivity; clear nasal discharge; dyspnea; salivation		

^{*}Bio-Test Laboratories, Inc., 1970

Death occurred in 3/10 rats exposed to 200 ppm propyl chloroformate for 1 hour (BASF, 1970a). Clinical signs included restlessness, mucous membrane irritation, and dyspnea. Acute lung emphysema was noted at necropsy.

Death occurred in 12/12 rats exposed to an "atmosphere enriched or saturated" with propyl chloroformate vapor at 20EC for 3 minutes. (BASF, 1970b). Clinical signs included vigorous escape behavior, extremely severe mucous membrane irritation, and gasping. Lung congestion and edema were noted at necropsy.

An oral LD_{50} value of 650 mg/kg was reported for Charles River albino rats (Bio-Test Laboratories, Inc., 1970). Oral LD_{50} values of 1212 mg/kg (BASF, 1980) and 872 mg/kg were reported for Sprague-Dawley rats (BASF, 1970c).

IV.2.1.2. Mice

 Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 25, 50, 75, or 100 ppm propyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted propyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

directed into a 6 L stainless steel chamber which was continuously evacuated at 18.3 L/min. An RD_{50} of 83.5 ± 2.17 ppm was calculated. Results are summarized in Table IV-2.

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TABLI	E IV-2. Exposure of Male Swiss-Webster	r Mice to Propyl Chloroformate	for 30 minutes*
Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs
25	255/225	12	0/4
50	280/205	27	1/4
75	270/150	44	2/4
100	245/95	61	0/4

^{*}Carpenter, 1982

IV.2.2. Nonlethal Toxicity

IV.2.2.1. Rabbits

Corneal opacity and iridal and conjunctival irritation were observed within one minute after installation of 0.1 ml undiluted propyl chloroformate into the eyes of albino rabbits (Bio-Test Laboratories, Inc., 1970). The irritation became progressively worse and within three to seven days, maximum damage was present in all ocular tissues. No improvement was observed after 14 days, and 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 (Bio-Test Laboratories, Inc., 1970). Severe erythema, edema, and burns were observed after dermal exposure of rabbits to 0.5 ml undiluted propyl chloroformate for 24 hours. Effects persisted through the 72-hr observation period.

IV.2.3. Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of propyl chloroformate was located in the available literature.

IV.2.4. Genotoxicity

Propyl chloroformate was negative in a preincubation test both with and without metabolic activation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 (BASF, 1988).

IV.2.5. Carcinogenicity

No information concerning the carcinogenicity of propyl chloroformate was located in the available literature.

IV.2.6 Summary

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

- Animal toxicity data are limited. A 30-min RD₅₀ of 83.5 ppm (nominal concentration) propyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). A 1-hr LC₅₀ of 410 ppm,
- 3 BMCL₀₅ of 216 ppm, and BMC₀₁ of 229 ppm were calculated for Charles River albino rats (Bio-Test
- 4 Laboratories, Inc., 1970).
- 5 Propyl chloroformate is severely irritating to the skin and eyes of albino rabbits (Bio-Test
- 6 Laboratories, Inc., 1970). The compound was negative in a Salmonella mutagenicity reversion assay.
- 7 No data concerning developmental/reproductive toxicity or carcinogenicity for exposure to propyl
- 8 chloroformate were located in the available literature.

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IV.3. DATA ANALYSIS AND AEGL-1

IV.3.1 Human Data Relevant to AEGL-1

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

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IV.3.2 Animal Data Relevant to AEGL-1

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

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IV.3.3 Derivation of AEGL-1

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AEGL-1 values for propyl chloroformate are not recommended due to insufficient data (Table IV-3).

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	TABLE I	V-3. AEGL-1 Va	lues for Propyl Cl	nloroformate	
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

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IV.4. DATA ANALYSIS AND AEGL-2

Human Data Relevant to AEGL-2

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IV.4.1

No human data were available.

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IV.4.2 Animal Data Relevant to AEGL-2

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No robust animal data were available.

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IV.4.3 Derivation of AEGL-2

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No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for propyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 333 ppm; 10/10 at

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1000 ppm; Bio-Test Laboratories, Inc., 1970). The AEGL-2 values for propyl chloroformate are presented in Table IV-4, and the calculations for these AEGL-2 values are presented in Appendix IV-A.

	TABLE I	V-4. AEGL-2 Va	lues for Propyl C	hloroformate	
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	6.7 ppm (34 mg/m ³)	4.7 ppm (24 mg/m ³)	3.7 ppm (19 mg/m ³)	0.90 ppm (4.5 mg/m³)	0.47 ppm (2.4 mg/m ³)

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IV.5. DATA ANALYSIS AND AEGL-3

IV.5.1 Human Data Relevant to AEGL-3

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

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IV.5.2 Animal Data Relevant to AEGL-3

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A 1-hour rat LC_{50} of 410 ppm and $BMCL_{05}$ of 216 ppm were calculated (Bio-Test Laboratories, Inc., 1970). No deaths were noted at 249 ppm.

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IV.5.3 Derivation of AEGL-3

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The calculated 1-hour rat BMCL₀₅ of 216 ppm (Bio-Test Laboratories, Inc., 1970) will be used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because propyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. A modifying factor of 2 will be applied because the key study reported nominal, not analytical, concentrations and there are no other confirmatory studies. Thus, the total uncertainty/modifying factor is 20. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for propyl chloroformate are presented in Table IV-5, and the calculations for these AEGL-3 values are presented in Appendix IV-A.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

	TABLE I	V-5. AEGL-3 Va	lues for Propyl Cl	hloroformate	
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	20 ppm (100 mg/m³)	14 ppm (70 mg/m³)	11 ppm (55 mg/m³)	2.7 ppm (14 mg/m³)	1.4 ppm (7.0 mg/m³)

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IV.6. **SUMMARY OF AEGLS**

IV.6.1 **AEGL Values and Toxicity Endpoints**

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The derived AEGL values are summarized in Table IV-6. AEGL-1 values are not recommended due to insufficient data. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on a 1-hour BMCL $_{05}$ in rats.

TABLE IV-6. Summary of AEGL Values for Propyl Chloroformate

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Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2	6.7 ppm	4.7 ppm	3.7 ppm	0.90 ppm	0.47 ppm
(Disabling)	(34 mg/m³)	(24 mg/m³)	(19 mg/m ³)	(4.5 mg/m ³)	(2.4 mg/m ³)
AEGL-3	20 ppm	14 ppm	11 ppm	2.7 ppm	1.4 ppm
(Lethal)	(100 mg/m³)	(70 mg/m ³)	(55 mg/m ³)	(14 mg/m ³)	(7.0 mg/m³)

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

IV.6.2. **Comparison with Other Standards and Guidelines**

No extant values were located for propyl chloroformate.

IV.6.3 **Data Quality and Research Needs**

Data are extremely limited. Human data do not exist and animal data are limited to rat acute lethality studies and one mouse RD₅₀ study. The limited data set necessitated the application of a modifying factor for AEGL value derivation.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

IV.7. REFERENCES

1 2

- 3 BASF. 1970a. Report on the study of the acute inhalation of chloroformic acid propyl ester in rats.
- Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, 4
- 5 Germany. February 3, 1970.

6

- 7 BASF. 1970b. Report on the study of the acute inhalation hazard of chloroformic acid propyl ester in
- 8 rats (inhalation hazard test). Unpublished report, BASF Aktiengesellschaft, Experimental
 - Toxicology and Ecology, Ludwigshafen, Germany. February 3, 1970.

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- 11 BASF. 1970c. Report on the study of the acute oral toxicity of chloroformic acid propyl ester in rats.
- 12 Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen,
- Germany. February 3, 1970. 13

14

- 15 BASF. 1980. Report on the study of the acute oral toxicity. Unpublished report, BASF
- 16 Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. December 11,
- 17 1990.

18

- 19 BASF. 1988. Report on the study of chloroformic acid propyl ester in the Ames test (preincubation
- 20 test with Salmonella typhimurium) Unpublished Report. Project No. 40M0523/874090. September 7,
- 21 1988, on behalf of BG Chemie.

22

25

- 23 Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG
- 24 Industries, Inc. IBT No. A8345. OTS0570701.
- 26 Carpenter, C.P. 1982. Ethyl chloroformate, n-propyl chloroformate, Isobutyl chloroformate, Sec
 - butyl chloroformate. Sensory Irritation. Report by Mellon Institute. Report to PPG Industries, Inc., 27

 - 28 Chemicals Division. Report No. 82-49S.

29

- 30 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute
- 31 Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.

32

- 33 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response
- 34 relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

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37 38

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1	
2	APPENDIX IV-A:
3	
4	Derivation of AEGL Values for Propyl Chloroformate
5	
6	

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1
2
3 **DERIVATION OF AEGL-1 VALUES FOR PROPYL CHLOROFORMATE**4
5 AEGL-1 values are not recommended for propyl chloroformate due to a lack of data.

1

_		
2		
3	•	Derivation of AEGL-2 Values for Propyl Chloroformate
4		
5		
6	Key study: Bio-Test I	Laboratories, Inc., 1970
7		
8	Toxicity Endpoint: 1/3	of the AEGL-3 values
9		
10		
11		
12		
13	10 ' AEGL 2	20
14	<u>10-min AEGL-2</u> :	$20 \text{ ppm} \div 3 = 6.7 \text{ ppm}$
15 16	30-min AEGL-2:	14 ppm $\div 3 = 4.7$ ppm
17	<u> 50-111111 AEGE-2</u> .	14 ppiii ÷3 = 4.7 ppiii
18	1-hr AEGL-2:	11 ppm \div 3 = 3.7 ppm
19	1 III TADOL 2.	11 ppm . 3 = 3.7 ppm
20	4-hr AEGL-2:	2.7 ppm $\div 3 = 0.90$ ppm
21		- Francis Constitution
22	8-hr AEGL-2:	$1.4 \text{ ppm} \div 3 = 0.47 \text{ ppm}$
23		11

```
DERIVATION OF AEGL-3 VALUES FOR PROPYL CHLOROFORMATE
 1
 2
 3
       Key study: Bio-Test Laboratories, Inc., 1970
       Toxicity Endpoint: Calculated BMCL<sub>05</sub> (216 ppm) from a 1-hour exposure in rats.
 4
 5
 6
       Scaling:
                    10-minutes and 30-minutes
                    C^3 \times t = k
 7
                    (216 \text{ ppm})^3 \times 1 \text{ hr} = 10077696 \text{ ppm}^{\text{th}} \text{r}
 8
 9
10
                    4-hours and 8-hours
                    C^1 \times t = k
11
                    (216 \text{ ppm})^1 \times 1 \text{ hr} = 216 \text{ ppm}^{\text{th}}
12
13
14
       Uncertainty Factors:
            3 for interspecies variability
15
            3 for intraspecies variability
16
17
       Modifying Factor:
18
            2 for sparse data base and use of key study with nominal concentrations
19
20
       10-min AEGL-3:
           C^3 \times 0.167 \text{ hr} = 10,077,696 \text{ ppm}^{\text{th}}
21
            C^3 = 60345485 \text{ ppm}
22
            C = 392 ppm
23
24
            10-min AEGL-3 = 392/20 = 20 ppm
25
26
       30-min AEGL-3
           C^3 \times 0.5 \text{ hr} = 10.077,696 \text{ ppm'hr}
27
            C^3 = 20155392 \text{ ppm}
28
29
            C = 272 \text{ ppm}
30
            30-min AEGL-3 = 272/20 = 14 ppm
31
32
       1-hr AEGL-3
33
            1-hr AEGL-3 = 216/20 = 11 ppm
34
35
       4-hr AEGL-3
           C^1 \times 4 \text{ hr} = 216 \text{ ppm}^{\text{th}} \text{r}
36
            C^1 = 54 \text{ ppm}
37
           C = 54 \text{ ppm}
38
39
            4-hr AEGL-3 = 54/20 = 2.7 ppm
40
41
       8-hr AEGL-3
           C^1 \times 8 \text{ hr} = 216 \text{ ppm}^{\text{th}} \text{r}
42
            C^1 = 27 \text{ ppm}
43
           C = 27 ppm
44
45
            8-hr AEGL-3 = 27/20 = 1.4 \text{ ppm}
```

1	APPENDIX IV-B:
2	
3	Derivation Summary for Propyl Chloroformate AEGLS

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-1 VALUES FOR PROPYL CHLOROFORMATE

1	
2	
3	
4	
5	
6	Re
7	Te
8	Ex
9	Eff
10	En
11	Un
12	Mo
13	An

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16

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10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Strai	n/Number: NA			
Exposure Route/C	Concentrations/Du	ations: NA		
Effects: NA				
Endpoint/Concent	tration/Rationale: I	NA		
Uncertainty Facto	rs/Rationale: NA			
Modifying Factor	: NA			
Animal to Human	Dosimetric Adjus	tment: NA		
Time Scaling: NA				
Data quality and r	esearch needs: AE	GL-1 values are not	recommended for propy	d chloroformate. Data are

insufficient to derive values

1

AEGL-2 VALUES FOR PROPYL CHLOROFORMATE						
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
6.7 ppm	4.7 ppm	3.7 ppm	0.90 ppm	0.47 ppm		
	st Laboratories, Inc. 1 dustries, Inc. IBT No.		tudies on n-propyl c	chloroformate. Report to		
Test Species/Strain/Nur	mber: See AEGL-3 De	erivation summary tab	le			
Exposure Route/Conce	ntrations/Durations: S	ee AEGL-3 Derivation	n summary table			
Effects: See AEGL-3 Derivation summary table						
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 333 ppm; 10/10 at 1000 ppm; Bio-Test Laboratories, Inc., 1970).						
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table						
Modifying Factor: NA						
Animal to Human Dosimetric Adjustment: NA						
Time Scaling: See AEGL-3 Derivation summary table						
Data quality and resear	Data quality and research needs: See AEGL-3 Derivation summary table.					

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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	3
	4
	5
	6 7
	′
	8
	8 9
1 1	9 0 1
1 1	9 0 1 2
1 1	9 0 1

AEGL-3 VALUES FOR PROPYL CHLOROFORMATE

10-Minute 30-Minute 1-Hour 4-Hour 8-Hour
20 ppm 14 ppm 11 ppm 2.7 ppm 1.4 ppm

Key Reference: Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG Industries, Inc. IBT No. A8345.

Test Species/Strain/Sex/Number: Albino rats/ 5/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour (Calculated $BMCL_{05}$ of 216 ppm was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: $BMCL_{05}$ in rats after a 1 hr-exposure/ 216 ppm/Estimated threshold for death for 1 hour exposure in rats

Effects: $LC_{50} = 410 \text{ ppm}$; $BMC_{01} = 229 \text{ ppm}$; $BMCL_{05} = 216 \text{ ppm}$

Uncertainty Factors/Rationale:

Interspecies = 3:

Intraspecies = 3:

Propyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

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Modifying Factor: 2: Sparse data base and use of key study with nominal, not analytical, concentrations reported

Animal to Human Dosimetric Adjustment: Insufficient data

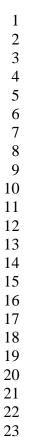
Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n=1 when extrapolating to longer time points (4-hours and 8-hours).

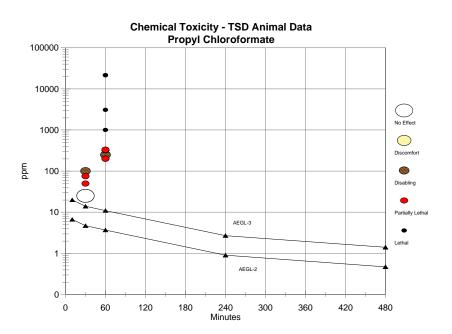
Data Quality and Research Needs: Sparse data set.

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	
2	APPENDIX IV-C:
3	
4	Category Plot for Propyl Chloroformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate





INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
APPENDIX IV-D:
Benchmark Concentration Calculation for Propyl Chloroformate

1

```
BMDS MODEL RUN
 2
 3
         The form of the probability function is:
 4
        P[response] = Background
 5
6
7
8
                + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
         where CumNorm(.) is the cumulative normal distribution function
         Dependent variable = Mean
 9
         Independent variable = Dose
10
        Slope parameter is not restricted
11
12
         Total number of observations = 3
13
        Total number of records with missing values = 0
14
        Maximum number of iterations = 250
15
        Relative Function Convergence has been set to: 1e-008
16
        Parameter Convergence has been set to: 1e-008
17
18
         User has chosen the log transformed model
19
                 Default Initial (and Specified) Parameter Values
20
                   background =
                                       0
21
                    intercept = -14.8454
22
                      slope =
                                2.39641
23
24
             Asymptotic Correlation Matrix of Parameter Estimates
25
26
             ( *** The model parameter(s) -background
27
                 have been estimated at a boundary point, or have been specified by the user,
28
                 and do not appear in the correlation matrix )
29
30
               intercept
                            slope
31
       intercept
                  NA
                              NA
32
          slope
                             NA
                  NA
33
34
       NA - This parameter's variance has been estimated at zero.
35
36
                      Parameter Estimates
37
38
           Variable
                          Estimate
                                         Std. Err.
39
          background
                                0
                                          NA
40
          intercept
                          -99.4462
                                          20016.9
41
             slope
                          16.977
                                        3446.36
42
43
       NA - Indicates that this parameter has hit a bound
44
          implied by some inequality constraint and thus
45
          has no standard error.
46
                     Analysis of Deviance Table
47
48
           Model
                     Log(likelihood) Deviance Test DF
                                                         P-value
49
          Full model
                         -5.00402
50
                                                           0.9998
        Fitted model
                         -5.00402 7.62052e-008
                                                   1
51
        Reduced model
                           -20.1904
                                        30.3727
                                                          <.0001
52
53
             AIC:
                        14.008
54
```

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

22 23

		Scaled				
Dose	EstProb.	Expected	Observed	Size	Residual	
249.0000	0.0000	0.000	0	10 -0.0	0001952	
333.0000	0.2000	2.000	2	10 4.1	15e-007	
1000.0000	1.0000	10.000	10	10	0	

Chi-square = 0.00 DF = 1P-value = 0.9998

Goodness of Fit

Benchmark Dose Computation

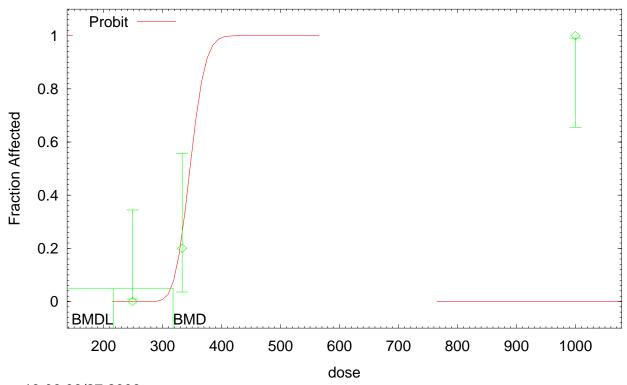
Specified effect = 0.05

Risk Type Extra risk

BMD =317.612

Confidence level = 0.95 BMDL =216.399

Probit Model with 0.95 Confidence Level



13:06 09/27 2006

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2

CHAPTER V: Isopropyl Chloroformate

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	UMAN TOXICITY DATA	
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	Non-lethal Toxicity	
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	Genotoxicity	
	Carcinogenicity	
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V.5.5	Delivation of Fibel 1	•
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	JMMARY OF AEGLS	
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ua pr	EFEDENICES	
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7	
8	
9	
10	
11	
12	

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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9	V-6. AEGL-2 Values for Isopropyl Chloroformate
10	V-7. AEGL-3 Values for Isopropyl Chloroformate
11	V-8. Summary of AEGL Values for Isopropyl Chloroformate
12	V-9. Extant Standards and Guidelines for Isopropyl Chloroformate
13	
14	

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: ISOPROPYL CHLOROFORMATE

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Data were insufficient for derivation of AEGL-1 values for isopropyl chloroformate. Therefore, AEGL-1 values are not recommended.

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No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for isopropyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001).

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One-third of the 1-hr LC₅₀ value in rats (300 ppm x $\frac{1}{3}$ = 100 ppm) (Bio Test Laboratories, Inc., 1970) was used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

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Summary of AEGL Values For Isopropyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data	
AEGL-2 (Disabling)	6.0 ppm (30 mg/m ³)	4.3 ppm (22 mg/m³)	3.3 ppm (17 mg/m ³)	0.83 ppm (4.2 mg/m ³)	0.43 ppm (2.2 mg/m ³)	1/3 the AEGL-3 values (Bio Test Laboratories, Inc., 1970)	
AEGL-3 (Lethality)	18 ppm (90 mg/m ³)	13 ppm (65 mg/m ³)	10 ppm (50 mg/m³)	2.5 ppm (13 mg/m³)	1.3 ppm (6.5 mg/m³)	Estimated lethality threshold in the rat after a 1-hour exposure (Bio Test Laboratories, Inc., 1970)	

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

References

Bio-Test Laboratories, Inc. 1970. Acute vapor inhalation toxicity study with IPCF in albino rats. Report to PPG Industries, Inc. IBT No. N9129.

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

1

2

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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V.1. HUMAN TOXICITY DATA

V.1.1 Acute Lethality

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Information concerning death in humans following inhalation exposure to isopropyl chloroformate is not available.

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V.1.2 Non-lethal Toxicity

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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. Exposures were considered potential because, due to the acute toxicity of isopropyl chloroformate, employees wore full-face supplied-air respirators, neoprene gloves, rubber boots, and neoprene clothing. Four personal monitoring results ranged from 0.2 ppm to 5.6 ppm for the sampled activity (20-40 minutes). Two area sample results were 0.06 ppm and 1.7 ppm.

18 19 20

V.1.3 Developmental/Reproductive Toxicity

21 22

Developmental/reproductive studies regarding acute human exposure to isopropyl chloroformate were not available.

23 24 25

V.1.4 Genotoxicity

26 27

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

28 29 30

V.1.5 Carcinogenicity

31 32

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

33 34

V.1.6 Summary

35 36

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No reports regarding lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available. One industrial hygiene report was available; however, worker exposures were considered "potential" due to protective clothing.

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V23. ANIMAL TOXICITY DATA

- V.2.1 Acute Lethality 41 V.2.1.1. Rats
- 42

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Groups of five male and five female young adult Charles River albino rats were exposed to nominal concentrations of 300, 1640, or 15,600 ppm isopropyl chloroformate vapor for up to one hour (Bio-Test Laboratories, Inc., 1970). Vapor was generated by bubbling clean, dry air through undiluted

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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 exhausted 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 minutes after the initiation of exposure and exhibited convulsions and salivation. Low-concentration animals exhibited gasping and slight salivation. Necropsy of animals that died revealed moderate to severe lung hyperemia. Rats that survived the 14-day observation period exhibited no gross abnormalities at necropsy. The 1-hour LC₅₀ was determined to be 300 ppm. Data are summarized in Table V-1

1	0
1	1
1	2

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TABLE V-1. Exposure of Albino Rats 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	3 at 2 hr; 1 each at 2 and 10 days			
1640	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			

Bio-Test Laboratories, Inc., 1970

Death occurred in 0/12 rats exposed to 200 ppm isopropyl chloroformate vapor for 1 hour (BASF, 1968a). Clinical signs included slight mucosal irritation. No abnormalities were noted at necropsy.

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

In a repeated-exposure study (Collins and Proctor, 1984), groups of 4 male and 4 female Sprague-Dawley rats were exposed to 0, 25, 50, or 100 ppm isopropyl chloroformate (analytical concentrations) 6 hr/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 prior to 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 V.2.2.

 Groups of four male and four female Alderly Park SPF rats were exposed to 5 ppm (unspecified exposure time), 20 ppm (twenty 6-hr exposures), 50 ppm (eleven 6-hr exposures), or 200 ppm (one 5-hr exposure) isopropyl chloroformate vapor in isopropanol (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 5 ppm, nasal irritation was observed at 20 ppm, respiratory difficulty, weight loss, and one death with lung hemorrhage were observed at 50 ppm, and two male rats died at 200 ppm. No further details were provided.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

In an acute oral toxicity study (Bio-Test Laboratories, Inc., 1971), Charles River albino rats (2/sex/dose) were administered 118.5, 177.8, 266.7, or 400 mg/kg isopropyl chloroformate by gavage and observed up to 14 days. There were no deaths at the low dose, 2/4 animals died at 177.8 mg/kg, and all animals died at the two highest doses. Deaths occurred between one hour and 5 days post-exposure. Hypoactivity, muscular weakness, ptosis, hyperpnea, and ruffed fur were observed following dosing. Hemorrhages were observed in the stomachs of animals that died during the study. An LD_{50} of 177.8 mg/kg was calculated. An approximate oral LD_{50} of 800 mm³ was reported in rats (BASF, 1968c).

V.2.1.2. Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 50, 75, 100, 200, or 500 ppm isopropyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted isopropyl chloroformate was delivered to a Pitt #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 20 L/min. An RD $_{50}$ of 104 ppm was calculated. Data are summarized in Table V-2.

TABLE V-2. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 30 minutes* Concentration Respiratory rates(control/exposed) Mortality within 24 hr. % Decrease in respiratory (ppm) rate 320/260 1/4 225/150 3/4 260/110 4/4 275/55 4/4 4/4 (died in exposure)

Carpenter, 1982

In another study (Anderson, 1984), groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 177, 306, 443, or 883 ppm isopropyl chloroformate vapor for 15 minutes. The vapor was introduced through a Harvard apparatus syringe drive into a Pitt #1 generator. The glass exposure chamber and had a capacity of 2.2 L, and air flow was 8.8 L/min. Baseline respiratory rates of each mouse were recorded for 10 minutes before exposure. Respiratory rates were recorded at 5 and 10 minutes into the 15 minute exposure period, and percent respiratory depression was calculated from these values. Lung weights were obtained at necropsy following death from exposure or scheduled sacrifice. In this study, the RD₅₀ is calculated to be 375 ppm, and a 15-min. LC₅₀ is estimated to be between 283 and 345 ppm. Concentration-related increases in lung weight, indicative of pulmonary edema, were observed in treated animals compared to controls. Data are summarized in Table V-3.

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

	TABLE V-3. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 15 minutes*							
Concentration (ppm)		% Decrease in respiratory rate		Mean lung weight (g)	Lung/Body wt. Ratio (x100)	Mortality within 24 hr.		
Nominal	Analytical	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	
443	345	45	41	43	0.39	1.23	2/4	
883	730	70	85	76	0.45	1.45	4/4	

Anderson, 1984

V.2.2 Nonlethal Toxicity

As briefly described in Section V.2.1.1, Collins and Proctor (1984) exposed groups of 4 male and 4 female Sprague-Dawley rats to 0, 25, 50, or 100 ppm isopropyl chloroformate vapor 6 hr/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 exposure chambers were 600 L stainless-steel and glass whole body 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 chamber concentrations were 25, 50, and 100 ppm and corresponding measured concentrations were 22, 42, and 86 ppm, respectively. The study authors' attribute these differences to the low accuracy of the orifice plate system used to measure flow rate through the chamber. Three high-concentration males and three high-concentration females died during the exposure period. Clinical observations on the day prior to death included lethargy, labored breathing, staining around the muzzle, muscular weakness, and low body temperature. Treatment-related body weight loss was observed postexposure in 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 when compared to 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 midconcentration 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.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

V.2.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding animal exposure to isopropyl chloroformate were not available.

V.2.4 Genotoxicity

Isopropyl chloroformate was negative in the standard plate test and preincubation test both with and without metabolic activation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and in *E. coli* WP2 uvrA (BASF, 1999).

V.2.5 Carcinogenicity

Animal carcinogenicity data for isopropyl chloroformate were not available.

V.2.6 Summary

Animal toxicity data are limited. A 30-min RD₅₀ of 104 ppm (nominal concentration) isopropyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982), while a 15-minute RD₅₀ of 375 ppm (analytical concentration) and estimated 15-min LC₅₀ of 283 to 345 ppm were determined for male Swiss-Webster mice (Anderson, 1984). A 1-hr LC₅₀ of 300 ppm was calculated for Charles River albino rats (Bio-Test Laboratories, Inc., 1970). Repeated exposure to 100 ppm isopropyl chloroformate resulted in death in Sprague-Dawley rats, while lower concentrations resulted in body weight loss, increased lung weight, and bronchiolitis. Increased lung weight and edema were consistently observed in decedents in most studies. Isopropyl chloroformate was negative in the Ames assay. No data concerning developmental/reproductive toxicity or carcinogenicity from exposure to isopropyl chloroformate were located in the available literature. Animal inhalation data are summarized in Table V-4.

	Table V-4. Summary of Inhalation Data of Animals Exposed to Isopropyl Chloroformate					
Species	Concentration Exposure (ppm) Duration		Effect	Reference		
			Acute Exposure			
Rat	15,600 (nominal)	17-41 minutes	10/10 dead	Bio Test Labs, Inc., 1970		
Rat	1640 (nominal)	40-60 minutes	10/10 dead	Bio Test Labs, Inc., 1970		
Rat	200 (approximate)	1 hour	0/12 dead	BASF, 1968a		
Rat	300 (nominal)	1 hour	LC ₅₀	Bio Test Labs, Inc., 1970		
Rat	200	5 hours	2/8 dead	Gage, 1970		
Mouse	283-345	15 minutes	LC ₅₀	Anderson, 1984		
Mouse	375	15 minutes	RD ₅₀	Anderson, 1984		

Isopropyl Chloroformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	Mouse	104	30 minutes	RD ₅₀	Carpenter, 1982
2				Repeated Exposure	
3	Rat	20	6 hr/day, 20 days	Nasal irritation	Gage, 1970
4	Rat	50	6 hr/day, 11 days	Respiratory difficulty, weight loss, lung hemorrhage, 1/8 dead	Gage, 1970
5	Rat	22	6 hr/day, 5 days	Decreased body weight gain, increased lung weight, enlarged bronchial lymph nodes, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema	Collins & Proctor, 1984
6	Rat	42	6 hr/day, 5 days	Body weight loss, increased lung weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema	Collins & Proctor, 1984
7	Rat	86	6 hr/day, 5 days	Body weight loss, increased lung weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, focal pulmonary emphysema 3/4 males dead: deaths after 2, 4, and 5 days treatment 3/4 females dead: deaths after 3, 3, and 5 days treatment	Collins & Proctor, 1984

V.3. DATA ANALYSIS AND AEGL-1

V.3.1 Human Data Relevant to AEGL-1

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

V.3.2 Animal Data Relevant to AEGL-1

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

V.3.3 Derivation of AEGL-1

AEGL-1 values for isopropyl chloroformate are not recommended due to insufficient data (Table V-5).

TABLE V-5. AEGL-1 Values for Isopropyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
AEGL-1	NR	NR	NR	NR	NR	

NR: Not Recommended. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 will be without effect.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

V.4. DATA ANALYSIS AND AEGL-2

V.4.1 Human Data Relevant to AEGL-2

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

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V.4.2 **Animal Data Relevant to AEGL-2**

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

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V.4.3 Derivation of AEGL-2

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No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for isopropyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). The AEGL-2 values for propyl chloroformate are presented in Table V-6, and the calculations for these AEGL-2 values are presented in Appendix V-A.

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	TABLE V-6. AEGL-2 Values for Isopropyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
AEGL-2	6.0 ppm (30 mg/m ³)	4.3 ppm (22 mg/m ³)	3.3 ppm (17 mg/m ³)	0.83 ppm (4.2 mg/m³)	0.43 ppm (2.2 mg/m ³)			

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The derived AEGL-2 values are considered protective because rats exposed to 20 ppm isopropyl chloroformate 6 hours/day for 20 days exhibited only nasal irritation (Gage, 1970)

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V.5. DATA ANALYSIS AND AEGL-3

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V.5.1

V.5.2

Human Data Relevant to AEGL-3

Animal Data Relevant to AEGL-3

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

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A rat 1-hr LC₅₀ value of 300 ppm was calculated (Bio Test, 1970). A 15-minute mouse LC₅₀ of 283-345 was estimated (Anderson, 1984).

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V.5.3 Derivation of AEGL-3

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One-third of the 1-hr LC_{50} value in rats (300 ppm x $1\!/\!_3=100$ ppm) (Bio-Test Laboratories, Inc., 1970) will be used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This

concentration is considered an estimated threshold for lethality and is supported by the fact that 0/12 40 41

rats died when exposed to approximately 200 ppm for 1 hour (BASF, 1968a). Interspecies and

intraspecies uncertainty factors of 3 each will be applied because isopropyl chloroformate is highly

reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for isopropyl chloroformate are presented in Table V-7, and the calculations for these AEGL-3 values are presented in Appendix V-A.

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TABLE V-7. AEGL-3 Values for Isopropyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	18 ppm (90 mg/m³)	13 ppm (65 mg/m ³)	10 ppm (50 mg/m³)	2.5 ppm (13 mg/m³)	1.3 ppm (6.5 mg/m ³)

The derived AEGL-3 values are considered protective because no deaths were noted in rats exposed to 42 ppm isopropyl chloroformate 6 hours/day for 5 days (Collins and Proctor, 1984).

V.6.1

V.6. SUMMARY OF AEGLS

The derived AEGL values are summarized in Table V-8. AEGL-1 values are not recommended for isopropyl chloroformate due to inufficient data. AEGL-2 values were derived by dividing AEGL-3 values by 3, and AEGL-3 values were based on an estimated 1-hour lethality threshold in rats.

TABLE V-8. Summary of AEGL Values for Isopropyl Chloroformate						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	6.0 ppm (30 mg/m³)	4.3 ppm (22 mg/m³)	3.3 ppm (17 mg/m ³)	0.83 ppm (4.2 mg/m ³)	0.43 ppm (2.2 mg/m^3)	
AEGL-3 (Lethal)	18 ppm (90 mg/m³)	13 ppm (65 mg/m³)	10 ppm (50 mg/m ³)	2.5 ppm (13 mg/m³)	1.3 ppm (6.5 mg/m ³)	

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

V.6.2. Comparison with Other Standards and Guidelines

AEGL Values and Toxicity Endpoints

The following standards were located for isopropyl chloroformate.

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32 33 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

C '11'			Exposure Durati	ion		
Guideline	10 minutes	30 minutes	1 hour	4 hours	8 hours	
AEGL-1	NR	NR	NR	NR	NR	
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppn	
AEGL-3	18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm	
ERPG-1 ^a			Insufficient Dat	a		
ERPG-2 ^a			5 ppm			
ERPG-3 ^a		20 ppm				
Dutch MAC ^b					1 ppm	

^aERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2005)

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. No ERPG-1 for isopropyl chloroformate is derived because of insufficient data.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for isopropyl chloroformate is based on animal irritation studies.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for isopropyl chloroformate is based on animal lethality data.

bMAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA.

V.6.3 Data Quality and Research Needs

Animal data are limited to acute and repeated-exposure rat inhalation studies and a two mouse RD₅₀ studies. The support provided by the repeated-exposure studies adds to confidence in the derived AEGL values.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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3	APPENDIX V-A:
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5	DERIVATION OF AEGL VALUES FOR ISOPROPYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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DERIVATION OF AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE

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AEGL-1 values are not recommended for isopropyl chloroformate due to insufficient data.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

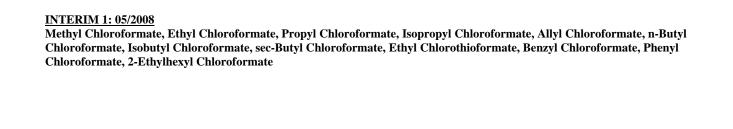
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	Deri	vation of AEGL-2 Values for Isopropyl Chloroformate
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8	Key study: Bio-Test Lab	oratories, Inc., 1970
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10	Toxicity Endpoint: 1/3 of	the AEGL-3 values
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16	<u>10-min AEGL-2</u> :	$18 \text{ ppm} \div 3 = 6.0 \text{ ppm}$
17		
18	<u>30-min AEGL-2</u> :	$13 \text{ ppm} \div 3 = 4.3 \text{ ppm}$
19		
20	<u>1-hr AEGL-2</u> :	$10 \text{ ppm} \div 3 = 3.3 \text{ ppm}$
21		
22	<u>4-hr AEGL-2</u> :	$2.5 \text{ ppm } \div 3 = 0.83 \text{ ppm}$
23		
24	<u>8-hr AEGL-2:</u>	$1.3 \text{ ppm} \div 3 = 0.43 \text{ ppm}$
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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                  DERIVATION OF AEGL-3 VALUES FOR ISOPROPYL CHLOROFORMATE
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        Key study: Bio-Test Laboratories, Inc., 1970
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       Toxicity Endpoint: Estimated LC_{01} (1/3 the LC_{50}) from a 1-hour exposure in male rats.
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       LC50 = 300 \text{ ppm}; \frac{1}{3} \times 300 \text{ ppm} = 100 \text{ ppm} (point of departure)
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       Scaling: <u>10-minutes and 30-minutes</u>
                 \mathbf{C}^3 \times t = k
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                 (100 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 1,000,000 \text{ ppm}^{\text{th}} r
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            4-hours and 8-hours
            \mathbf{C}^1 \times t = k
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            (100 \text{ ppm})^1 \times 1 \text{ hr} = 100 \text{ ppm}^{\text{th}}
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        Uncertainty Factors:
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            3 for interspecies variability
20
            3 for intraspecies variability
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        <u>10-min AEGL-3</u>:
            C^3 \times 0.167 \text{ hr} = 1,000,000 \text{ ppm}^{\text{th}} \text{r}
23
            C^3 = 5988024 \text{ ppm}
24
25
            C = 182 ppm
26
             10-min AEGL-3 = 182/10 = 18 ppm
27
28
        30-min AEGL-3
            C^3 \times 0.5 \text{ hr} = 1,000,000 \text{ ppm'hr}
29
            C^3 = 2,000,000 \text{ ppm}
30
31
            C = 126 \text{ ppm}
32
            30-min AEGL-3 = 126/10 = 13 ppm
33
34
        1-hr AEGL-3
35
             1-hr AEGL-3 = 100/10 = 10 ppm
36
37
        4-hr AEGL-3
            C^1 \times 4 \text{ hr} = 100 \text{ ppm}^{\text{th}} \text{r}
38
            C^1 = 25 \text{ ppm}
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40
            C = 25 \text{ ppm}
41
            4-hr AEGL-3 = 25/10 = 2.5 ppm
42
43
        8-hr AEGL-3
            C^1 \times 8 \text{ hr} = 100 \text{ ppm}^{1}\text{hr}
44
            C^1 = 12.5 \text{ ppm}
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

- 1 C = 12.5 ppm
- 2 8-hr AEGL-3 = 12.5/10 = 1.3 ppm



1 APPENDIX V-B:
2
3 Derivation Summary for Isopropyl Chloroformate AEGLS

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE							
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
NR	NR	NR	NR	NR			
Reference: NA	Reference: NA						
Test Species/Stra	in/Number: NA						
Exposure Route/	Concentrations/E	Ourations: NA					
Effects: NA							
Endpoint/Concer	ntration/Rational	e: NA					
Uncertainty Fact Interspecies : Intraspecies : (Alarie method re	= NA	onal UF)					
Modifying Factor	Modifying Factor: NA						
Animal to Huma	Animal to Human Dosimetric Adjustment: NA						
Time Scaling: NA	4						
Data quality and	research needs:	AEGL-1 values are	not recommended for	isopropyl chloroformate. Data			

were insufficient for deriving values.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm	
Key Reference: Bio-Test Laboratories, Inc. 1970. Acute vapor inhalation toxicity study with IPCF in albino rats. Report to PPG Industries, Inc. IBT No. N9129.					
Test Species/Strain/Number: See AEGL-3 Derivation summary table					
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table					
Effects: See AEGL-3 Derivation summary table					
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape.					
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table					
Modifying Factor: NA	Λ				
Animal to Human Dos	imetric Adjustment: N	A			
Time Scaling: See AEGL-3 Derivation summary table					
Data quality and research needs: See AEGL-3 Derivation summary table. Values are considered protective because rats showed only nasal irritation when exposed to 20 ppm, 6 hours/day for 20 days (Gage, 1970).					

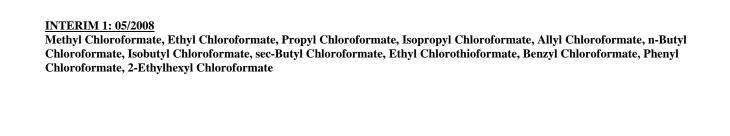
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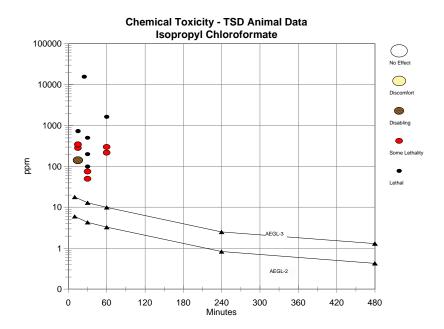
	AEGL-3 VALUES I	OR ISOPROPVI	CHI OROFORMA	TE		
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour		
18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm		
Key Reference: Bio-Test Laboratories, Inc. 1970. Acute vapor inhalation toxicity study with IPCF in albino rats. Report to PPG Industries, Inc. IBT No. N9129.						
Test Species/Strain/Sex	/Number: Albino rats	/ 5/sex/group				
Exposure Route/Concert (1/3 the 1-hour rat LC ₅₀)				ppm)		
Endpoint/Concentration exposure in rats	/Rationale: 1/3 the 1-h	our rat LC ₅₀ / 100 p	pm/Estimated thresh	old for death for 1 hour		
Effects: LC ₅₀ =300 ppm	l					
In	terspecies = 3: traspecies = 3: e is highly reactive an			rect chemical effect on the ndividuals.		
Modifying Factor: NA						
Animal to Human Dosi	metric Adjustment: I	nsufficient data				
Time Scaling: c ⁿ x t= k, = 1 when extrapolating			•	utes and 30-minutes) and n		
Data Quality and Resea	rch Needs: Sparse act	ite toxicity data set,	with repeated-expos	ure studies available for		

support. Values are considered protective because no deaths were noted in rats exposed to 42 ppm, 6 hours/day

for 5 days (Collins and Proctor, 1984).



1 APPENDIX V-C: 2 3 CATEGORY PLOT FOR ISOPROPYL CHLOROFORMATE



	<u>INTERIM 1: 05/2008</u> Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1	CHAPTER VI: ALLYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: ALLYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for allyl chloroformate. Therefore, AEGL-1 values are not recommended for allyl chloroformate.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for allyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm; Stillmeadow, 1970).

The calculated 1-hour rat BMCL $_{05}$ of 21 ppm (Stillmeadow Inc., 1987) was used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because allyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

Summary of AEGL Values For Allyl Chloroformate								
Classification	Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour Endpoint (Reference							
AEGL-1 (Nondisabling)	NR	NR	NR	NR	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)		1/3 the AEGL-3 values (Stillmeadow Inc., 1987)		
AEGL-3 (Lethality)	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-hour rat BMCL ₀₅ (Stillmeadow Inc., 1987)		

 *NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

References

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

Stillmeadow. 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.

1 2 3 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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VI.1. HUMAN TOXICITY DATA

V.1.1 Acute Lethality

Information concerning death in humans following inhalation exposure to allyl chloroformate is not available.

V.1.2 Non-lethal Toxicity

Information concerning non-lethal toxicity in humans following inhalation exposure to allyl chloroformate is not available.

V.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to allyl chloroformate were not available.

V.1.4 Genotoxicity

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

V.1.5 Carcinogenicity

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

V.1.6 Summary

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

VI.2. ANIMAL TOXICITY DATA

VI.2.1 Acute Lethality

VI.2.1.1. Rats

 Groups of five male and five female Sprague Dawley rats were exposed to 33.7, 65.0, 77.7, 134.5, 175.7, or 233.3 ppm allyl chloroformate for 1 hour, followed by a 14-day observation period (Stillmeadow Inc., 1987). Animals were exposed in a 200 liter stainless steel dymanic flow inhalation chamber. The 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 minute intervals during the exposure period. The concentration of allyl chloroformate in the exposure atmosphere was determined analytically at 30 and 60 minutes via gas chromatography. Clinical signs were noted in all exposure groups and included decreased activity, body tremors, constricted pupils, diarrhea, emaciation, epistaxis, gasping, lacrimation, nasal discharge,

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

piloerection, polyuria, ptosis, respiratory gurgle, and salivation. Nine of the ten rats exposed to 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 to higher concentrations and surviving the 14-day observation period lost weight. Gross necropsy findings included discoloration of the lungs, pulmonary edema, clear fluid in the thoracic cavity, gas distended gastrointestinal tract, and discoloration of gastrointestinal tract contents. An LC₅₀ of 65.1 ppm, a BMCL₀₅ of 21 ppm, and a BMC₀₁ of 25.7 ppm were calculated. Data are summarized in Table VI-1.

TABLE V1-1. Exposure of Sprague Dawley Rats to Allyl Chloroformate 1 hour*						
Concentration (ppm)	Mortality- Males	Mortality- Females	Mortality- Combined Males & 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				

^{*}Stillmeadow Inc., 1987

VI.2.2 Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of allyl chloroformate was located in the available literature.

VI.2.3 Genotoxicity

No information concerning the genotoxicity of allyl chloroformate was located in the available literature.

VI.2.4 Carcinogenicity

No information concerning the carcinogenicity of allyl chloroformate was located in the available literature.

VI.2.5 Summary

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Animal toxicity data are limited to one well-conducted rat lethality study, yielding an LC_{50} of 65.1 ppm, a $BMCL_{05}$ of 21 ppm, and a BMC_{01} of 25.7 ppm and showing clinical signs consistent with severe irrritation. No reproductive/developmental toxicity data, genotoxicity data, or carcinogenicity data were located.

VI.3. DATA ANALYSIS AND AEGL-1

VI.3.1 Human Data Relevant to AEGL-1

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

VI.3.2 Animal Data Relevant to AEGL-1

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

VI.3.3 Derivation of AEGL-1

Data are insufficient for the derivation of AEGL-1 values for allyl chloroformate . Therefore, AEGL-1 values are not recommended (Table VI-2).

TABLE VI-2. AEGL-1 Values for Allyl Chloroformate							
Classification	Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-1	NR	NR	NR	NR	NR		

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

VI.4. DATA ANALYSIS AND AEGL-2

VI.4.1 Human Data Relevant to AEGL-2

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

VI.4.2 Animal Data Relevant to AEGL-2

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

VI.4.3 Derivation of AEGL-2

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for allyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm; Stillmeadow Inc., 1987). The AEGL-2 values for allyl chloroformate are presented in Table VI-3, and the calculations for these AEGL-2 values are presented in Appendix VI-A.

 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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TABLE VI-3. AEGL-2 Values for Allyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour		
AEGL-2	1.3 ppm (6.4 mg/m³)	0.87 ppm (4.3 mg/m ³)	0.70 ppm (3.4 mg/m ³)	0.18 ppm (0.88 mg/m ³)	0.090 ppm (0.44 mg/m³)		

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VI.5. DATA ANALYSIS AND AEGL-3

VI.5.1 Human Data Relevant to AEGL-3

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

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VI.5.2 Animal Data Relevant to AEGL-3

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

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VI.5.3 Derivation of AEGL-3

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The calculated 1-hour rat BMCL₀₅ of 21 ppm (Stillmeadow Inc., 1987) will be used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because allyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for allyl chloroformate are presented in Table VI-4, and the calculations for these AEGL-3 values are presented in Appendix VI-A.

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TABLE VI-4. AEGL-3 Values for Allyl Chloroformate							
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
AEGL-3	3.8 ppm (19 mg/m³)	2.6 ppm (13 mg/m ³)	2.1 ppm (10 mg/m³)	0.53 ppm (2.6 mg/m³)	0.26 ppm (1.3 mg/m ³)		

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VI.6. SUMMARY OF AEGLS

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

VI.6.1 AEGL Values and Toxicity Endpoints

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Chemical-specific data were insufficient for derivation of AEGL-1 values for allyl chloroformate. AEGL-1 values are not recommended, and AEGL-2 values were based on a three-fold reduction of AEGL-3 values. AEGL-3 values were based on the BMCL₀₅ from a 1-hour rat study.

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TABLE VI-5. Summary of AEGL Values for Allyl Chloroformate								
Classification	10-minute	30-minute	1-hour	4-hour	8-hour			
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR			
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)	0.090 ppm (0.44 mg/m ³)			
AEGL-3 (Lethal)	3.8 ppm (19 mg/m³)	2.6 ppm (13 mg/m³)	2.1 ppm (10 mg/m ³)	0.53 ppm (2.6 mg/m³)	0.26 ppm (1.3 mg/m ³)			

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

VI.6.2. Comparison with Other Standards and Guidelines

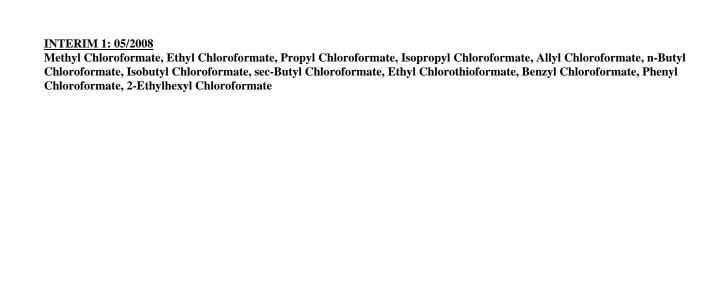
VI.6.3 Data Quality and Research Needs

No other extant values were located for allyl chloroformate.

Data are very sparse. Data were insufficient to derive AEGL-1 values for allyl chloroformate.

AEGL-2 values were obtained by reducing the AEGL-3 values three-fold. AEGL-3 values were based on a calculated BMCL₀₅ from a well-conducted rat study.

1	VI.7. REFERENCES
2	
3	NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute
4	Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
5	
6	Stillmeadow Inc. 1987. Rat Acute Inhalation Toxicity: Allyl Chloroformate. Stillmeadow, Inc.
7	Biological Testing Laboratory. Houston, TX. Project No. 4438-86. Report Submitted to PPG
8	Industries, Inc., Chicago, IL. February 19, 1987. OTS0536028.
9	
10	ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response
11	relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309
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1 APPENDIX VI-A:
2
3 DERIVATION OF AEGL VALUES FOR ALLYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR ALLYL CHLOROFORMATE

AEGL-1 values for allyl chloroformate are not recommended.

1 2 3 4 5	D	erivation of AEGL-2 Values for Allyl Chloroformate
6	Key study: Stillmeadow	Inc. 1987
7	ncy study. Stiffficadow	inc., 1707
8	Toxicity Endpoint: 1/3 of	the AEGL-3 values
9	, 1	
10		
11		
12		
13		
14	<u>10-min AEGL-2</u> :	$3.8 \text{ ppm} \div 3 = 1.3 \text{ ppm}$
15	20 : AEGL 2	2 6 0 07
16	30-min AEGL-2:	$2.6 \text{ ppm} \div 3 = 0.87 \text{ ppm}$
17	1 by AECL 2	2.1 mm : 2 = 0.70 mm
18 19	1-hr AEGL-2:	$2.1 \text{ ppm} \div 3 = 0.70 \text{ ppm}$
20	4-hr AEGL-2:	$0.53 \text{ ppm } \div 3 = 0.18 \text{ ppm}$
21	1 III TILOL 2.	0.00 ррш . 0 – 0.10 ррш
22	8-hr AEGL-2:	$0.26 \text{ ppm} \div 3 = 0.090 \text{ ppm}$

```
1
 2
 3
            DERIVATION OF AEGL-3 VALUES FOR ALLYL CHLOROFORMATE
 4
 5
        Key study: Stillmeadow Inc., 1987
 6
 7
        Toxicity Endpoint: 1-hour rat BMCL<sub>05</sub> (21 ppm)
 8
 9
10
        Scaling: 10-minutes and 30-minutes
                 C^3 \times t = k
11
                 (21 \text{ ppm})^3 \times 1 \text{ hr} = 9261 \text{ ppm}^{\text{hr}}
12
13
14
            4-hours and 8-hours
            C^1 \times t = \overline{k}
15
            (21 \text{ ppm})^1 \times 1 \text{ hr} = 21 \text{ ppm}^{\text{th}}
16
17
18
        Uncertainty Factors:
19
            3 for interspecies variability
20
            3 for intraspecies variability
21
22
        <u>10-min AEGL-3</u>:
            C^3 \times 0.167 \text{ hr} = 9261 \text{ ppm}^{\text{th}} \text{r}
23
            C^3 = 55455 \text{ ppm}
24
25
            C = 38 \text{ ppm}
26
             10-min AEGL-3 = 38/10 = 3.8 ppm
27
        30-min AEGL-3
28
            C^3 \times 0.5 \text{ hr} = 9261 \text{ ppm}^{\text{th}}r
29
            C^3 = 18522 \text{ ppm}
30
31
            C = 26.4 \text{ ppm}
32
            30-min AEGL-3 = 26.4/10 = 2.6 ppm
33
34
        1-hr AEGL-3
35
             1-hr AEGL-3 = 21/10 = 2.1 ppm
36
37
        4-hr AEGL-3
            C^1 \times 4 \text{ hr} = 21 \text{ ppm}^{\text{th}} \text{r}
38
            C^1 = 5.25 \text{ ppm}
39
40
            C = 5.25 \text{ ppm}
            4-hr AEGL-3 = 5.25/10 = 0.53 ppm
41
42
43
        8-hr AEGL-3
            C^1 \times 8 \text{ hr} = 21 \text{ ppm}^{1} \text{hr}
44
45
            C^1 = 2.63 \text{ ppm}
```

```
\begin{array}{ll} 1 & C = 2.63 \ ppm \\ 2 & 8\text{-hr AEGL-3} = 2.63/10 \ = 0.26 \ ppm \\ 3 & 4 & \end{array}
```

1	
2	APPENDIX VI-B:
3	
4	Derivation Summary for Allyl Chloroformate AEGLS

1
2

10 minutes	30 minutes	1 hour	4 hour	8 hou
NR	NR	NR	NR	NR
Key Reference: Che	mical-specific data were	insufficient for derivi	ng AEGL-1 values.	
Test Species/Strain/I	Number:			
Exposure Route/Cor	centrations/Durations:			
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale:				
Modifying Factor:				
Animal to Human D	osimetric Adjustment:			
Time Scaling:				
Data Quality and Re	search Needs: No chemi	cal-specific data were	available for derivation	of AEGL-1 va

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2					
3	AEGL-2 VALUES FOR ALLYL CHLOROF				
4	10-Minute	30-Minute	1-Hour	4	
5	1.3 ppm	0.87 ppm	0.70 ppm	0.1	
6 7 8	Key Reference: Stillmeadow Inc. 1987. Rat Acute Inhalation Toxicity: A Inc. Biological Testing Laboratory. Houston, TX. Project PPG Industries, Inc., Chicago, IL. February 19, 1987. OT				
9	Test Species/Strain/Nu	ımber: See AEGL-3 D	erivation summary tab	le	
10	Exposure Route/Conce	entrations/Durations: S	ee AEGL-3 Derivation	ı summ	
11	Effects: See AEGL-3 Derivation summary table				
12 13 14	Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. C to escape. This approach is justified based on the steep concentration curve mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm				
15	Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
16	Modifying Factor: NA				
17	Animal to Human Dosimetric Adjustment: NA				
18	Time Scaling: See AEGL-3 Derivation summary table				
19	Data quality and resear	rch needs: See AEGL-	3 Derivation summary	table.	
20					

21

AEGL-2 VALUES FOR ALLYL CHLOROFORMATE					
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour					
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.090 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/Nu	ımber: See AEGL-3 D	erivation summary tab	le		
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table					
Effects: See AEGL-3 Derivation summary table					
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm; Stillmeadow Inc., 1970).					
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table					
Modifying Factor: NA					
Animal to Human Dosimetric Adjustment: NA					
Time Scaling: See AEGL-3 Derivation summary table					

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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4 5 6

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9 10

11 12

13 14

15 16 17

22 23 24

2526

27 28

29

30

AEGL-3 VALUES FOR ALLYL CHLOROFORMATE

10-Minute 30-Minute 1-Hour 4-Hour 8-Hour

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: Sprague Dawley rats/ 5/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour (Calculated $BMCL_{05}$ of 21 ppm was the point-of-departure for AEGL-3)

 $Endpoint/Concentration/Rationale: BMCL_{05}\ in\ rats\ after\ a\ 1\ hr\text{-}exposure/\ 21\ ppm/Estimated\ threshold\ for\ death\ for\ 1\ hour\ exposure\ in\ rats$

Effects: $LC_{50} = 65.1 \text{ ppm}$; $BMC_{01} = 25.7 \text{ ppm}$; $BMCL_{05} = 21 \text{ ppm}$

Uncertainty Factors/Rationale:

Interspecies = 3:

Intraspecies = 3:

Allyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

Modifying Factor: NA

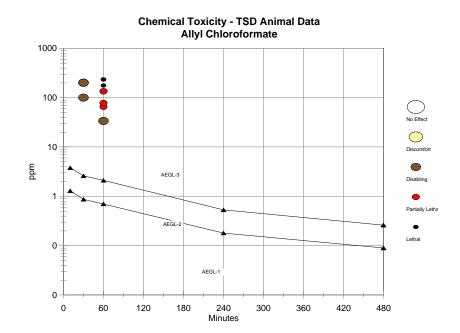
Animal to Human Dosimetric Adjustment: Insufficient data

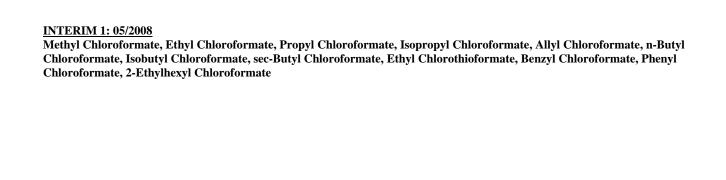
Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n=1 when extrapolating to longer time points (4-hours and 8-hours).

Data Quality and Research Needs: Sparse data set.

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 3 APPENDIX VI-C: 4 5 Category Plot for Allyl Chloroformate





1 APPENDIX VI-D:

Benchmark Concentration Calculation for Allyl Chloroformate

```
1
       BMDS MODEL RUN
 2
 3
         The form of the probability function is:
 4
        P[response] = Background
 5
6
7
                + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
         where CumNorm(.) is the cumulative normal distribution function
 8
         Dependent variable = Mean
 9
         Independent variable = Dose
10
        Slope parameter is not restricted
11
12
         Total number of observations = 6
13
        Total number of records with missing values = 0
14
        Maximum number of iterations = 250
15
        Relative Function Convergence has been set to: 1e-008
16
        Parameter Convergence has been set to: 1e-008
17
        User has chosen the log transformed model
18
                 Default Initial (and Specified) Parameter Values
19
                   background =
20
                    intercept = -7.2918
21
                      slope =
                                1.72308
22
23
             Asymptotic Correlation Matrix of Parameter Estimates
24
             ( *** The model parameter(s) -background
25
                 have been estimated at a boundary point, or have been specified by the user,
26
                 and do not appear in the correlation matrix )
27
               intercept
                            slope
28
       intercept
                              -1
                      1
29
          slope
                              1
                     -1
30
31
                      Parameter Estimates
32
33
           Variable
                                         Std. Err.
                          Estimate
34
          background
                                0
                                          NA
35
          intercept
                          -10.3866
                                          2.68182
36
             slope
                         2.48392
                                        0.621724
37
38
       NA - Indicates that this parameter has hit a bound
39
          implied by some inequality constraint and thus
40
          has no standard error.
41
42
                     Analysis of Deviance Table
43
44
           Model
                    Log(likelihood) Deviance Test DF P-value
45
          Full model
                         -16.0896
46
        Fitted model
                         -17.3239
                                      2.46858
                                                 4
                                                        0.6503
47
        Reduced model
                           -36.6519
                                        41.1245
                                                   5
                                                         <.0001
48
49
                       38.6478
             AIC:
50
                   Goodness of Fit
51
                                            Scaled
52
          Dose Est._Prob. Expected Observed Size
                                                             Residual
53
54
         33.7000
                    0.0495
                                0.495
                                           0
                                                   10
                                                         -0.7219
```

 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

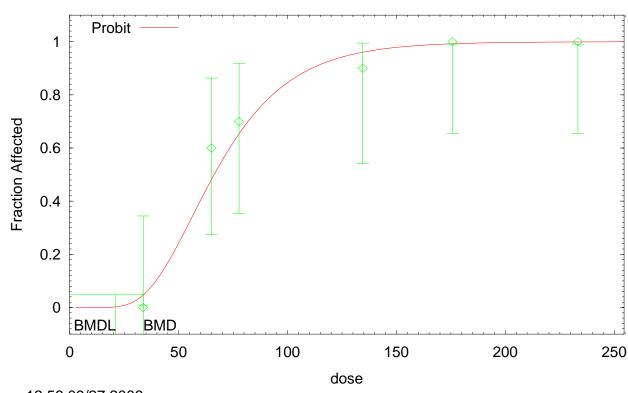
65.0000	0.4929	4.929	6	10	0.6774
77.7000	0.6648	6.648	7	10	0.236
134.5000	0.9632	9.632	9	10	-1.06
175.7000	0.9929	9.929	10	10	0.2674
233.3000	0.9992	9.992	10	10	0.08938
Chi-square	= 2.24	DF = 4	P-valu	e = 0.69	19

Benchmark Dose Computation

Specified effect = 0.05 Risk Type = Extra risk Confidence level = 0.95

> BMD = 33.7621BMDL = 21.098

Probit Model with 0.95 Confidence Level



INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
CHAPTER VII:
n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

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12	
13	

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for n-butyl chloroformate. Therefore, AEGL-1 values are not recommended for n-butyl chloroformate.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for n-butyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). The resulting values are considered protective because rats showed no effects when exposed to 1.8 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 2.9 ppm 6 hours/day for 5 days (HRC 1990).

 One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl chloroformate (200 ppm x $\frac{1}{3}$ = 66.7 ppm) (BASF, 1970) was used as the point-of-departure for n-butyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because n-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor was 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by c^n x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The resulting values are considered protective because no rats died when exposed to 5.1 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 28.4 ppm 6 hours.day for 5 days (HRC 1990).

	Summary of AEGL Values for n-Butyl Chloroformate								
Classification 10-Minute		30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)			
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data			
AEGL-2 (Disabling)	4.0 ppm (22 mg/m ³)	2.8 ppm (33 mg/m ³)	2.2 ppm (27 mg/m³)	0.57 ppm (6.7 mg/m ³)	0.28 ppm (3.3 mg/m ³)	1/3 AEGL-3 values			
AEGL-3 (Lethality)	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-hr lethality threshold in rats (BASF, 1970)			

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-5

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the AEGL-1, AEGL-2, and AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.

5	
6	
7	

}	Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate								
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)			
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	By analogy to n-butyl chloroformate			
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)	By analogy to n-butyl chloroformate			
AEGL-3 (Lethality)	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 \text{ ppm} $ (10 mg/m^3)	By analogy to n-butyl chloroformate			

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2

VII.1. HUMAN TOXICITY DATA

VII.1.1 Acute Lethality

Information concerning death in humans following inhalation exposure to n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate is not available.

VII.1.2 Non-lethal Toxicity

Information concerning non-lethal toxicity in humans following inhalation exposure to n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate is not available.

VII.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate were not available.

VII.1.4 Genotoxicity

Genotoxicity studies regarding acute human exposure to n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate were not available.

VII.1.5 Carcinogenicity

Carcinogenicity studies regarding human exposure to n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate were not available.

VII.1.6 Summary

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

VII.2. ANIMAL TOXICITY DATA

Acute Lethality

VII.2.1

n-Butyl Chloroformate

 Death occurred in 4/10 rats exposed to 200 ppm n-butyl chloroformate for 1 hour (BASF, 1970). Clinical signs included dyspnea, and pulmonary emphysema was noted at necropsy.

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

Oral LD_{50} values of 1325 mg/kg (administered in 10% aqueous tragacanth gum emulsion) and n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-7

2 3

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

2120 mg/kg (administered in 20% aqueous tragacanth gum emulsion) were reported for rats (BASF, 1970). An oral LD_{50} of 2610 mg/kg was reported for male and female Sprague-Dawley rats when n-butyl chloroformate was administered in olive oil (BASF, 1980).

VII.2.2 Non-lethal Toxicity

n-Butyl Chloroformate

In an inhalation range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to 0, 2.9, 9.9, or 28.4 ppm n-butyl chloroformate 6 hours/day for 5 days (HRC, 1990). None of the rats died. There was a concentration-related decrease in food consumption 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 noted in high-concentration males throughout the study; whereas, high-concentration females showed initial body weight loss, followed by decreased body weight gain. Lung 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 0, 0.50, 1.8, or 5.1 ppm n-butyl chloroformate 6 hours/day, 5 days/week for 4 weeks (HRC, 1990). None of the rats died. Piloerection was noted in the 5.1 ppm group during exposure. High-concentration males had increased lung weight. Histological examination of the lungs showed 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.

Isobutyl Chloroformate

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 25, 50, 100, 150, or 200 ppm isobutyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted isobutyl chloroformate was delivered to a Pitt #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 are summarized in Table VII-1.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Mortality Within 24-hrs

1	TABLE	VII-1. Exposure of Male Swiss-Webster	r Mice to Isobutyl Chloroformate	e for 30 minutes*
2 3	Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality With
4	25	265/20	25	0/4
5	50	260/155	40	0/4
6	100	310/155	50	0/4
7	150	290/145	50	0/4
8	200	295/85	71	0/4

^{*}Carpenter, 1982

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sec-Butyl Chloroformate

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 50, 100, 150, or 200 ppm sec-butyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted sec-butyl chloroformate was delivered to a Pitt #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 are summarized in Table VII-2.

TABLE V	TABLE VII-2. Exposure of Male Swiss-Webster Mice to sec-butyl Chloroformate for 30 minutes*								
Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs						
50	195/175	10	0/4						
100	280/165	41	0/4						
150	295/130	55	0/4						
200	225/40	82	1/4						

^{*}Carpenter, 1982

VII.2.3 Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate was located in the available literature.

VII.2.4 Genotoxicity

N-Butyl chloroformate was negative in a preincubation test both with and without metabolic activation in Salmonella typhimurium strains TA 98, TA 100, TA 1535, and TA 1537 (BASF, 1988), and was negative both with and without activation in a chromosome aberration assay in Chinese hamster V79 cells (CCR, 1990). No genotoxicity data were available for isobutyl chloroformate or sec-butyl chloroformate.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

VII.2.5 Carcinogenicity

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No information concerning the carcinogenicity of n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate was located in the available literature.

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VII.2.6 **Summary**

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Animal data regarding lethal and non-lethal toxicity of n-butyl chloroformate are limited to rat studies. Clinical signs were consistent with severe irritation and respiratory distress. Animal data for isobutyl chloroformate and sec-butyl chloroformate were limited to mouse RD₅₀ studies. n-Butyl chloroformate was negative in both bacterial reverse mutation and mammalian cell chromosome aberration assays, and no genotoxicity data were available for isobutyl chloroformate or sec-butyl chloroformate. No developmental/reproductive toxicity or carcinogenicity data were available for nbutyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate.

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VII.3. DATA ANALYSIS AND AEGL-1

VII.3.1 **Human Data Relevant to AEGL-1**

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

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VII.3.2 **Animal Data Relevant to AEGL-1**

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

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VII.3.3 **Derivation of AEGL-1**

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Data are insufficient for the derivation of AEGL-1 values for n-butyl chloroformate, isobutyl chloroformate, or sec-butyl chloroformate. Therefore, AEGL-1 values are not recommended (Table VII-3).

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TABLE VII-3. AEGL-1 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
AEGL-1	NR	NR	NR	NR	NR	

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> NR: Not Recommended. Absence of derived AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

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VII.4. DATA ANALYSIS AND AEGL-2

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VII.4.1 **Human Data Relevant to AEGL-2**

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

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VII.4.2 **Animal Data Relevant to AEGL-2**

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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

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VII.4.3 **Derivation of AEGL-2**

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n-Butyl Chloroformate

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No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for n-butyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). The AEGL-2 values for n-butyl chloroformate are presented in Table VII-4, and the calculations for these AEGL-2 values are presented in Appendix VII-A.

TABLE VII-4. AEGL-2 Values for n-Butyl Chloroformate							
Classification 10-Minute 30-Minute 1-Hour 4-Hour							
AEGL-2	4.0 ppm (22 mg/m³)	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)		

These values are considered protective because rats showed no effects when exposed to 1.8 ppm nbutyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 2.9 ppm 6 hours/day for 5 days (HRC 1990).

Isobutyl Chloroformate and sec-Butyl Chloroformate

Chemical-specific data were insufficient for the derivation of AEGL-2, values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD₅₀ values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the , AEGL-2 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate. The AEGL-2 values for isobutyl chloroformate and sec-butyl chloroformate are presented in Table VII-5.

TABLE VII-5. AEGL-2 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour		
AEGL-2	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)		

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VII.5. DATA ANALYSIS AND AEGL-3

VII.5.1 **Human Data Relevant to AEGL-3**

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

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VII.5.2 **Animal Data Relevant to AEGL-3**

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Death occurred in 4/10 rats exposed to 200 ppm n-butyl chloroformate for 1 hour (BASF, 1970). n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-11

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

VII.5.3 Derivation of AEGL-3

n-Butyl Chloroformate

One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl chloroformate (200 ppm x $\frac{1}{3}$ = 66.7 ppm) (BASF, 1970) will be used as the point-of-departure for n-butyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each will be applied because n-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by c^n x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for n-butyl chloroformate are presented in Table VII-6, and the calculations for these AEGL-3 values are presented in Appendix VII-A.

TABLE VII-6. AEGL-3 Values for n-Butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
AEGL-3	12 ppm (68 mg/m³)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m ³)	1.7 ppm (20 mg/m³)	0.83 ppm (10 mg/m^3)	

These values are considered protective because rats showed no deaths when exposed to 5.1 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 28.4 ppm 6 hours.day for 5 days (HRC 1990).

Isobutyl Chloroformate and sec-Butyl Chloroformate

Chemical-specific data were insufficient for the derivation of AEGL-3, values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the , AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate. The AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate are presented in Table VII-7.

TABLE VII-7. AEGL-3 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour		
AEGL-3	12 ppm (68 mg/m³)	8.4 ppm (100 mg/m ³)	6.7 ppm (80 mg/m ³)	1.7 ppm (20 mg/m³)	0.83 ppm (10 mg/m³)		

VII.6. SUMMARY OF AEGLS

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

VII.6.1 **AEGL Values and Toxicity Endpoints**

Chemical-specific data were insufficient for derivation of AEGL-1 values for n-butyl chloroformate; therefore, AEGL-1 values are not recommended. AEGL-2 values for n-butyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for n-butyl chloroformate were based on an estimated lethality threshold from a 1-hour rat study.

TABLE VII-8: Summary of AEGL Values for n-butyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
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 (Lethality)	12 ppm (68 mg/m³)	8.4 ppm (100 mg/m ³)	6.7 ppm (80 mg/m ³)	1.7 ppm (20 mg/m ³)	$0.83 \text{ ppm} \ (10 \text{ mg/m}^3)$

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity. Thus, the AEGL-1, AEGL-2, and AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate

TABLE VII-9: Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
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/m³)
AEGL-3 (Lethality)	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 \text{ ppm} $ (10 mg/m^3)

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

VII.6.2. **Comparison with Other Standards and Guidelines**

The Dutch MAC for n-butyl chloroformate is 1 ppm [MAC (Maximaal Aanvaarde Concentratie) (Maximal Accepted Concentration)], is defined analogous to the ACGIH-TLV-TWA (SDU Uitgevers, 2001).

The threshold Limit Value (TLV) for n-butyl chloroformate is 1 ppm in Australia and the United Kingdom (BG Chemie, 2005).

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 No extant values were located for isobutyl chloroformate or sec-butyl chloroformate. 2 3 4 VII.6.3 **Data Quality and Research Needs** 5 6 No human data are available and animal data are sparse. 7 8 VII.7. REFERENCES 9 10 BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. N-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung. Unpublished Report No. XIX 352. 11 12 13 BASF. 1980. BASF AG, Gewerbehygiene und Toxilologie. Prufung der akutenoralen Toxizitat von 14 N-Butylchlorformial an der ratte. Unpublished Report. 15 BASF. 1988. Report on the study of chloroformic acid butyl ester in the Ames test (preincubation 16 test with Salmonella typhimurium) Unpublished Report. Project No. 40M0522/874089. September 7, 17 18 1988, on behalf of BG Chemie. 19 20 BG Chemie. 2005. Chlorofomic acid butyl ester. CAS No. 592-34-7. Toxicological Evaluation No. 21 160. Updated 02/2005. BG Chemie (Institution for Statutory Accident Insurance and Prevention in 22 the Chemical Industry). Heidelberg, Germany. 23 24 Carpenter, C.P. 1982. Ethyl chloroformate, n-propyl chloroformate, Isobutyl chloroformate, Sec-25 butyl chloroformate. Sensory Irritation. Report by Mellon Institute. Report to PPG Industries, Inc., Chemicals Division. Report No. 82-49S. 26 27 28 CCR (Cytotest Cell Research). 1990. Chromosome aberration assay in Chinese hamster V79 cells in 29 vitro with chloroformic acid, n-butylester. Unpublished report. CCR Project 148803. Sponsor: BG 30 Chemie (Institution for Statutory Accident Insurance and Prevention in the Chemical Industry). Heidelberg, Germany. July 18, 1990. (cited in BG Chemie, 2005) 31 32 33 HRC (Huntingdon Research Centre, Ltd.) 1990. N-Butyl chloroformate- 28-day inhalation study in the 34 rat. Unpublished Report, Report No. BGH 12/90156. (cited in BG Chemie, 2005) 35 36 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC. 37 38 39 SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, 40 The Netherlands 2001. 41 42 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response

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relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Methyl Chlorof	IM 1: 05/2008 Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Cormate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Cormate, 2-Ethylhexyl Chloroformate
	APPENDIX VII-A:
]	DERIVATION OF AEGL VALUES FOR N-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and SEC-BUTYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR N-BUTYL CHLOROFORMATE, ISOBUTYL
CHLOROFORMATE, and SEC-BUTYL CHLOROFORMATE

AEGL-1 values for n-butyl chloroformate, isobutyl chloroformate, and sec-butyl chloroformate are not recommended.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 Derivation of AEGL-2 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-**Butyl Chloroformate** 3 4 5 6 **n-Butyl Chloroformate** Key study: BASF, 1970 7 8 9 Toxicity Endpoint: 1/3 of the AEGL-3 values 10 11 <u>10-min AEGL-2</u>: $12 \text{ ppm} \div 3 = 4.0 \text{ ppm}$ 12 13 $8.4 \text{ ppm} \div 3 = 2.8 \text{ ppm}$ <u>30-min AEGL-2</u>: 14 15 $6.7 \text{ ppm} \div 3 = 2.2 \text{ ppm}$ <u>1-hr AEGL-2</u>: 16 17 1.7 ppm $\div 3 = 0.57$ ppm <u>4-hr AEGL-2</u>: 18 19 8-hr AEGL-2: $0.83 \text{ ppm} \div 3 = 0.28 \text{ ppm}$ 20 21 22 23 **Isobutyl Chloroformate and sec-Butyl Chloroformate** 24 25 AEGL-2 values for n-butyl chloroformate were adopted as AEGL-2 values for isobutyl chloroformate

and sec-butyl chloroformate.

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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1
            Derivation of AEGL-3 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl
                                                                   Chloroformate
 2
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        Key study: BASF, 1970
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        Toxicity Endpoint: 1-hour rat lethality threshold estimate
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 7
            Scaling:10-minutes and 30-minutes
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                 C^3 \times t = k
 9
                 (66.7 \text{ ppm})^3 \times 1 \text{ hr} = 296,741 \text{ ppm}^{\text{h}}\text{r}
10
11
            4-hours and 8-hours
            \mathbf{C}^1 \times t = k
12
13
            (66.7 \text{ ppm})^1 \times 1 \text{ hr} = 66.7 \text{ ppm}^{\text{th}}
14
15
        Uncertainty Factors:
16
            3 for interspecies variability
17
            3 for intraspecies variability
18
19
        10-min AEGL-3:
            C^3 \times 0.167 \text{ hr} = 296,741 \text{ ppm}^{\text{hr}}
20
21
            C^3 = 1,776,892 \text{ ppm}
22
            C = 121 \text{ ppm}
23
             10-min AEGL-3 = 121/10 = 12 ppm
24
25
        30-min AEGL-3
            C^3 \times 0.5 \text{ hr} = 296,741 \text{ ppm}^{\text{hr}}
26
            C^3 = 593482 \text{ ppm}
27
28
            C = 84.0 \text{ ppm}
29
            30-min AEGL-3 = 84.0/10 = 8.4 ppm
30
31
        1-hr AEGL-3
32
            1-hr AEGL-3 = 66.7/10 = 6.7 ppm
33
34
        4-hr AEGL-3
            C^1 \times 4 \text{ hr} = 66.7 \text{ ppm}^{1}\text{hr}
35
            C^1 = 16.8 \text{ ppm}
36
37
            C = 16.8 \text{ ppm}
38
            4-hr AEGL-3 = 16.8/10 = 1.7 ppm
39
40
        8-hr AEGL-3
            C^1 \times 8 \text{ hr} = 66.7 \text{ ppm}^{\text{th}}
41
            C^1 = 8.34 \text{ ppm}
42
43
            C = 8.34 \text{ ppm}
44
            8-hr AEGL-3 = 8.34/10 = 0.83 ppm
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        Isobutyl Chloroformate and sec-Butyl Chloroformate
        AEGL-3 values for n-butyl chloroformate adopted as AEGL-3 values for isobutyl chloroformate and sec-butyl
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chloroformate.

	Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2	APPENDIX VII-B:
3 4 5	Derivation Summary for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate AEGLS

10 minutes	30 minutes	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR
Key Reference: Chem	ical-specific data were	insufficient for derivin	ng AEGL-1 values.	
Test Species/Strain/N	umber:			
Exposure Route/Conc	entrations/Durations:			
Effects:				
Endpoint/Concentration	on/Rationale:			
Uncertainty Factors/R	ationale:			
Modifying Factor:				
Animal to Human Do	simetric Adjustment:			
Time Scaling:	v			

10 minutes	30 minutes	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR
Key Reference:				
Test Species/Strain/N	Number:			
Exposure Route/Con	centrations/Durations:			
Effects:				
Endpoint/Concentrat	ion/Rationale:			
Uncertainty Factors/	Rationale:			
Modifying Factor:				
Animal to Human De	osimetric Adjustment:			
Time Scaling:				
	search Needs: No chemi le to derive values by a		available for derivation	of AEGL-1 va

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lorokohlensaureester-	1-Hour 2.2 ppm ewerbehygienisch-Pha -Gewerbetoxikologisch	4-Hour 0.57 ppm	8-Hour 0.28 ppm
. 1970. BASF AG, G lorokohlensaureester-	ewerbehygienisch-Pha		0.28 ppm
lorokohlensaureester-		rmakologisches Ins	
nber: See AEGL-3 D	_		stitut. N- published Report No. XIX 352
	erivation summary tabl	le	
ntrations/Durations: S	See AEGL-3 Derivation	n summary table	
erivation summary ta	ıble		
/Rationale: 3-fold red	duction of AEGL-3 val	ues. Considered th	reshold for the inability to esca
tionale: See AEGL-3	Derivation summary ta	ıble	
metric Adjustment: N	ΙA		
L-3 Derivation sumn	nary table		
ıtyl chloroformate for	r 6 hours/day, 5 days/w		
n ci	L-3 Derivation summarks have detailed by the control of the contro		L-3 Derivation summary table h needs: Sparse data set. Values are considered protective becatyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (H

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
4.0 ppm	2.8 ppm	2.2 ppm	0.57 ppm	0.28 ppm
	ed by analogy to n-buty es for isobutyl chlorofo			GL-2 values adopted as AEG
Test Species/Strain/N	umber:			
Exposure Route/Conc	entrations/Durations:			
Effects:				
Endpoint/Concentration	on/Rationale:			
Uncertainty Factors/R	ationale:			
Modifying Factor: N	A			
Animal to Human Do	simetric Adjustment: N.	A		
Time Scaling:				
values for isobutyl chloroformate are struand sec-butyl chlorofo	loroformate and sec-but actural analogs of n-buty ormate are of similar tox roformate and 117 ppm	yl chloroformate. Ho yl chloroformate and i cicity (Carpenter, 198 for sec-butyl chlorofo	wever, isobutyl chlorof mouse RD ₅₀ data sugges 2) (male Swiss-Webster ormate). Thus, the AEC	st that isobutyl chloroformate mouse RD ₅₀ values are 97 GL-2 values for n-butyl

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR n-BUTYL CHLOROFORMATE							
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
12 ppm	8.4 ppm	6.7 ppm	1.7 ppm	0.83 ppm			
Key Reference: BASF. Butylch XIX 35	lorokohlensaureester-			stitut. N- npublished Report No.			
Test Species/Strain/Sex	/Number: Sprague Da	wley rats/ 5/sex/gro	oup				
Exposure Route/Concer (1/3 the concentration ca				-3)			
Endpoint/Concentration ppm; Estimated thresho		•	death in 4/10 rats af	ter a 1 hr-exposure; 66.7			
Effects:							
In	terspecies = 3: traspecies = 3: is highly reactive and			ct chemical effect on the ndividuals.			
Modifying Factor: NA							
Animal to Human Dosi	metric Adjustment: In	nsufficient data					
Time Scaling: c ⁿ x t= k, = 1 when extrapolating				nutes and 30-minutes) and			
Data Quality and Resea deaths when exposed to exposed to 28.4 ppm 6	5.1 ppm n-butyl chlo	roformate for 6 hou					

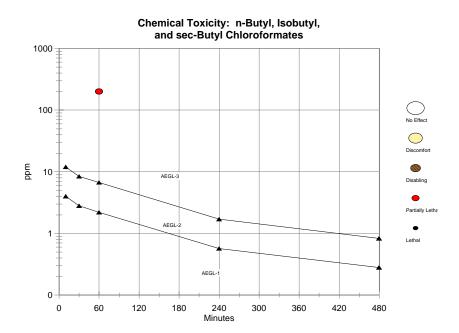
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl $Chloroformate, Isobutyl\ Chloroformate, sec-Butyl\ Chloroformate,\ Ethyl\ Chlorothioformate,\ Benzyl\ Chloroformate,\ Phenyl\ Phenyl$ Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VA	LUES FOR ISOBUTY	L CHLOROFORM	ATE and sec-BUT	YL CHLOROFORMATE
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
12 ppm	8.4 ppm	6.7 ppm	1.7 ppm	0.83 ppm
	ved by analogy to n-buty les for isobutyl chlorofo			AEGL-3 values adopted as A
Test Species/Strain/N	umber:			
Exposure Route/Cond	centrations/Durations:			
Effects:				
Endpoint/Concentrati	on/Rationale:			
Uncertainty Factors/F	Rationale:			
Modifying Factor: N	A			
Animal to Human Do	simetric Adjustment: N	A		
Time Scaling:				
values for isobutyl ch chloroformate are strund sec-butyl chlorof opm for isobutyl chlo	loroformate and sec-bu- actural analogs of n-but- ormate are of similar to:	tyl chloroformate. Ho yl chloroformate and n xicity (Carpenter, 1982 for sec-butyl chlorofo	wever, isobutyl chlorouse RD ₅₀ data sug 2) (male Swiss-Web ormate). Thus, the A	ent for the derivation of AEC proformate and sec-butyl ggest that isobutyl chloroformoster mouse RD ₅₀ values are SAEGL-3 values for n-butyl

THE COLUMN TO THE CONTROL OF THE CON							
10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
12 ppm	8.4 ppm	6.7 ppm	1.7 ppm	0.83 ppm			
Key Reference: Derived by analogy to n-butyl chloroformate. n-Butyl chloroformate AEGL-3 values adopted as AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate.							
Test Species/Strain/Nu	ımber:						
Exposure Route/Conce	entrations/Durations:						
Effects:							
Endpoint/Concentration	on/Rationale:						
Uncertainty Factors/R	ationale:						
Modifying Factor: NA	4						
Animal to Human Dos	simetric Adjustment: N	Ā					
Time Scaling:							
values for isobutyl chl chloroformate are stru and sec-butyl chlorofo	oroformate and sec-bu ctural analogs of n-but ormate are of similar to	tyl chloroformate. Ho yl chloroformate and n xicity (Carpenter, 1982	wever, isobutyl chlo nouse RD ₅₀ data sug 2) (male Swiss-Web	ient for the derivation of AEGL-3 oroformate and sec-butyl ggest that isobutyl chloroformate oster mouse RD ₅₀ values are 97 AEGL-3 values for n-butyl			

	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2	APPENDIX VII-C:
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4 5	Category Plot for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate



Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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CHAPTER VIII: BENZYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: BENZYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for benzyl chloroformate. Therefore, AEGL-1 values are not recommended for benzyl chloroformate.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for benzyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 0/10 at 18.6 ppm; 5/10 at 84.6 ppm (BASF, 1990)) and because observed clinical signs resolved (were reversible).

The experimental concentration causing no deaths in rats (18.6 ppm) after a 4-hour exposure (BASF, 1990) was used as the point-of-departure for benzyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because benzyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and the resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by c^n x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value.

Summary of AEGL Values For Benzyl Chloroformate							
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						Endpoint (Reference)	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data	
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)	1/3 the AEGL-3 values (BASF, 1990)	
AEGL-3 (Lethality)	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)	Concentration causing no death in rats; 4-hr exposure (BASF, 1990)	

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

VIII.1. HUMAN TOXICITY DATA

VIII.1.1 Acute Lethality

Information on death in humans following inhalation exposure to benzyl chloroformate is not available.

VIII.1.2 Non-lethal Toxicity

Information on non-lethal toxicity in humans following inhalation exposure to benzyl chloroformate is not available.

VIII.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to benzyl chloroformate were not available.

VIII.1.4 Genotoxicity

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

VIII.1.5 Carcinogenicity

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

VIII.1.6 Summary

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

VIII.2. ANIMAL TOXICITY DATA VIII.2.1 Acute Lethality

Groups of five male and five female SPF Wistar rats were exposed to 18.6 or 84.6 ppm (analytical concentrations) benzyl chloroformate for 4-hours followed by a 14-day observation period (BASF, 1990). The nose-only exposures were performed in a 55 L glass-steel system; animals were restrained in tubes and noses projected into the chamber. Benzyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs noted 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 during the post-exposure observation period included accelerated respiration and ruffled fur in low-concentration rats and intermittent respiration, respiratory sounds, reddish nasal discharge, aggressiveness (males only), ruffled fur, and deteriorated general state. All clinical signs had 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 adjusted to normal body weight. There were no gross treatment-related effects noted at necropsy in animals surviving

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

to study termination. Gross examination of animals that died during the study showed lung 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 are summarized in Table VIII-1.

Table VIII-1. Mortality in Rats Exposed to Benzyl Chloroformate for 4 hours*

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Cumulative lethality on day	18.6 j	ppm	84.6 ppm		
	Males	Females	Males	Females	
0	0/5	0/5	0/5	1/5	
1	-	-	-	-	
2	-	-	-	3/5	
7	-	-	-	-	
14	-	-	2/5	-	
Total at end of study	0/1	0	5/	10	

*BASF, 1990.

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

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VIII.2.2 Non-lethal Toxicity

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Information on non-lethal toxicity in animals following inhalation exposure to benzyl chloroformate is not available.

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VIII.2.3 Developmental/Reproductive Toxicity

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No information on the developmental/reproductive toxicity of benzyl chloroformate was located in the available literature.

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VIII.2.4 Genotoxicity

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Benzyl chloroformate was negative in a reverse mutation assay in *Salmonella typhimuium* strains TA 98, TA 100, TA1535, and TA 1537 in the presence and absence of S9 mix (Allen and Panfili, 1986).

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VIII.2.5 Carcinogenicity

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No information on the carcinogenicity of benzyl chloroformate was located.

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VIII.2.6 Summary

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Animal toxicity data are limited for benzyl chloroformate. An approximate 4-hr rat LC_{50} of 85 ppm was reported and no deaths were noted in rats exposed to 18.6 ppm for 4 hours. Benzyl chloroformate was negative for mutation in an Ames assay. No animal data developmental/reproductive toxicity or carcinogenicity were available.

VIII.3. DATA ANALYSIS AND AEGL-1

VIII.3.1 Human Data Relevant to AEGL-1

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

VIII.3.2 Animal Data Relevant to AEGL-1

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

V.III.3.3 Derivation of AEGL-1

Data are insufficient for the derivation of AEGL-1 values for benzyl chloroformate. Therefore, AEGL-1 values are not recommended (Table VIII-2).

TABLE VIII-2. AEGL-1 Values for Benzyl Chloroformate							
Classification	Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-1	NR	NR	NR	NR	NR		

NR: Not Recommended. Absence of derived AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

VIII.4. DATA ANALYSIS AND AEGL-2

VIII.4.1

I.4.1 Human Data Relevant to AEGL-2

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

VIII.4.2 Animal Data Relevant to AEGL-2

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

VIII.4.3 Derivation of AEGL-2

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for benzyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 0/10 at 18.6 ppm; 5/10 at 84.6 ppm BASF, 1990) and because observed clinical signs resolved (were reversible). The AEGL-2 values for benzyl chloroformate are presented in Table VIII-3, and the calculations for these AEGL-2 values are presented in Appendix VIII-A.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

TABLE VIII-3. AEGL-2 Values for Benzyl Chloroformate						
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-2	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/m³)	

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VIII.5. DATA ANALYSIS AND AEGL-3

VIII.5.1 Human Data Relevant to AEGL-3

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

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VIII.5.2 Animal Data Relevant to AEGL-3

15 16 No deaths were noted in rats exposed to 18.6 ppm benzyl chloroformate for 4-hours, and an approximate LC_{50} of 85 ppm was reported (BASF, 1990).

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VIII.5.3 Derivation of AEGL-3

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The concentration causing no deaths in rats (18.6 ppm) after a 4-hour exposure (BASF, 1990) will be used as the point-of-departure for benzyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because benzyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemicalspecific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value. The AEGL-3 values for benzyl chloroformate are presented in Table VIII-4, and the calculations for these AEGL-3 values are presented in Appendix VIII-A.

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TABLE VIII-4. AEGL-3 Values for Benzyl Chloroformate						
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-3	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/m³)	0.93 ppm (6.5 mg/m ³)	

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VIII.6. SUMMARY OF AEGLS

VIII.6.1 AEGL Values and Toxicity Endpoints

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Data were insufficient for derivation of AEGL-1 values for benzyl chloroformate; therefore, AEGL-1 values are not recommended. AEGL-2 values for benzyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for benzyl chloroformate were based on a concentration causing no mortality in a 4-hour rat study.

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VIII.6.3

TABLE VIII-5. Summary of AEGL Values for Benzyl Chloroformate							
Classification 10-minute 30-minute 1-hour 4-hour 8-hour							
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR		
AEGL-2 (Disabling)	1.2 ppm (8.7 mg/m³)	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/m³)	0.93 ppm (6.5 mg/m ³)		

VIII.6.2. Comparison with Other Standards and Guidelines

No extant values were located for benzyl chloroformate.

Data Quality and Research Needs

No human toxicity data were available. The only animal toxicity data available were from two rat

No human toxicity data were available. The only animal toxicity data available were from two rat studies.

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of

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	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1	APPENDIX VIII-A:
1 2 3	DERIVATION OF AEGL VALUES FOR BENZYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR BENZYL CHLOROFORMATE

AEGL-1 values for benzyl chloroformate are not recommended.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 3 4]	Derivation of AEGL-2 Values for Benzyl Chloroformate
5		
6 7	Key study: BASF, 1990	
8	Toxicity Endpoint: 1/3 of	the AEGL-3 values
9	J 1	
10		
11		
12		
13		
14	<u>10-min AEGL-2</u> :	$3.7 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
15		
16	30-min AEGL-2:	$3.7 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
17		
18	<u>1-hr AEGL-2</u> :	$2.9 \text{ ppm} \div 3 = 0.97 \text{ ppm}$
19		
20	<u>4-hr AEGL-2</u> :	1.9 ppm \div 3 = 0.63 ppm
21		
22	8-hr AEGL-2:	$0.93 \text{ ppm} \div 3 = 0.31 \text{ ppm}$

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

```
1
 2
 3
            DERIVATION OF AEGL-3 VALUES FOR BENZYL CHLOROFORMATE
 4
 5
       Key study: BASF, 1990
 6
 7
       Toxicity Endpoint: Concentration causing no mortality in 4-hour rat study (18.6 ppm)
 8
 9
10
       Scaling: <u>30-minutes and 1-hr</u>
                C^3 \times t = k
11
                (18.6 \text{ ppm})^3 \text{ x } 4 \text{ hr} = 25739 \text{ ppm}^{\text{th}} \text{r}
12
13
14
        <u>8-h</u>ours
            C^1 \times t = k
15
            (18.6 \text{ ppm})^1 \times 4 \text{ hr} = 74.4 \text{ ppm}^{\text{h}} \text{r}
16
17
18
       Uncertainty Factors:
19
            3 for interspecies variability
20
            3 for intraspecies variability
21
22
       10-min AEGL-3: 30-minute value adopted as 10-minute value = 3.7 ppm
23
24
25
       30-min AEGL-3
            C^3 \times 0.5 \text{ hr} = 25739 \text{ ppm} \text{hr}
26
            C^3 = 51478 \text{ ppm}
27
28
            C = 37.2 \text{ ppm}
29
            30-min AEGL-3 = 37.2/10 = 3.7 ppm
30
31
       1-hr AEGL-3
           C^3 \times 1 \text{ hr} = 25739 \text{ ppm}^{\text{th}} \text{r}
32
            C^3 = 25739 \text{ ppm}
33
34
            C = 29.5 \text{ ppm}
            1-hr AEGL-3 = 29/10 = 2.9 ppm
35
36
37
       4-hr AEGL-3
38
            4-hr AEGL-3 = 18.6/10 = 1.9 ppm
39
40
       8-hr AEGL-3
           C^1 \times 8 \text{ hr} = 74.4 \text{ ppm}^{1}\text{hr}
41
           C^1 = 9.3 \text{ ppm}
42
43
            C = 9.3 \text{ ppm}
            8-hr AEGL-3 = 9.3/10 = 0.93 ppm
44
```

Chloroforma	roformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Bute, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Pheny
Chloroforma	te, 2-Ethylhexyl Chloroformate
	APPENDIX VIII-B:
	Derivation Summary for Benzyl Chloroformate AEGLS

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1

AEGL-1 VALUES FOR BENZYL CHLOROFORMATE							
10 minutes 30 minutes 1 hour 4 hour 8 hour							
NR	NR	NR	NR	NR			
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values							

O	Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values	ies.

rest Sp	becies/Strain/Number:

9 Effects:

Endpoint/Concentration/Rationale:

Uncertainty Factors/Rationale:

Modifying Factor:

Animal to Human Dosimetric Adjustment:

Time Scaling:

Data Quality and Research Needs: No chemical-specific data were available for derivation of AEGL-1 values for benzyl_chloroformate.

16 17 18

15

10

11

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	AEGL-2 VALUES FOR BENZYL CHLOROFORMATE						
2	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour		
3	1.2 ppm	1.2 ppm	0.97 ppm	0.63 ppm	0.31 ppm		
4 5 6	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.						
7	Test Species/Strain/Number: See AEGL-3 Derivation summary table						
8	Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table						
9	Effects: See AEGL-3 Derivation summary table						
10 11 12 13	Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered a threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 0/10 at 18.6 ppm; 5/10 at 85 ppm; BASF, 1990) and because observed clinical signs resolved (were reversible).						
14	Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table						
15	Modifying Factor: NA						
16	Animal to Human Dosimetric Adjustment: NA						
17	Time Scaling: See AEGL-3 Derivation summary table						
18	Data quality and research needs: See AEGL-3 Derivation summary table.						
19							

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR BENZYL CHLOROFORMATE							
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
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: Sprague Da	awley rats/ 5/sex/gro	oup				
Exposure Route/Concen (Concentration causing 1				·-3)			
Endpoint/Concentration/ for 4 hour exposure in ra		ation causing no mo	rtality/18.6 ppm/Esti	imated threshold for death			
Effects: No mortality = 1	18.6 ppm; 5/10 dead	= 84.6 ppm					
Into Benzyl chloroformate is tissues; this type of effective and the state of the s	erspecies = 3: raspecies = 3: highly reactive and of the is not expected to value and the concertainty factors of a tethyl chloroformate action VII.5.3), and the	vary greatly between 3 each were also app (Section II.5.3), isopnese resulting AEGL	a species or among in blied when AEGL-3 propyl chloroformate L values were consid	ndividuals. Furthermore, values were calculated for e (Section V.5.3), and n-			

24 Modifying Factor: NA

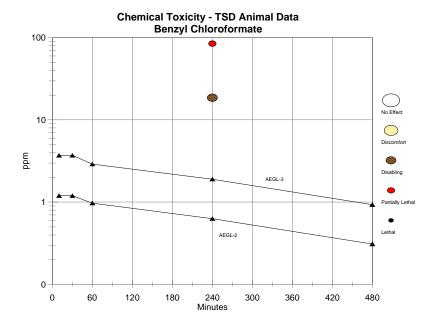
Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n=1 when extrapolating to longer time points (8-hours). 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value.

Data Quality and Research Needs: Sparse data set.

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 APPENDIX VIII-C: 2 3 Category Plot for Benzyl Chloroformate Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate



	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1	CHAPTER IX: PHENYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: PHENYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for phenyl chloroformate. Therefore, AEGL-1 values are not recommended for phenyl chloroformate.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for phenyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 2/10 at 15.6 ppm; 7/10 at 44.5 ppm; 9/10 at 74.9 ppm; BASF, 1990; Hoechst, 1989), and because observed clinical signs resolved (were reversible) at 15.6 ppm (BASF, 1990).

The 4-hour rat BMCL $_{05}$ of 3.6 ppm from the combined BASF (1990) and Hoechst (1989) studies was used as the point-of-departure for phenyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because phenyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value.

Summary of AEGL Values For Phenyl Chloroformate								
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour Endpoint (Reference)								
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data		
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)		1/3 the AEGL-3 values (BASF, 1990; Hoechst, 1989)		
AEGL-3 (Lethality)	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)	4-hr rat BMCL ₀₅ (BASF, 1990; Hoechst, 1989)		

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

IX.1. HUMAN TOXICITY DATA

IX.1.1 Acute Lethality

Information concerning death in humans following inhalation exposure to phenyl chloroformate is not available.

IX.1.2 Non-lethal Toxicity

Information concerning non-lethal toxicity in humans following inhalation exposure to phenyl chloroformate is not available.

IX.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to phenyl chloroformate were not available.

IX.1.4 Genotoxicity

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

IX.1.5 Carcinogenicity

Carcinogenicity studies regarding human exposure to phenyl chloroformate were not available.

IX.1.6 Summary

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

IX.2. ANIMAL TOXICITY DATA

IX.2.1 Acute Lethality

IX.2.1.1 Rats

Groups of five male and five female SPF Wistar rats were exposed to 15.6, 74.9, or 159.3 ppm (analytical concentrations) phenyl chloroformate for 4-hours followed by a 14-day observation period (BASF, 1990). The nose-only exposures were performed in a 55 L glass-steel system; animals were restrained in tubes and noses projected into the chamber. Phenyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs noted during exposure included accelerated respiration and restlessness in the low-concentration group, irregular/intermittent respiration, eyelid closure, salivation, nasal discharge, escape attempts, and decreased pain reflex in mid- and high-concentration animals. Clinical signs during the post-exposure observation period included accelerated respiration, respiratory sounds, reddish ocular and nasal discharge and aggressiveness in all exposure groups. In addition, squatting position, urine-contaminated fur, high-stepping gait, and deteriorated general state were noted in mid- and high-concentration animals, and piloerection was noted only in high-concentration animals. All clinical signs in

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

low-concentration animals had resolved by day 3 post-exposure; clinical signs persisted through observation day 13 in mid- and high-concentration animals. Body weight gain was decreased (compared to 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 adjusted to normal body weight. Body weight gain of mid-concentration females and high-concentration males and females was decreased during week one of the observation period; all animals in these groups died by week 2. There were no gross treatment-related effects noted 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 showed lung emphysema with hyperemia and pneumonia and necrotic foci and grey-brown lobular periphery of the liver. Four-hour LC₅₀ values of 46.8 ppm, 15.8 ppm and 28 ppm (95% CI: 16-48 ppm) were reported for male rats, female rats, male and female rats combined, respectively. BMCL₀₅ and BMC₀₁ values were calculated and are presented in Table IX-1; however, the toxicological validity of these values is questionable because of a lack of study concentrations in the lower portion of the concentration-response curve. Mortality data are summarized in Table IX-1.

1	5	
1	6	

Table 1	Table IX-1. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*								
	Males Females Combined Males and Females								
15.6 ppm	0/5	2/5	2/10						
74.9 ppm	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						

*BASF, 1990

Groups of five male and five female SPF Wistar rats were exposed to 1.76, 44.5, 97, 156 or 311 ppm (analytical concentrations) phenyl chloroformate for 4-hours followed by a 14-day observation period (Hoechst, 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 minutes during exposure using gas chromatography. Clinical signs noted in all treatment-groups in a concentration-related manner 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 noted 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 on the lungs were noted at necropsy in animals surviving to study termination from the 44.5 ppm group. Gross examination of animals that died during the study showed dark red colored lungs with red foci, foamy liquid in the lungs, dark colored liver and adrenals, and light-colored spleen. Four hour LC₅₀ values of 38.9 ppm and 43 ppm were calculated for males and females, respectively. Mortality data are summarized in Table IX-2.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Table IX-2. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*							
	Males Females Combined 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				

^{*}Hoechst, 1989

Table IX-3 summarizes the mortality data from the BASF (1990) and Hoechst (1989) studies combined. Because mortality results are similar in both studies, the data sets were combined to provide a more complete concentration-response curve, especially at the lower-concentration portion of the curve. Combination of the data sets is justified because both studies are nose-only exposures of Wistar rats and morality data are similar for both studies.

Table IX-3. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*						
	Males	Females	Combined Males and Females	Reference		
1.76 ppm	0/5	0/5	0/10	Hoechst, 1989		
15.6 ppm	0/5	2/5	2/10	BASF, 1990		
44.5 ppm	4/5	3/5	7/10	Hoechst, 1989		
74.9 ppm	4/5	5/5	9/10	BASF, 1990		
97 ppm	5/5	4/5	9/10	Hoechst, 1989		
156 ppm	5/5	5/5	10/10	Hoechst, 1989		
159.3 ppm	5/5	5/5	10/10	BASF, 1990		
311 ppm	5/5	5/5	10/10	Hoechst, 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	_		

^{*}BASF, 1990; Hoechst, 1989 Data Combined

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Death occurred in 0/10 rats exposed to 200 ppm phenyl chloroformate for 1 hour (BASF, 1970). Clinical signs included mucous membrane irritation. No gross effects were noted at necropsy.

Death occurred in 0/12, 4/6, 6/6, and 6/6 rats exposed to an "atmosphere enriched or saturated" with phenyl chloroformate vapor at 20EC for 3 minutes, 10 minutes, 30, minutes, and 1 hour, respectively (BASF, 1970). Clinical signs included vigorous escape behavior, mucous membrane irritation, and altered respiration. Lung edema was noted at necropsy.

IX.2.2 Non-lethal Toxicity IX.2.2.1 Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 4.5, 6.25, 12.5, 17.5, 25, 50, or 100 ppm phenyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted phenyl chloroformate was delivered to a Pitt #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 20 L/min. An RD₅₀ of 19.5 ppm was calculated. Results are summarized in Table IX-4.

TABLE IX-4. Exposure of Male Swiss-Webster Mice to Phenyl Chloroformate for 30 minutes*							
Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs				
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				

*Carpenter, 1982

IX.2.3 Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of phenyl chloroformate was located in the available literature.

IX.2.4 Genotoxicity

No information concerning the genotoxicity of phenyl chloroformate was located in the available literature.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

IX.2.5 Carcinogenicity

No information concerning the carcinogenicity of phenyl chloroformate was located in the available literature.

IX.2.6 Summary

 Animal data are limited for phenyl chloroformate. Two 4-hour rat inhalation studies were available, yielding LC_{50} values of 28 ppm (BASF, 1990) and 39.6 ppm (Hoechst, 1989). No mortality was noted in rats exposed to 200 ppm phenyl chloroformate for 1 hour (BASF, 1970). A 30-min RD_{50} of 19.5 ppm phenyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). No animal data regarding developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

IX.3. DATA ANALYSIS AND AEGL-1 IX.3.1 Human Data Relevant to AEGL-1

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

IX.3.2 Animal Data Relevant to AEGL-1

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

IX.3.3 Derivation of AEGL-1

Data are insufficient for the derivation of AEGL-1 values for phenyl chloroformate. Therefore, AEGL-1 values are not recommended (Table IX-5).

TABLE IX-5. AEGL-1 Values for Phenyl Chloroformate						
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-1	NR	NR	NR	NR	NR	

NR: Not Recommended. Absence of derived AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

IX.4. DATA ANALYSIS AND AEGL-2 IX.4.1 Human Data Relevant to AEGL-2

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

IX.4.2 Animal Data Relevant to AEGL-2

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

IX.4.3 Derivation of AEGL-2

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

2 values for phenyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 2/10 at 15.6 ppm; 7/10 at 44.5 ppm; 9/10 at 74.9 ppm; BASF, 1990; Hoechst, 1989), and because observed clinical signs resolved (were reversible) at 15.6 ppm (BASF, 1990). The AEGL-2 values for phenyl chloroformate are presented in Table IX-6, and the calculations for these AEGL-2 values are presented in Appendix IX-A.

TABLE IX-6. AEGL-2 Values for Phenyl Chloroformate							
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
AEGL-2	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)	0.060 ppm (0.38 mg/m ³)		

IX.5. DATA ANALYSIS AND AEGL-3 IX.5.1 Human Data Relevant to AEGL-3

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

IX.5.2 Animal Data Relevant to AEGL-3

Four-hour LC₅₀ values of 28 ppm (BASF, 1990) and 39.6 ppm (Hoechst, 1989) have been reported for combined male and female rat data. A 4-hour LC₅₀ value of 30.00 ppm and BMCL₀₅ value of 3.6 ppm was calculated for male and female rats when the BASF (1990) and Hoechst (1989) studies were combined.

IX.5.3 Derivation of AEGL-3

The 4-hour rat BMCL₀₅ of 3.6 ppm from the combined BASF (1990) and Hoechst (1989) studies will be used as the point-of-departure for phenyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because phenyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemicalspecific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value. The AEGL-3 values for phenyl chloroformate are presented in Table IX-7, and the calculations for these AEGL-3 values are presented in Appendix IX-A.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

TABLE IX-7. AEGL-3 Values for Phenyl Chloroformate								
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour			
AEGL-3	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)			

IX.6. SUMMARY OF AEGLS

IX.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for phenyl chloroformate; therefore, AEGL-1 values are not 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-hour rat BMCL $_{05}$ value.

TABLE IX-8. Summary of AEGL Values for Phenyl Chloroformate								
Classification	10-minute	30-minute	1-hour	4-hour	8-hour			
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR			
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)	0.060 ppm (0.38 mg/m ³)			
AEGL-3 (Lethal)	0.72 ppm (4.6 mg/m³)	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)			

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

IX.6.2. Comparison with Other Standards and Guidelines

No extant values were located for phenyl chloroformate.

IX.6.3 Data Quality and Research Needs

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

IX.7. REFERENCES

BASF. 1970. Study of the acute inhalation hazard (rats). Inhalation hazard test. Phenyl chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. May 20, 1970.

4

7

11

14

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

- BASF. 1990. Study on the acute inhalation toxicity LC₅₀ of phenyl chloroformate as a vapor in rats, 4-hour exposure. Project No. 13I0675/887076. Unpublished report, BASF Aktiengesellschaft, Experimental
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- NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
- ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2 3	APPENDIX IX-A: DERIVATION OF AEGL VALUES FOR PHENYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR PHENYL CHLOROFORMATE

AEGL-1 values for phenyl chloroformate are not recommended.

1 2 3 4		Derivation of AEGL-2 Values for Phenyl Chloroformate
5 6	Vay studies DACE 1000	O. Hooghst, 1000
7	Key studies: BASF, 1990	J, Hoechst, 1989
8	Toxicity Endpoint: 1/3 of	the AEGL-3 values
9		
10		
11		
12		
13		
14	<u>10-min AEGL-2</u> :	$0.72 \text{ ppm} \div 3 = 0.24 \text{ ppm}$
15		
16	<u>30-min AEGL-2</u> :	$0.72 \text{ ppm} \div 3 = 0.24 \text{ ppm}$
17		
18	<u>1-hr AEGL-2</u> :	$0.57 \text{ ppm} \div 3 = 0.19 \text{ ppm}$
19		
20	4-hr AEGL-2:	$0.36 \text{ ppm } \div 3 = 0.12 \text{ ppm}$
21	0.1	0.40
22	<u>8-hr AEGL-2:</u>	$0.18 \text{ ppm} \div 3 = 0.060 \text{ ppm}$

```
1
 2
 3
            DERIVATION OF AEGL-3 VALUES FOR PHENYL CHLOROFORMATE
 4
 5
       Key studies: BASF, 1990; Hoechst, 1989
 6
 7
       Toxicity Endpoint: 4-hour rat BMCL<sub>05</sub> (3.6 ppm)
 8
 9
10
       Scaling: <u>30-minutes and 1-hr</u>
                \mathbf{C}^3 \times t = k
11
12
                (3.6 \text{ ppm})^3 \times 4 \text{ hr} = 186.7 \text{ ppm}^4 \text{hr}
13
14
        8-hours
            C^1 \times t = k
15
            (3.6 \text{ ppm})^1 \times 4 \text{ hr} = 14.4 \text{ ppm}^{\text{h}} \text{r}
16
17
18
       Uncertainty Factors:
19
            3 for interspecies variability
20
            3 for intraspecies variability
21
22
       <u>10-min AEGL-3</u>: 30-minute value adopted as 10-minute value = 0.72 ppm
23
24
25
       30-min AEGL-3
            C^3 \times 0.5 \text{ hr} = 186.7 \text{ ppm}hr
26
            C^3 = 373.4 \text{ ppm}
27
28
            C = 7.2 \text{ ppm}
29
            30-min AEGL-3 = 7.2/10 = 0.72 ppm
30
31
       1-hr AEGL-3
            C^3 \times 1 \text{ hr} = 186.7 \text{ ppm}^{\text{th}} \text{r}
32
            C^3 = 186.7 \text{ ppm}
33
34
            C = 5.7 \text{ ppm}
35
            1-hr AEGL-3 = 5.7/10 = 0.57 ppm
36
37
       4-hr AEGL-3
38
            4-hr AEGL-3 = 3.6/10 = 0.36 ppm
39
40
       8-hr AEGL-3
            C^1 \times 8 \text{ hr} = 14.4 \text{ ppm}^{\text{th}}
41
            C^1 = 1.8 \text{ ppm}
42
43
            C = 1.8 \text{ ppm}
            8-hr AEGL-3 = 1.8/10 = 0.18 ppm
44
```

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate Chloroformate, 2-Ethylhexyl Chloroformate

Derivation Summary for Phenyl Chloroformate AEGLS

1

1	AEGL-1 VALUES FOR PHENYL CHLOROFORMATE							
2	10 minutes	30 minutes	1 hour	4 hour	8 hour			
3	NR	NR	NR	NR	NR			
4	Key Reference: Chen	Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.						
5	Test Species/Strain/N	umber:						
6	Exposure Route/Concentrations/Durations:							
7	Effects:							
8	Endpoint/Concentration/Rationale:							
9	Uncertainty Factors/Rationale:							
10	Modifying Factor:							
11	Animal to Human Dosimetric Adjustment:							
12	Time Scaling:							
13 14 15	Data Quality and Res		ical-specific data were	available for derivation	of AEGL-1 values for			

AEGL-2 VALUES FOR PHENYL CHLOROFORMATE						
10-Minute 30-Minute 1-Hour 4-Hour 8-						
0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.060 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/Number: See AEGL-3 Derivation summary table						
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table						
Effects: See AEGL-3 Derivation summary table						
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality, and because observed clinical signs resolved (were reversible) at 15.6 ppm (BASF, 1990).						
Uncertainty Factors/Ra	ationale: See AEGL-3	Derivation summary ta	able			
Modifying Factor: NA						
Animal to Human Dosimetric Adjustment: NA						
Time Scaling: See AEGL-3 Derivation summary table						
Data quality and resear	rch needs: See AEGL-	3 Derivation summary	table.			

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR PHENYL CHLOROFORMATE					
10-Minute	4-Hour	8-Hour			
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 LC₅₀. Hofmann, T. Hoechst Pharmaceutical Research Toxicology. Report No. 89.0761. April 26, 1989.

Test Species/Strain/Sex/Number: Sprague Dawley rats/ 5/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours

(BMCL₀₅, 3.6 ppm, was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: BMCL₀₅/3.6 ppm/Estimated threshold for death for 4 hour exposure in rats

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:

Interspecies = 3:

Intraspecies = 3:

Phenyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

Modifying Factor: NA

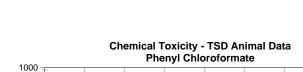
Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n=1 when extrapolating to longer time points (8-hours). 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value.

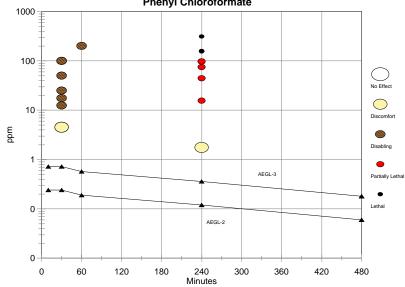
Data Quality and Research Needs: Sparse data set.

	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2 3 4	APPENDIX IX-C: CATEGORY PLOT FOR PHENYL CHLOROFORMATE

Chloroformate, 2-Ethylhexyl Chloroformate



 $Chloroformate, Isobutyl\ Chloroformate, sec-Butyl\ Chloroformate,\ Ethyl\ Chlorothioformate,\ Benzyl\ Chloroformate,\ Phenyl\ Phenyl$



	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2 3	APPENDIX IX-D: BENCHMARK CONCENTRATION CALCULATION FOR PHENYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

```
1
        BMDS MODEL RUN
 2
 3
4
5
6
7
8
         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
 9
         Dependent variable = Mean
10
         Independent variable = Dose
11
         Slope parameter is not restricted
12
13
         Total number of observations = 8
14
         Total number of records with missing values = 0
15
         Maximum number of iterations = 250
16
         Relative Function Convergence has been set to: 1e-008
17
         Parameter Convergence has been set to: 1e-008
18
19
         User has chosen the log transformed model
20
                  Default Initial (and Specified) Parameter Values
                    background =
22
                    intercept = -2.32244
23
                      slope = 0.759796
24
25
              Asymptotic Correlation Matrix of Parameter Estimates
26
             ( *** The model parameter(s) -background
27
                 have been estimated at a boundary point, or have been specified by the user,
28
                 and do not appear in the correlation matrix )
30
               intercept
                            slope
31
       intercept
                             -0.98
                       1
32
         slope
                   -0.98
                               1
33
34
                      Parameter Estimates
35
36
           Variable
                          Estimate
                                          Std. Err.
37
          background
                                          NA
38
          intercept
                          -4.60327
                                          1.20324
39
             slope
                          1.35407
                                        0.307109
40
41
       NA - Indicates that this parameter has hit a bound
42
          implied by some inequality constraint and thus
43
          has no standard error.
44
45
                     Analysis of Deviance Table
46
47
           Model
                     Log(likelihood) Deviance Test DF
                                                         P-value
48
          Full model
                         -17.6143
49
                         -18.0291
                                     0.829451
                                                         0.9913
         Fitted model
                                                  6
50
        Reduced model
                            -47.9918
                                         60.755 7
                                                          <.0001
51
52
              AIC:
                        40.0581
53
54
```

55

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Goodness of Fit

13

19 20

21 22

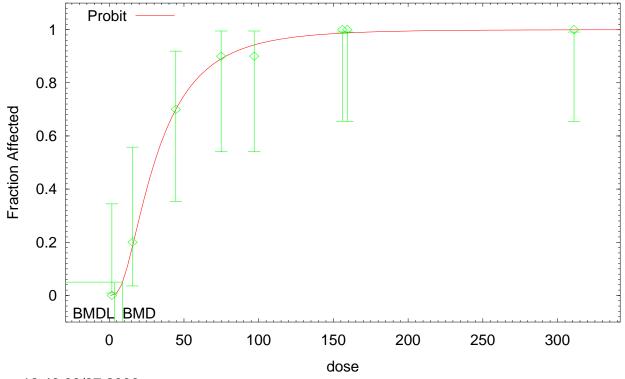
28

			Scale	1		
Dose	EstProb.	Expected	Observed	Siz	ze 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-squar	e = 0.64	DF = 6	P-value	= 0.99	956	

Benchmark Dose Computation

 $\begin{array}{lll} \text{Specified effect} = & 0.05 \\ \text{Risk Type} & = & \text{Extra risk} \\ \text{Confidence level} = & 0.95 \\ \text{BMD} = & 8.88924 \\ \text{BMDL} = & 3.57025 \end{array}$

Probit Model with 0.95 Confidence Level



12:46 09/27 2006

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

29 30

CHAPTER X: 2-ETHYLHEXYL CHLOROFORMATE

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3	X.1.4	Genotoxicity	X-5
4	X.1.5	Carcinogenicity	X-5
5	X.1.6	Summary	X-5
6	T7.0 4.3	WALL TO WARTE DATE	
7		NIMAL TOXICITY DATA	
8		Acute Lethality	
9		1Rats	
0.		Non-lethal Toxicity	
1		Developmental/Reproductive Toxicity	
2		Genotoxicity	
23		Carcinogenicity	
4	X.2.6	Summary	X-7
5			
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8		Human Data Relevant to AEGL-1	
9		Animal Data Relevant to AEGL-1	
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4	X.4.2	Animal Data Relevant to AEGL-2	
5	X.4.3	Derivation of AEGL-2	
6	110	2 til (
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5		Data Quality and Research Needs	
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY:2-ETHYLHEXYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for 2-ethylhexyl chloroformate. Therefore, AEGL-1 values are not recommended for 2-ethylhexyl chloroformate.

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for 2-ethylhexyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 0/20 at 22.8 ppm; 5/20 at 26.6 ppm; 9/20 at 34.3 ppm; 20/20 at 46.9 ppm; BASF, 1985).

The 4-hour male rat BMCL $_{05}$ of 18.1 ppm from the BASF (1985) study was used as the point-of-departure for 2-ethylhexyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because 2-ethylhexyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value.

	Summary of AEGL Values For 2-Ethylhexyl Chloroformate							
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)		
AEGL-1 (Nondisabling)	NR	NR	NR	NR	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)	1/2 the AEGL-3 values (BASF, 1985)		
AEGL-3 (Lethality)	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)	4-hr rat BMCL ₀₅ (BASF, 1985)		

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2

3

HUMAN TOXICITY DATA X.1.

X.1.1 Acute Lethality

4 5 Information concerning death in humans following inhalation exposure to 2-ethylhexyl chloroformate is not available.

6

X.1.2 Non-lethal Toxicity

8 9 10

7

Information concerning non-lethal toxicity in humans following inhalation exposure to 2-ethylhexyl chloroformate is not available.

11 12 13

X.1.3 Developmental/Reproductive Toxicity

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Developmental/reproductive studies regarding acute human exposure to 2-ethylhexyl chloroformate were not available.

16 17 18

X.1.4 Genotoxicity

19 20

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

21 22

X.1.5 Carcinogenicity

23 24

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

25 26

X.1.6 Summary

27 28

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

29 30 31

32

X.2. ANIMAL TOXICITY DATA

33 X.2.1 Acute Lethality

X.2.1.1 Rats

34 35

36 Groups of ten male and ten female SPF Wistar rats were exposed to 22.8, 26.6, 34.3, or 46.9 ppm 37 (analytical concentrations) 2-ethylhexyl chloroformate for 4-hours followed by a 14-day observation period 38 (BASF, 1985). The whole body exposures were performed in a 200 L glass-steel inhalation chamber, and 2-39 ethylhexyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs noted during exposure included closed palpebral fissure, red ocular and nasal discharge, and 40 41 irregular respiration, restlessness, squatting posture, and ruffled fur in the 26.6, 34.3, and 46.9 ppm groups. 42 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 noted in the

- 43 34.3 and 46.9 ppm groups, and squatting posture and ruffled fur was noted in the 26.6, 34.3, and 46.9 ppm 44
- 45 groups. No clinical signs were noted during or after exposure in the 22.8 ppm group. There were no gross
- treatment-related effects noted at necropsy in animals surviving to study termination. Gross examination of 46

Males

0/10

4/10

7/10

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Time to death

2 dead: Day of exposure

2 dead: Day 1 post-exposure

2 dead: Day of exposure

5 dead: Day 1 nost-exposure

animals that died during the study showed venous congestion and lung emphysema with pneumonia. A 4-hour LC_{50} value of 33.9 ppm was reported for male and female rats combined. 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 X-1, and mortality data are also summarized in Table X-1.

Table X-1. Mortality in Rats Exposed to 2-Ethylhexyl Chloroformate for 4 hours*

Females

0/10

1/10

2/10

Time to death

1 dead: Day 14 post-exposure

2 dead: Day 1 post-exposure

Combined Males and Females

0/20

5/20

9/20

7	
7	
8	
9	
10	
11	
10	
12	
13	
13	

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2

4 5

6

		5 dead. Day 1 post-exposure			
46.9 ppm	10/10	8 dead: Day of exposure	10/10 3 dead: Day of exposure		20/20
		2 dead: Day 1 post-exposure	7 dead: Day 1 post-exposure		
LC ₅₀	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

*BASF, 1985

22.8 ppm

26.6 ppm

34.3 ppm

18 19 20

21

2223

24

14

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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 at 20EC for 3 minutes, 10 minutes, 30 minutes, 1 hour, and 2 hours, respectively (BASF, 1968). The approximate concentration was reported as 270 ppm 2-ethylhexyl chloroformate and 40 ppm phosgene contaminant. Clinical signs included mucous membrane irritation and difficulty breathing. Lung edema was noted at necropsy.

252627

X.2.2 Non-lethal Toxicity

28 29

30

No information concerning the non-lethal toxicity of 2-ethylhexyl chloroformate was located in the available literature.

31 32

X.2.3 Developmental/Reproductive Toxicity

33 34 35

No information concerning the developmental/reproductive toxicity of 2-ethylhexyl chloroformate was 2-Ethylhexyl Chloroformate X-6

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

located in the available literature.

X.2.4 Genotoxicity

No information concerning the genotoxicity of 2-ethylhexyl chloroformate was located in the available literature.

X.2.5 Carcinogenicity

No information concerning the carcinogenicity of 2-ethylhexyl chloroformate was located in the available literature.

X.2.6 Summary

Animal data are limited for 2-ethylhexyl chloroformate. One 4-hour rat inhalation study was available, yielding an LC_{50} value of 33.9 ppm for male and female rats combined (BASF, 1985). No animal data regarding developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

X.3. DATA ANALYSIS AND AEGL-1

 X.3.1 Human Data Relevant to AEGL-1

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

X.3.2 Animal Data Relevant to AEGL-1

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

X.3.3 Derivation of AEGL-1

Data are insufficient for the derivation of AEGL-1 values for 2-ethylhexyl chloroformate. Therefore, AEGL-1 values are not recommended (Table X-2).

TABLE X-2. AEGL-1 Values for 2-Ethylhexyl Chloroformate							
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
AEGL-1	NR	NR	NR	NR	NR		

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

X.4. DATA ANALYSIS AND AEGL-2 X.4.1 Human Data Relevant to AEGL-2

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

X.4.2 Animal Data Relevant to AEGL-2

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

2-Ethylhexyl Chloroformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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X.4.3 Derivation of AEGL-2

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No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for 2-ethylhexyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 0/20 at 22.8 ppm; 5/20 at 26.6 ppm; 9/20 at 34.3 ppm; 20/20 at 46.9 ppm; BASF, 1985). The AEGL-2 values for 2-ethylhexyl chloroformate are presented in Table X-3, and the calculations for these AEGL-2 values are presented in Appendix X-A.

1-Hour

0.97 ppm

 (7.7 mg/m^3)

4-Hour

0.60 ppm

 (4.7 mg/m^3)

8-Hour

0.30 ppm

 (2.4 mg/m^3)

TABLE X-3. AEGL-2 Values for 2-Ethylhexyl Chloroformate

10 11 12

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14

15

Classification

AEGL-2

16 17

18 19

20

X.5. DATA ANALYSIS AND AEGL-3 X.5.1 Human Data Relevant to AEGL-3

10-Minute

1.2 ppm

 (9.5 mg/m^3)

21 22

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

30-Minute

1.2 ppm

 (9.5 mg/m^3)

23 24

X.5.2 Animal Data Relevant to AEGL-3

25 26

27 28

Four-hour LC_{50} values of 29.9 ppm, 36.3 ppm, and 33.9 ppm were calculated for male rats, female rats, and male and female rats combined, respectively (BASF, 1985). Four-hour BMCL₀₅ values of 18.1 ppm, 26.0 ppm, and 20.1 ppm were calculated for male rats, female rats, and male and female rats combined, respectively (BASF, 1985).

29 30 31

X.5.3 Derivation of AEGL-3

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The 4-hour male rat BMCL₀₅ of 18.1 ppm from the BASF (1985) study will be used as the point-ofdeparture for 2-ethylhexyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because 2-ethylhexyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeatedexposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective

- 43
- AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling 44
- was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n=1 when 45

2 3

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value. The AEGL-3 values for 2-ethylhexyl chloroformate are presented in Table X-4, and the calculations for these AEGL-3 values are presented in Appendix X-A.

TABLE X-4. AEGL-3 Values for 2-Ethylhexyl Chloroformate						
Classification 10-Minute 30-Minute 1-Hour 4-Hour 8-Hour						
AEGL-3	3.6 ppm (28 mg/m³)	3.6 ppm (28 mg/m³)	2.9 ppm (23 mg/m ³)	1.8 ppm (14 mg/m³)	0.91 ppm (7.2 mg/m ³)	

X.6. SUMMARY OF AEGLS

X.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for 2-ethylhexyl chloroformate; therefore, AEGL-1 values are not 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-hour rat $BMCL_{05}$ value.

TABLE X-5. Summary of AEGL Values for 2-Ethylhexyl Chloroformate							
Classification	10-minute	30-minute	1-hour	4-hour	8-hour		
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR		
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/m³)	1.8 ppm (14 mg/m ³)	0.91 ppm (7.2 mg/m ³)		

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.

X.6.2. Comparison with Other Standards and Guidelines

No extant values were located for 2-ethylhexyl chloroformate.

X.6.3 Data Quality and Research Needs

No human toxicity were available. The only animal toxicity data available were from acute lethality studies in rats.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	
2	
3	X.7. REFERENCES

- 5 BASF. 1968. Study of the acute inhalation hazard (rats). Inhalation hazard test. 2-Ethylhexyl chloroformate.
- 6 Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen,
- 7 Germany. December 9, 1968.

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15

18 19

8
9 BASF. 1985. Acute inhalation toxicity LC₅₀ 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.
- NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
- ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Chioro	formate, 2-Ethylhexyl Chloroformate
	APPENDIX X-A:
	DERIVATION OF AEGL VALUES FOR 2-ETHYLHEXYL CHLOROFORMAT

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

2 3

1

4 AEGL-1 values for 2-ethylhexyl chloroformate are not recommended.

1 2 3 4	De	rivation of AEGL-2 Values for 2-Ethylhexyl Chloroformate
5	IZ 4 1' DAGE 100/	_
6	Key studies: BASF, 1985	
7 8	Toxicity Endnaint 1/ of	the AECL 2 volves
8 9	Toxicity Endpoint: 1/3 of	the AEGL-3 values
10		
11		
12		
13		
14	10-min AEGL-2:	$3.6 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
15	TO MINITIEGE 2.	3.6 pp.m · 3 1.2 pp.m
16	30-min AEGL-2:	$3.6 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
17	<u></u>	The state of the s
18	<u>1-hr AEGL-2</u> :	$2.9 \text{ ppm} \div 3 = 0.97 \text{ ppm}$
19		
20	<u>4-hr AEGL-2</u> :	$1.8 \text{ ppm } \div 3 = 0.60 \text{ ppm}$
21		
22	<u>8-hr AEGL-2:</u>	$0.91 \text{ ppm} \div 3 = 0.30 \text{ ppm}$

```
1
 2
 3
            DERIVATION OF AEGL-3 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE
 4
 5
       Key studies: BASF, 1985
 6
 7
       Toxicity Endpoint: 4-hour rat BMCL<sub>05</sub> (18.1 ppm)
 8
 9
10
       Scaling: <u>30-minutes and 1-hr</u>
                C^3 \times t = k
11
                (18.1 \text{ ppm})^3 \text{ x 4 hr} = 23,719 \text{ ppm}^{\text{th}}r
12
13
14
        <u>8-h</u>ours
            C^1 \times t = k
15
            (18.1 \text{ ppm})^1 \times 4 \text{ hr} = 72.4 \text{ ppm}^{\text{h}} \text{r}
16
17
18
       Uncertainty Factors:
19
            3 for interspecies variability
20
            3 for intraspecies variability
21
22
       <u>10-min AEGL-3</u>: 30-minute value adopted as 10-minute value = 3.6 ppm
23
24
25
       30-min AEGL-3
            C^3 \times 0.5 \text{ hr} = 23,719 \text{ ppm} \text{ hr}
26
            C^3 = 47438 \text{ ppm}
27
28
            C = 36.2 \text{ ppm}
29
            30-min AEGL-3 = 36.2/10 = 3.6 ppm
30
31
       1-hr AEGL-3
           C^3 \times 1 \text{ hr} = 23,719 \text{ ppm}^{\text{th}} \text{r}
32
            C^3 = 23,719 \text{ ppm}
33
34
            C = 28.7 \text{ ppm}
            1-hr AEGL-3 = 28.7/10 = 2.9 ppm
35
36
37
       4-hr AEGL-3
38
            4-hr AEGL-3 = 18.6/10 = 1.8 ppm
39
40
       8-hr AEGL-3
           C^1 \times 8 \text{ hr} = 72.4 \text{ ppm}^{1}\text{hr}
41
           C^1 = 9.1 \text{ ppm}
42
43
            C = 9.1 \text{ ppm}
            8-hr AEGL-3 = 9.1/10 = 0.91 ppm
44
```

INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate **APPENDIX X-B:**

1

Derivation Summary for 2-Ethylhexyl Chloroformate AEGLS

1						
10 minutes	30 minutes	1 hour	4 hour	8 hour		
NR	NR	NR	NR	NR		
Key Reference: Cher	nical-specific data were	insufficient for derivi	ng AEGL-1 values.			
Test Species/Strain/N	lumber:					
Exposure Route/Con-	centrations/Durations:					
Effects:						
Endpoint/Concentration/Rationale:						
Uncertainty Factors/Rationale:						
Modifying Factor:						
Animal to Human Dosimetric Adjustment:						
Time Scaling:						
Data Quality and Research Needs: No chemical-specific data were available for derivation of AEGL-1 values for 2-ethylhexyl chloroformate.						

1	AEGL-2 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE								
2	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour				
3	1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm				
4 5 6	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.								
7	Test Species/Strain/Number: See AEGL-3 Derivation summary table								
8	Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table								
9	Effects: See AEGL-3 Derivation summary table								
10 11	Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality.								
12	Uncertainty Factors/Ra	Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table							
13	Modifying Factor: NA	Modifying Factor: NA							
14	Animal to Human Dos	Animal to Human Dosimetric Adjustment: NA							
15	Time Scaling: See AEGL-3 Derivation summary table								
16	Data quality and resear	rch needs: See AEGL-	3 Derivation summary	table.					
17									

 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE							
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour							
3.6 ppm 3.6 ppm 2.9 ppm 1.8 ppm 0.91 ppm							

Key Reference: BASF. 1985. Acute inhalation toxicity LC₅₀ 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: Wistar rats/ 10/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours (Male BMCL₀₅, 18.1 ppm, was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: BMCL₀₅/3.6 ppm/Estimated threshold for death for 4 hour exposure in rats

Effects: Concentration	Male Mortality	Female Mortality	Combined 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:

Interspecies = 3:

Intraspecies = 3:

2-Ethylhexyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

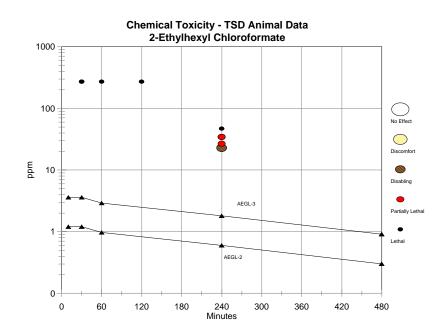
Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $c^n x t = k$, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n=1 when extrapolating to longer time points (8-hours). 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value.

Data Quality and Research Needs: Sparse data set.

	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1 2	APPENDIX X-C: CATEGORY PLOT FOR 2-ETHYLHEXYL CHLOROFORMATE



	INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
1	A DDENININ N. D. DENICHMA DIZ CONICENTED ATTION CAT CHILATTION
2 3	APPENDIX X-D: BENCHMARK CONCENTRATION CALCULATION FOR 2-ETHYLHEXYL CHLOROFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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2
3
4
5
6
7
       Dependent variable = Mean
       Independent variable = Dose
       Slope parameter is not restricted
         Total number of observations = 4
         Total number of records with missing values = 0
 8
         Maximum number of iterations = 250
 9
         Relative Function Convergence has been set to: 1e-008
10
         Parameter Convergence has been set to: 1e-008
11
12
         User has chosen the log transformed model
13
                  Default Initial (and Specified) Parameter Values
14
                    background =
15
                    intercept = -15.0226
                       slope =
16
                                 4.37693
17
18
              Asymptotic Correlation Matrix of Parameter Estimates
19
              (*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user,
20
                 and do not appear in the correlation matrix )
21
               intercept
                             slope
23
24
        intercept
                       1
                               -1
25
          slope
                      -1
                               1
26
27
28
                       Parameter Estimates
29
30
           Variable
                          Estimate
                                          Std. Err.
31
          background
                                           NA
32
                          -18.7737
           intercept
                                           5.12639
33
             slope
                          5.52218
                                          1.51755
34
35
       NA - Indicates that this parameter has hit a bound
36
          implied by some inequality constraint and thus
37
          has no standard error.
38
39
                      Analysis of Deviance Table
40
41
           Model
                     Log(likelihood) Deviance Test DF
                                                          P-value
42
          Full model
                         -12.8388
43
         Fitted model
                          -14.2231
                                                  2
                                                          0.2505
                                       2.76871
44
        Reduced model
                            -27.6759
                                         29.6742
                                                    3
                                                           <.0001
45
46
              AIC:
                        32.4462
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Goodness of Fit

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26 27 28

					Sc	caled				
Dose	Est	Prob.	Expe	cted	Obser	ved	Size	e	Resid	ual
22.8000	0.0	659	0.6	559	0		10	-0.8	398	
26.6000	0.2	559	2.5	559	4		10	1.0	44	
34.3000	0.7	728	7.7	728	7		10	-0.5	491	
46.9000	0.9	934	9.9	934	10		10	0.2	2587	
Chi-squar	e =	2.16	DF	= 2	P-va	lue =	= 0.339	90		

Benchmark Dose Computation

Specified effect = 0.05

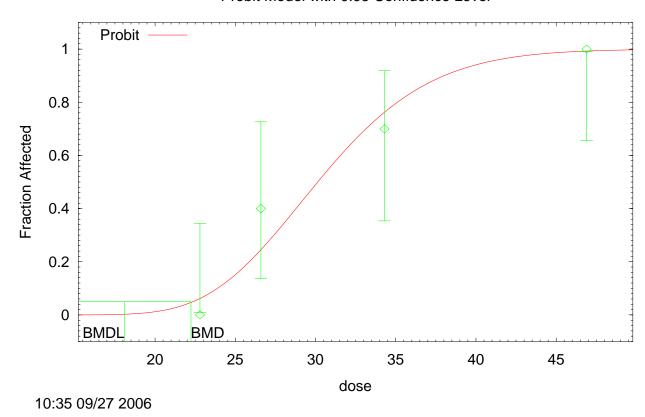
Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.2386

BMDL = 18.0971

Probit Model with 0.95 Confidence Level



Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2

CHAPTER XI: ETHYL CHLOROTHIOFORMATE

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

SUMMARY: ETHYL CHLOROTHIOFORMATE

Data were insufficient for the derivation of AEGL-1 values for ethyl chlorothioformate. Therefore, AEGL-1 values are not recommended.

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for ethyl chlorothioformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; (Stauffer, 1983)).

An estimated 4-hour rat lethality threshold of 15 ppm ($\frac{1}{3}$ the 4-hr LC₅₀: $\frac{1}{3}$ x 45 ppm = 15 ppm) (Stauffer, 1983) was used for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies uncertainty factor of 3 was applied because ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 was applied to protect against potential delayed systemic effects that may occur due to the thio-moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by c^n x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in extrapolating from a 4-hour point-of-departure.

The calculated values are listed in the table below.

Summary of AEGL Values For Ethyl Chlorothioformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	0.33 ppm (1.7 mg/m ³)	0.33 ppm (1.7 mg/m^3)	0.26 ppm (1.3 mg/m ³)	0.17 ppm (0.87 mg/m ³)	0.083 ppm (0.42 mg/m ³)	1/3 the AEGL-3 values (Stauffer, 1983)
AEGL-3 (Lethality)	1.0 ppm (5.1 mg/m ³)	1.0 ppm (5.1 mg/m ³)	0.79 ppm (4.0 mg/m ³)	0.50 ppm (2.6 mg/m ³)	0.25 ppm (1.3 mg/m ³)	Estimated 4-hour rat lethality threshold (Stauffer, 1983)

NR: Not Recommended. The lack of AEGL-1 values does not imply that concentrations below AEGL-2 will be without effect.

References:

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

Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 3

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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XI.1. HUMAN TOXICITY DATA

XI.1.1 Acute Lethality

Information concerning death in humans following inhalation exposure to ethyl chlorothioformate is not available.

XI.1.2 Non-lethal Toxicity

Information concerning non-lethal toxicity in humans following inhalation exposure to ethyl chlorothioformate is not available.

XI.1.3 Developmental/Reproductive Toxicity

Developmental/reproductive studies regarding acute human exposure to ethyl chlorothioformate were not available.

XI.1.4 Genotoxicity

Genotoxicity studies regarding acute human exposure to ethyl chlorothioformate were not available.

XI.1.5 Carcinogenicity

Carcinogenicity studies regarding human exposure to ethyl chlorothioformate were not available.

XI.1.6 Summary

No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, genotoxicity, or carcinogenicity were available.

XI.2. ANIMAL TOXICITY DATA

XI.2.1 Acute Lethality

Groups of ten male and ten female Sprague-Dawley rats were exposed to 263 ppm ethyl chlorothioformate for 1 hour (Stauffer, 1982). Animals were exposed in stainless steel and glass chambers with a volume of 447 liters. The ethyl chlorothioformate was aerosolized using a fritted bubbler and was delivered through a 1 inch diameter flexible stainless steel tubing to the chamber inlet. Actual chamber concentrations were measured coulimetrically at 15, 30, and 45 minutes after exposure initiation. During exposure, all rats showed lacrimation, salivation, and closed eyes within 15 minutes of the start of exposure. Prostration and gasping were noted in a majority of rats within 30 minutes of the start of exposure. All rats died within 24-hours of exposure; effects at necropsy included respiratory tract findings (Red mottling of lungs in 20/20 rats; frothiness of the trachea in 17/20 rats; moist, spongy lungs in 8/20; wetness around the nares in 20/20 rats).

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

In another study (Stauffer, 1983), groups of ten male and ten female Sprague-Dawley rats were exposed to 0, 33, 59, 65, 69, or 124 ppm ethyl chlorothioformate for 4 hours, followed by a 14-day observation period. The exposure protocol was similar to that described above (Stauffer, 1982) except that chamber concentrations were measured hourly during the 4 hour exposure period. During exposure, animals in all treatment groups showed lethargy, lacrimation, excessive salivation, and breathing difficulty. Clinical signs after exposure included rough coats, rhinorrhea, chromorhinorrhea, salivation, dyspnea, rales, dacryrrhea, chromodachrrhea, and paleness. Rats that survived the exposure became dehydrated and/or 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, spleen and lymph node necrosis, and lymphoid cell depletion were also noted. Deaths in rats during or shortly after exposure were attributed to respiratory tract corrosion; whereas, those occurring after exposure were attributed to a combination of local corrosive and systemic effects. LC₅₀ values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC₅₀ value of 45 ppm was also calculated. Data are summarized in Table XI-1.

TABLE XI-1*. M	TABLE XI-1*. Mortality of Rats Exposed to Ethyl Chlorothioformate for 4-hours								
	Males								
Concentration (ppm)	Incidence		Tin	ne of De	eath (Day	ys Post-	Expo	sure)	
		0	1	2	3	4	5	6	7-14
33	2/10	0	2	0	0	0	0	0	0
59	6/10	0	5	1	0	0	0	0	0
65	10/10	0	8	2	0	0	0	0	0
69	8/10	1	7	0	0	0	0	0	0
124	10/10	6	4	0	0	0	0	0	0
LC_{50}	51 ppm								
		Femal	les						
33	2/10	0	1	0	0	0	0	0	1
59	8/10	0	3	3	1	0	0	0	1
65	10/10	0	6	2	2	0	0	0	0
69	10/10	0	6	4	0	0	0	0	0
124	10/10	4	6	0	0	0	0	0	0
LC_{50}	41 ppm								
Combined Male and Female LC ₅₀				45 ppi	n				

^{*}Stauffer, 1983

XI.2.2 Non-lethal Toxicity

No data on non-lethal effects were available for ethyl chlorothioformate.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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XI.2.3 Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of ethyl chlorothioformate was located in the available literature.

XI.2.4 Genotoxicity

Ethyl chlorothioformate was negative both with and without metabolic activition in a bacterial reverse mutation assay in Salmonella typhimurium strains TA97, TA98, TA1535, and TA1537 (Zeiger et al., 1988).

XI.2.5 Carcinogenicity

No information concerning the carcinogenicity of ethyl chlorothioformate was located in the available literature.

XI.2.6 Summary

Four-hour LC₅₀ values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC₅₀ value of 45 ppm was also calculated (Stauffer, 1983). Signs of toxicity were consistent with severe respiratory tract irritation/corrosion, and necropsy findings suggest that ethyl chlorothioformate may cause both portal of entry and systemic effects. These systemic effects are likely due to the ability of the thio moiety to interact with other biomolecules. Ethyl chlorothioformate was negative in an Ames assay, and no animal data regarding non-lethal toxicity, developmental/reproductive toxicity, or carcinogenicity were available.

XI.3. DATA ANALYSIS AND AEGL-1

XI.3.1 Human Data Relevant to AEGL-1

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

XI.3.2 Animal Data Relevant to AEGL-1

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

XI.3.3 Derivation of AEGL-1

AEGL-1 values are not recommended for ethyl chlorothioformate due to insufficient data (Table XI-2).

TABLE XI-2. AEGL-1 Values for Ethyl Chlorothioformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

XI.4. DATA ANALYSIS AND AEGL-2

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

XI.4.2 Animal Data Relevant to AEGL-2

XI.4.1 Human Data Relevant to AEGL-2

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

XI.4.3 Derivation of AEGL-2

 No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for ethyl chlorothioformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; Stauffer, 1983). The AEGL-2 values for ethyl chlorothioformate are presented in Table XI-3, and the calculations for these AEGL-2 values are presented in Appendix XI-A.

TABLE XI-3. AEGL-2 Values for Ethyl Chlorothioformate					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	0.33 ppm (1.7 mg/m³)	0.33 ppm (1.7 mg/m ³)	0.26 ppm (1.3 mg/m ³)	0.17 ppm (0.87 mg/m ³)	0.083 ppm (0.42 mg/m ³)

XI.5. DATA ANALYSIS AND AEGL-3

XI.5.1 Human Data Relevant to AEGL-3

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

XI.5.2 Animal Data Relevant to AEGL-3

 Four-hour LC₅₀ values of 51 ppm and 41 ppm were calculated for male and female rats, respectively, and the combined sexes LC₅₀ was 45 ppm (Stauffer, 1983).

XI.5.3 Derivation of AEGL-3

An estimated 4-hour rat lethality threshold of 15 ppm ($\frac{1}{3}$ the 4-hr LC₅₀: $\frac{1}{3}$ x 45 ppm = 15 ppm) (Stauffer, 1983) will be used for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

uncertainty factor of 3 will be applied because ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 will be applied to protect against potential delayed systemic effects that may occur due to the thio- moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by cⁿ x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in extrapolating from a 4-hour point-of-departure. The AEGL-3 values for ethyl chlorothioformate are presented in Table XI-4, and the calculations for these AEGL-3 values are presented in Appendix XI-A.

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	TABLE XI	-4. AEGL-3 Val	ues for Ethyl Chlo	rothioformate	
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	1.0 ppm (5.1 mg/m ³)	1.0 ppm (5.1 mg/m ³)	0.79 ppm (4.0 mg/m ³)	0.50 ppm (2.6 mg/m ³)	0.25 ppm (1.3 mg/m ³)

XI.6. SUMMARY OF AEGLS

XI.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for ethyl chlorothioformate. The AEGL-2 values were obtained by a three-fold reduction of AEGL-3 values, and the AEGL-3 values were based on an estimated 4-hour rat lethality threshold.

TABLE XI-5. Summary of AEGL Values for Ethyl Chlorothioformate					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.33 ppm (1.7 mg/m ³)	0.33 ppm (1.7 mg/m ³)	0.26 ppm (1.3 mg/m ³)	0.17 ppm (0.87 mg/m ³)	$0.083 \text{ ppm} $ (0.42 mg/m^3)
AEGL-3 (Lethal)	1.0 ppm (5.1 mg/m ³)	1.0 ppm (5.1 mg/m ³)	0.79 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m ³)	0.25 ppm (1.3 mg/m^3)

NR: Not Recommended

XI.6.2. Comparison with Other Standards and Guidelines

No extant values were located for ethyl chlorothioformate.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

XI.6.3 Data Quality and Research Needs

1 2

No human toxicity data were available. Animal toxicity data available were limited to rat lethality studies.

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 XI.7. REFERENCES

2

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5

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INTERIM 1: 05/2008 Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1	APPENDIX XI-A:
2	
3	Derivation of AEGL Values for Ethyl Chlorothioformate
4	
5	

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2 3

DERIVATION OF AEGL-1 VALUES FOR ETHYL CHLOROTHIOFORMATE

5 6

7

AEGL-1 values are not recommended for ethyl chlorothioformate due to insufficient data.

1 2					
3	Der	rivation of AEGL-2 Values for Ethyl Chlorothioformate			
4		·			
5					
6	Key study: Stauffer, 1983				
7					
8	Toxicity Endpoint: 1/3 the AEGL-3 values				
9					
10					
11					
12					
13	10 ' AEGL 2	1.0			
14	<u>10-min AEGL-2</u> :	$1.0 \text{ ppm} \div 3 = 0.33 \text{ ppm}$			
15	20 min AECL 2	10 mm : 2 = 0.22 mm			
16 17	30-min AEGL-2:	$1.0 \text{ ppm} \div 3 = 0.33 \text{ ppm}$			
18	<u>1-hr AEGL-2</u> :	$0.79 \text{ ppm} \div 3 = 0.26 \text{ ppm}$			
19	1-III ALOL-2.	0.79 ppin + 5 = 0.20 ppin			
20	4-hr AEGL-2:	$0.5 \text{ ppm } \div 3 = 0.17 \text{ ppm}$			
21	1 III / ILOL 2.	0.5 ррш . 5 – 0.17 ррш			
22	8-hr AEGL-2:	$0.25 \text{ ppm} \div 3 = 0.083 \text{ ppm}$			
23	<u> </u>	one primite on one primite			

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1
                 DERIVATION OF AEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE
 2
 3
      Key study: Stauffer, 1983
 4
 5
      Toxicity Endpoint: Estimated 4-hr rat lethality threshold of 15 ppm (1/3 the LC<sub>50</sub> of 45 ppm)
 6
 7
      Scaling:
                    30-minutes and 1-hour
 8
                    C^3 \times t = k
 9
                    (15 \text{ ppm})^3 \times 4 \text{ hr} = 13,500 \text{ ppm}^{\text{th}}r
10
11
                    8-hours
                    C^1 \times \overline{t} = k
12
                    (15 \text{ ppm})^1 \times 4 \text{ hr} = 60 \text{ ppm}^{\text{h}} \text{hr}
13
14
15
      Uncertainty Factors:
             3 for interspecies variability
16
17
           10 for intraspecies variability
18
19
      10-min AEGL-3:
           30-minute value adopted as 10-minute value because POD was 4-hours = 1.0 ppm
20
21
22
      30-min AEGL-3
           C^3 \times 0.5 \text{ hr} = 13,500 \text{ ppm}^{\text{th}} \text{r}
23
           C^3 = 27,000 \text{ ppm}
24
25
           C = 30 \text{ ppm}
26
           30-min AEGL-3 = 30/30 = 1.0 ppm
27
28
      1-hr AEGL-3
           C^3 \times 1 \text{ hr} = 13,500 \text{ ppm}^{\text{th}}
29
           C^3 = 13,500 \text{ ppm}
30
31
           C = 23.8 \text{ ppm}
32
           1-hr AEGL-3 = 23.8/30 = 0.79 ppm
33
34
      4-hr AEGL-3
           15 \text{ ppm} \div 30 = 0.50
35
36
37
      8-hr AEGL-3
           C^1 \times 8 \text{ hr} = 60 \text{ ppm}^{\text{th}} \text{r}
38
           C^1 = 7.5 \text{ ppm}
39
40
           C = 7.5 \text{ ppm}
           8-hr AEGL-3 = 7.5/30 = 0.25 \text{ ppm}
41
```

1	APPENDIX XI-B:
2	
3	Derivation Summary for Ethyl Chlorothioformate AEGLS
4	

10 minutes	30 minutes	1 hour	4 hour	8 hou
NR	NR	NR	NR	NR
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				

20 21 22

AEGL-2 VALUES FOR ETHYL CHLOROTHIOFORMATE					
10-Minute 30-Minute 1-Hour 4-Hour 8-Hour					
0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm	
Key Reference: Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.					
Test Species/Strain/Number: See AEGL-3 Derivation summary table					
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table					
Effects: See AEGL-3 Derivation summary table					
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; Stauffer, 1983).					
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table					
Modifying Factor: See AEGL-3 Derivation summary table					
Animal to Human Dosimetric Adjustment: NA					
Time Scaling: See AEGL-3 Derivation summary table					
Data quality and research needs: See AEGL-3 Derivation summary table.					

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 2						
3	AEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE					
4	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	
5	1.0 ppm	1.0 ppm	0.79 ppm	0.50 ppm	0.25 ppm	
6 7 8	Key Reference: Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.					
9	Test Species/Strain/Sex/Number: Sprague Dawley rats/ 10/sex/group					
10 11 12	Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours (Estimated lethality threshold of $\frac{1}{3}$ the 4-hr rat LC ₅₀ of 45 ppm ($\frac{1}{3}$ x 45 ppm = 15 ppm) is the point-of-departure for AEGL-3)					
13 14	Endpoint/Concentration/Rationale: $\frac{1}{3}$ the 4-hr rat LC ₅₀ of 45 ppm ($\frac{1}{3}$ x 45 ppm = 15 ppm)/ 15 ppm/Estimated threshold for death for 4 hour exposure in rats					
15	Effects: LC ₅₀ =51 ppm (male); 41 ppm (female); 45 ppm (combined male and female)					
16 17 18 19 20 21 22	Uncertainty Factors/Rationale: Interspecies = 3: Ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Intraspecies = 10: Protect against potential delayed systemic effects from the thio- moiety					
23	Modifying Factor:					
24	Animal to Human Dosi	Animal to Human Dosimetric Adjustment: Insufficient data				
25 26 27	Time Scaling: $c^n x t = k$, where $n=3$ when extrapolating to shorter time points (30-minutes and 1-hour) and $n=1$ when extrapolating to longer time points (8-hours). The 30-minute value was adopted as the 10-minute value because the point-of-departure was 4-hours.					

Data Quality and Research Needs: Data limited to rat lethality studies.

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1 APPENDIX XI-C:
2 3 Category Plot for Ethyl Chlorothioformate

Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chloroformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

