INTERIM 1: 05/2008

1 2	INTERIM 1: 05/
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4	INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
5	FOR
6	SELECTED CHLOROFORMATES
7	
8	Methyl Chloroformate
9	$C_2H_3ClO_2$ (CAS Reg. No. 79-22-1)
10	
11	Ethyl Chloroformate
12	$C_{3}H_{5}ClO_{2}$ (CAS Reg. No. 541-41-3)
13	
14	Propyl Chloroformate
15	C ₄ H ₇ ClO ₂ (CAS Reg. No. 109-61-5)
16	
17	Isopropyl Chloroformate
18	C ₄ H ₇ ClO ₂ (CAS Reg. No. 108-23-6)
19	
20	Allyl Chloroformate
21	$C_4H_5ClO_2$ (CAS Reg. No. 2937-50-0)
22	
23	n-Butyl Chloroformate
24	$C_5H_9ClO_2$ (CAS Reg. No. 592-34-7)
25	
26	Isobutyl Chloroformate
27	$C_5H_{10}ClO_2$ (CAS Reg. No. 543-27-1)
28	and Distril Chloreformate
29 20	sec-Butyl Chloroformate
30	C ₅ H ₉ ClO ₂ (CAS Reg. No. 17462-58-7)
31	Dongyl Chloroformata
32	Benzyl Chloroformate C ₈ H ₇ ClO ₂ (CAS Reg. No. 501-53-1)
33	$C_{8}\Pi_{7}CIO_{2}$ (CAS Keg. No. 501-55-1)
34	Dhanyi Chiana farma ata
35	Phenyl Chloroformate
36	$C_7H_5ClO_2$ (CAS Reg. No. 1885-14-9)
37	2 Ethylhavyl Chloraformata
38 20	2-Ethylhexyl Chloroformate C ₉ H ₁₇ ClO ₂ (CAS Reg. No. 24468-13-1)
39	$C_{9}\Pi_{17}CIO_2$ (CAS Keg. No. 24408-15-1)
40	Ethyl Chlorothioformate
41	Ethyl Chlorothioformate
42 43	C ₃ H ₅ ClO-S (CAS Reg. No. 2941-64-2)
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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

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,

36 could experience the effects described at concentrations below the corresponding AEGL.

1	TABLE OF CONTENTS	
2 3	PREFACE	ii
4	CHAPTER I: GENERAL INFORMATION FOR SELECTED CHLOROFORMATES	1
5	CHAPTER II. METHYL CHLOROFORMATE	1
6	CHAPTER III. ETHYL CHLOROFORMATE	1
7	CHAPTER IV: PROPYL CHLOROFORMATE	.23
8	CHAPTER V: ISOPROPYL CHLOROFORMATE	.23
9	CHAPTER VI: ALLYL CHLOROFORMATE	.25
10 11	CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec- BUTYL CHLOROFORMATE	.22
12	CHAPTER VIII: BENZYL CHLOROFORMATE	1
13	CHAPTER IX: PHENYL CHLOROFORMATE	. 19
14	CHAPTER X: 2-ETHYLHEXYL CHLOROFORMATE	1
15	CHAPTER XI: ETHYL CHLOROTHIOFORMATE	.21

1 CHAPTER I: GENERAL INFORMATION FOR SELECTED CHLOROFORMATES

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 2		TABLE OF CONTENTS: CHAPTER I: GENERAL INFORMATION FOR SELECTED CHLOROFORMATES	
3 4	LIST (OF TABLES: CHAPTER I. GENERAL INFORMATION	I-3
5	I.1.	General Chemical and Physical Properties	I-4
6	I.2.	Production and Use	. I-10
7	I.3.	Absorption, Metabolism, Disposition and Excretion	. I-10
8	I.4.	Mechanism of Toxicity	. I-10
9	I.5.	Concurrent Exposure Issues	. I- 11
10	I.6.	Species Sensitivity	. I-11
11	I.7.	Temporal Extrapolation	. I-11
12	I.8.	References	. I- 11

1		LIST OF TABLES: CHAPTER I. GENERAL INFORMATION	
2 3	TABLE I-1.	Chemical and Physical Data for Methyl Chloroformate	I-4
4	TABLE I-2.	Chemical and Physical Data for Ethyl Chloroformate	I-5
5	TABLE I-3.	Chemical and Physical Data for Propyl Chloroformate	I-5
6	TABLE I-4.	Chemical and Physical Data for Isopropyl Chloroformate	I-6
7	TABLE I-5.	Chemical and Physical Data for Allyl Chloroformate	I-6
8	TABLE I-6.	Chemical and Physical Data for n-Butyl Chloroformate	I-7
9	TABLE I-7.	Chemical and Physical Data for Isobutyl Chloroformate	I-7
10	TABLE I-8.	Chemical and Physical Data for sec-Butyl Chloroformate	I-8
11	TABLE I-9.	Chemical and Physical Data for Benzyl Chloroformate	I-8
12	TABLE I-10.	Chemical and Physical Data for Phenyl Chloroformate	I-9
13	TABLE I-11.	Chemical and Physical Data for 2-Ethylhexyl Chloroformate	I-9
14	TABLE I-12.	Chemical and Physical Data for Ethyl Chlorothioformate	I-10
15			

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 2

Chloroformates are generally clear, colorless liquids with relatively low freezing points and relatively high boiling points (>100°C). 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).

9 The chloroformates are reactive compounds possessing both acid chloride and alkyl 10 substituents. The alkyl substituent is responsible for the thermal stability of the chloroformate 11 in the following order of decreasing stability: aryl> primary alkyl> secondary alkyl> tertiary 12 alkyl (Kreutzberger, 2003).

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

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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 25°C	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	-61°C/71.0°C/12.2°C	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 ppm = 3.9 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 25°C	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	-80.6°C/95°C/27.8°C	HSDB, 2005b	
Solubility	Gradually decomposes in water	HSDB, 2005b	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.23 \text{ ppm}$ 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	$C_4H_7ClO_2$	HSDB, 2005c	
Molecular Weight	122.55	HSDB, 2005c	
Physical State	Colorless liquid	HSDB, 2005c	
Vapor Pressure	20 mm Hg at 25°C	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	112.4°C/34.4°C	HSDB, 2005c	
Solubility	Miscible in chloroform, benzene, ether	HSDB, 2005c	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ 1 ppm = 5.0 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-4. Chemical and Physical Data for Isopropyl Chloroformate			
Characteristic/Property	Data	Reference	
Common Name	Isopropyl Chloroformate	HSDB, 2005d	
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 47°C	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	104.6°C/27.8°C	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 ppm = 5.0 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 25°C	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	110°C/31.1°C	HSDB, 2005e	
Solubility	Hydrolyzes in water	HSDB, 2005e	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ 1 ppm = 4.9 mg/m ³		

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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	
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 20°C	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	77.6°C/46.0°C	Kreutzberger, 2003	
Conversion factors in air	$1 \text{ mg/m}^3 = 0.18 \text{ ppm}$ 1 ppm = 5.6 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	130°C/39.4°C	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 ppm = 5.6 mg/m ³		

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TABLE I-8. Chemical and Physical Data for sec-Butyl Chloroformate					
Characteristic/Property	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			
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/35.6°C	Kreutzberger, 2003			
Solubility					
Conversion factors in air	$1 \text{ mg/m}^3 = 0.18 \text{ ppm}$ 1 ppm = 5.6 mg/m ³				

TABLE I-9. Chemical and Physical Data for Benzyl Chloroformate					
Characteristic/Property	Data	Reference			
Common Name	Benzyl Chloroformate	Kreutzberger, 2003			
Synonyms	Carbonochloridic acid phenyl methyl ester; Carbobenzoxy chlorode; Chloroformic acid benzyl ester; Benzyl carbonyl chloride	O'Neil et al., 2001			
CAS Registry No.	501-53-1	O'Neil et al., 2001			
Chemical Formula	C ₈ H ₇ ClO ₂	O'Neil et al., 2001			
Molecular Weight	170.60	O'Neil et al., 2001			
Physical State	Clear to pale yellow liquid	HSDB, 2006			
Vapor Pressure	0.009 kPa at 85-87°C	IPCS, 1999			
Vapor Density $1 \text{ g/L} (\text{air} = 1)$		IPCS, 1999			
Density/Specific Gravity 1.22 g/cm ³		Kreutzberger, 2003			
Boiling/Flash Point 103°C/80°C		O'Neil et al., 2001			
Solubility	Decomposes in water	O'Neil et al., 2001			
Conversion factors in air $1 \text{ mg/m}^3 = 0.14 \text{ ppm}$ $1 \text{ ppm} = 7.0 \text{ mg/m}^3$					

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-10. Chemical and Physical Data for Phenyl Chloroformate					
Characteristic/Property	Reference				
Common Name	Phenyl Chloroformate	Kreutzberger, 2003			
Synonyms	Carbonochloridic acid phenyl ester; IPCS, 2005 Phenyl chlorocarbonate; Phenoxycarbonyl chloride; Formic acid, chloro-, phenyl ester				
CAS Registry No.	1885-14-9	IPCS, 2005			
Chemical Formula	C ₇ H ₅ ClO ₂	IPCS, 2005			
Molecular Weight	156.6	IPCS, 2005			
Physical State	Colorless liquid	IPCS, 2005			
Vapor Pressure	90 Pa at 20°C	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	188-189°C/69°C	IPCS, 2005			
Solubility	Decomposes in water	IPCS, 2005			
Conversion factors in air	$1 \text{ mg/m}^3 = 0.16 \text{ ppm}$ $1 \text{ ppm} = 6.4 \text{ mg/m}^3$				

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TABLE I-11. Chemical and Physical Data for 2-Ethylhexyl Chloroformate					
Characteristic/Property	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	$C_9H_{17}ClO_2$	RTECS, 2005			
Molecular Weight	192.71	RTECS, 2005			
Physical State	Clear, colorless liquid	RTECS, 2005			
Vapor Pressure	1 mm Hg at 45°C	RTECS, 2005			
Vapor Density	>1 g/L (air = 1)	RTECS, 2005			
Density/Specific Gravity	0.9914 g/cm ³	Kreutzberger, 2003			
Boiling/Flash Point	208°C/NA	Kreutzberger, 2003			
Solubility	Decomposes in water	RTECS, 2005			
Conversion factors in air	$1 \text{ mg/m}^3 = 0.13 \text{ ppm}$ 1 ppm = 7.9 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-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 21°C	Stauffer Chemical Company, 1983			
Vapor Density	—	-			
Density/Specific Gravity	1.19 g/cm^3	Stauffer Chemical Company, 1983			
Freezing/Boiling/Flash Point	-60°C/132°C/51.7°C	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 ppm = 5.1 mg/m ³				

I.2. Production and Use

5 Chloroformates are produced by the reaction of phosgene with alcohols or phenols. The 6 alkyl chloroformates of low molecular weight alcohols are prepared by reaction of anhydrous 7 alcohols with a molar excess of chlorine-free phosgene at low temperature. Hydrogen chloride 8 is evolved during the reaction and is collected in a tower with recovered excess phosgene 9 (Kreutzberger, 2003).

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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).

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I.3. Absorption, Metabolism, Disposition and Excretion

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

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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).

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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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

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 RD₅₀ 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 RD₅₀ 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

19 The concentration-exposure time relationship for many irritant and systemically-acting 20 vapors and gases can be described by the relationship $c^n x t = k$, where the exponent, n, ranges 21 from 0.8 to 3.5 (ten Berge et al., 1986). Thus, exponential scaling ($C^n x t = k$) will be used to 22 derive exposure duration-specific AEGL values for the chloroformates.

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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).

29 I.8. References

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CHAPTER II. METHYL CHLOROFORMATE

1	TABLE OF CONTENTS: CHAPTER II: METHYL CHLOR	OFORMATE
2	LIST OF TABLES: CHAPTER II. METHYL CHLOROFORMATE	II-3
3	EXECUTIVE SUMMARY: METHYL CHLOROFORMATE	II-4
4	II.1. HUMAN TOXICITY DATA	
5	II.1.1. Acute Lethality	II-5
6 7	II.1.2. Non-lethal Toxicity II.1.2.1. Case Reports	
8	II.1.3. Developmental/Reproductive Toxicity	II-6
9	II.1.4. Genotoxicity	II-6
10	II.1.5. Carcinogenicity	II-7
11	II.1.6. Summary	II-7
12	II.2. ANIMAL TOXICITY DATA	II-7
13 14 15	II.2.1. Lethality II.2.1.1. Rats II.2.1.2. Mice	II-7
16	II.2.2. Repeated-Exposure	II-11
17	II.2.3. Developmental/Reproductive Toxicity	II-13
18	II.2.4. Genotoxicity	II-13
19	II.2.5. Carcinogenicity	II-13
20	II.2.6. Summary	II-13
21	II.3. DATA ANALYSIS AND AEGL-1	II-16
22	II.3.1. Human Data Relevant to AEGL-1	II-16
23	II.3.2. Animal Data Relevant to AEGL-1	II-16
24	II.3.3. Derivation of AEGL-1	II-16
25	II.4. DATA ANALYSIS AND AEGL-2	II-17
26	II.4.1. Human Data Relevant to AEGL-2	II-17
27	II.4.2 Animal Data Relevant to AEGL-2	II-17
28	II.4.3 Derivation of AEGL-2	II-17
29	II	

1	II.5. DA	TA ANALYSIS AND AEGL-3	II-17
2	II.5.1.	Human Data Relevant to AEGL-3	II-17
3	II.5.2.	Animal Data Relevant to AEGL-3	II-18
4	II.5.3.	Derivation of AEGL-3	II-18
5	II.6. SUN	MMARY OF AEGL	II-19
6	II.6.1.	AEGL Values and Toxicity Endpoints	II-19
7	II.6.2.	Other Exposure Criteria	II-19
8	II.6.3.	Data Adequacy and Research Needs	II-19
9	II.7. REF	FERENCES	II - 19
10	APPENDIX	II-A: TIME SCALING CALCULATIONS FOR METHYL CHLOROFORMATE	II-22
11	APPENDIX	II-B: DERIVATION SUMMARY FOR METHYL CHLOROFORMATE	II-25
12	APPENDIX	II-C: CATEGORY PLOT FOR METHYL CHLOROFORMATE	II-28
13 14 15	APPENDIX	II-D: BENCHMARK CONCENTRATION CALCULATION FOR METHYL CHLOROFORMATE	II-29

1	L	IST OF TABLES: CHAPTER II. METHYL CHLOROFORMATI	E
2 3	TABLE II-S 1.	Summary of AEGL Values For Methyl Chloroformate	II-5
4	TABLE II-1.	Mortality of Rats Exposed to Methyl Chloroformate for 1-hour	II-7
5	TABLE II-2.	Mortality of Rats Exposed to Methyl Chloroformate for 1-hour	II-8
6	TABLE II-3.	Mortality of Rats Exposed to Methyl Chloroformate for 4-hours	II-9
7	TABLE II- 4.	Mortality of Rats Exposed to Methyl Chloroformate for 4-hours	II-10
8	TABLE II-5.	Exposure of Male Swiss-Webster Mice to Methyl Chloroformate for 30 minutes	II-11
9	TABLE II-6.	Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate	II-14
10	TABLE II-7.	AEGL-1 Values for Methyl Chloroformate	II-16
11	TABLE II-8.	AEGL-2 Values for Methyl Chloroformate	II-17
12	TABLE II-9.	AEGL-3 Values for Methyl Chloroformate	II-18
13	TABLE II-10.	Summary of AEGL Values For Methyl Chloroformate	II-19

1 2

5

EXECUTIVE SUMMARY: METHYL CHLOROFORMATE

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

6 No acute inhalation data consistent with the definition of AEGL-2 with both 7 concentration and duration parameters were available. Therefore, the AEGL-2 values for methyl 8 chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an 9 estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on 10 the steep concentration curve with regard to lethality (4-hour rat LC_{50} : 51-53 ppm, 0% mortality 11 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 12 13 no mortality (Fisher et al., 1981)).

14

15 The calculated 4-hr BMCL₀₅ 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 16 17 threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 18 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 each 19 were applied because methyl chloroformate is highly reactive and clinical signs are likely caused 20 by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly 21 between species or among individuals. Thus, the total uncertainty factor is 10. The 22 concentration-exposure time relationship for many irritant and systemically-acting vapors and 23 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et 24 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 25 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when 26 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 27 28 LC₅₀ study (Bio-Test, 1975); utilizing the BMCL₀₅ from this study yields a 10-min AEGL-3 value 29 of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986). 30

The AEGL values are listed in the table below.	
--	--

3 4

TABLE II-S 1. Summary of AEGL Values for Methyl Chloroformate						
Classification10-Min30-Min1-Hr4				4-Hr 8-Hr		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.

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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.

- 27
 - **II.1.2.** Non-lethal Toxicity
- 29 II.1.2.1. Case Reports

31 A healthy 41-year-old chemical production worker inhaled 2-3 breaths of an atmosphere 32 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 33 34 contaminated area immediately because of a penetrating odor and coworkers' warnings. About

1 an hour after exposure, he experienced slight eye irritation and an irritating cough and reported 2 to the medical facility at the factory. Auscultation of lungs was largely unremarkable; isolated 3 respiratory sounds were found in the upper lobes. The next day (about 24 hours later), a follow-4 up examination was performed. The worker reported increasing cough since early morning and 5 presented with abnormal respiratory sounds in the upper lung lobes during auscultation. A 6 codeine preparation (Codipront) was prescribed and a follow-up examination was scheduled for 7 the next day. However, the worker returned in the afternoon of the same day because of 8 increasingly severe signs and symptoms as the day progressed, as evidenced by extensive 9 abnormal sounds in the upper lung lobes, moderate dyspnea, and a temperature of 37.2°C. The 10 worker was kept for observation over night, with an oxygen supply, a bronchodilator (Brondilat) 11 and 40 mg Urbason i.v. During the night the symptoms receded and the worker slept well to the 12 early morning hours. At that time, the cough resumed and auscultation showed slight dry rales 13 in the right lower lung lobe. The worker was sent home following administration of Omnicillin 14 and Codipront. Examination on the next day revealed no notable complaints. The following 15 day, however, the worker complained of a severely irritating cough and dyspnea; slight cyanosis 16 of the lips was also observed. Auscultation of the lungs, revealing rales in all lung areas, 17 confirmed the subjective findings. The worker was then admitted to the factory's medical 18 facility and stayed there for about three days. Urbason, Brondilat, and Hostacyclin were 19 administered during this time period. The symptoms started to recede with a morning cough still 20 present, and drug treatment was discontinued.

 $\frac{1}{21}$

22 In another report, a 46-year-old male worker was exposed to methyl chloroformate in the 23 process of repairing a methyl chloroformate pipeline (Penkovitch and Anikin, 1988). The liquid 24 soaked his clothes and penetrated to the skin; he reported itching and burning. He was wearing a 25 gas mask during the accident; thus, no inhalation exposure occurred until he removed the gas 26 mask in the shower room. He then reported a sharp, choking smell and developed burning of the 27 eyes, tearing, sore throat, and a cough while showering for 3-5 minutes. Methyl chloroformate 28 concentrations were not reported. He returned to his home and reported no abnormal symptoms 29 for 4-5 hours. He then developed a sore, burning throat, chills, asthma, and productive cough. 30 The asthma and cough progressed, and he was admitted to a hospital 22 hours after the accident. 31 He presented with pulmonary edema which resolved within 24 hours after treatment with 32 Prednisolone and Lasix.

33

34 **II.1.3. Developmental/Reproductive Toxicity**

35

36 Developmental or reproductive studies regarding acute human exposure to methyl 37 chloroformate were not available.

38

39 **II.1.4. Genotoxicity**40

41 Genotoxic studies regarding acute human exposure to methyl chloroformate were not 42 available.

II.1.5. Carcinogenicity

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

II.1.6. Summary

6 7

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8 Case reports of methylchloroformate toxicity exist; however, details of exposure 9 concentration and duration are unreported. Signs of exposure included ocular and upper 10 respiratory irritation followed by a latent period which ultimately led to pulmonary edema. For 11 the workers in these reports the latency periods were 36 hours (Schuckmann, 1972) and 22 12 hours (Penkovitch and Anikin, 1988). No data concerning lethality, developmental/reproductive 13 toxicity, genotoxicity, and carcinogenicity in humans from methyl chloroformate exposure were 14 located in the available literature.

16 II.2. ANIMAL TOXICITY DATA

17 **II.2.1. Lethality**

- 18 **II.2.1.1. Rats**
- 19

20 Groups of five male and five female Charles River albino rats were exposed to 0, 145, 21 173, 233, or 274 ppm (nominal concentrations) methyl chloroformate vapor for 1 hour, followed 22 by a 14-day observation period (Bio-Test Laboratories, Inc., 1975). Vapor was generated by 23 bubbling clean, dry air through undiluted methyl chloroformate in a gas washing bottle. The 24 resulting air-vapor mixture was then introduced into the exposure chamber. The 1-hour LC_{50} 25 was determined to be 163 ppm, and the calculated $BMCL_{05}$ is 74 ppm. Males appear to be more 26 sensitive than females. Hypoactivity, ptosis, ruffed fur, enophthalmus, and dyspnea were 27 observed in all rats during exposure. Evidence of acute bronchiolitis followed by fibrosis of the 28 pulmonary parenchyma was observed in animals sacrificed on day 14 post-exposure and in rats 29 that died during the experiment. Data are summarized in Table II-1.

30

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)

32 In another study, groups of ten male Sprague Dawley rats were exposed to 735, 2947,

33 9610, or 66,235 ppm (nominal concentrations) methyl chloroformate for 1 hour (WARF Institute,

³¹

1 Inc., 1972). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air

2 flow was utilized. Methyl chloroformate was administered into the incoming air stream just

3 before it entered the chamber port, and exposure concentrations were calculated by dividing the 4 total amount spraved into the chamber by the total cubic feet of air circulated through the

4 total amount sprayed into the chamber by the total cubic feet of air circulated through the5 chamber. All animals died within 18 hours of exposure. Data are summarized in Table II-2.

6

TABLE II-2. Mortality of Rats Exposed to Methyl Chloroformate for 1-hour*				
Concentration (ppm) Results				
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)

7

8 9 Groups of five male and five female Fischer 344 rats (main group) were exposed to 0, 26, 10 110, 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 11 12 real time variable pathlength infrared photospectrometry. In addition 10, 10, and 20 rats/sex 13 (satellite rats) were concurrently exposed to 26, 110, or 133 ppm methyl chloroformate, 14 respectively. One satellite rat/sex/concentration and 2 rats/sex at the lower three concentrations 15 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 LC_{50} values were 100 ppm for 16 female rats, and between 92 and 123 ppm for male rats at 14 days post-exposure. Respiratory 17 18 distress occurred in all main group rats at 110, 133, 159, and 192 ppm during the first 24 hours 19 following exposure. The respiratory distress resolved within 24 hours in the 110 ppm group; 20 however, the effect persisted through day 14 in the other exposure groups and was accompanied 21 by lethargy, weakness, and inactivity. Concentration-related red or clear ocular and nasal 22 discharge and gross lung lesions were observed in rats at 110, 133, 159, and 192 ppm. Controls 23 and rats in the 26 ppm group were clinically normal. Rats in the satellite group responded 24 similarly to corresponding rats in the main group. In the main study group, decreased mean 25 body weight and body weight gain were observed in the 110, 133, 159, and 192 ppm rats and 26 correlated with poor clinical status prior to death or study termination. No effect on body weight 27 was observed in rats exposed to 26 ppm. Lesions in satellite rats exposed to 110 and 133 ppm 28 were comparable at all three sacrifice times and included severe degeneration, necrosis, erosion, 29 and ulceration of the nasal turbinates and tracheal mucosal epithelia; alveolar hemorrhage; and 30 erosion of bronchial and bronchiolar epithelia. By day 9 or 10, the nasal turbinate effects had 31 resolved, but regeneration was incomplete and purulent rhinitis persisted. Other respiratory tract 32 and lung lesions seen at 4 and 24 hours had resolved after 9 or 10 days. Pulmonary edema was 33 observed in some rats in the 110, 133, 159, and 192 ppm groups. No pulmonary edema was 34 observed in controls or in the group receiving 26 ppm. 35

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 Vernot et al. (1977) reported a 1-hour LC_{50} of 88 (64-123) ppm for male Sprague-Dawley 2 rats and a value of 103 (90-118) ppm for female Sprague-Dawley rats. Experiments were 3 performed in bell jars using groups of five rats per exposure level and concentrations were 4 analytically determined. No further experimental details were available.

5

6 Groups of five male and five female SPF Wistar rats were exposed to 35, 45, 57, or

7 73ppm (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

9 exposure chamber operated under dynamic flow conditions. Methyl chloroformate
 10 concentrations were measured every 15 minutes during exposure using a single beam

photometer, and were analytically measured every 120 minutes using as chromatography.

12 Clinical signs noted in all treatment-groups in a concentration-related manner included palpebral

13 fissure narrowed or closed, increased grooming, squatting posture, accelerated, irregular, and

14 jerky respiration, gasping, drowsiness, staggering movements, wimpering/crackling breathing

15 sounds, sneezing, and piloerection. Body weight gain was decreased in both sexes after

16 exposures, but animals surviving to study termination regained initial body weight. There were

17 no gross treatment-related effects noted at necropsy in animals surviving to study termination.

18 Gross examination of animals that died during the study showed dark red to black lungs, foamy

19 liquid in the lungs, red aqueous liquid in the thoracic cavity, and distended gastrointestinal tract.

20 Histopathological examination showed increased permeability in the alveolar septa and

21 corresponding damage to bronchial epithelium; this effect was noted in all treatment groups.

Four hour LC_{50} values of 51 ppm and 53 ppm were calculated for males and females,

23 respectively. A combined male and female $BMCL_{05}$ value of 42.4 ppm and combined male and

- female BMC_{01} value of 47.8 ppm were calculated. Mortality data are summarized in Table II-3.
- 25

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

26

27

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

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 encrustations, ruffled and sticky fur, staggering, distended abdomen, poor general state, attempts
- 2 to escape, impaired coordination, salivation, and squatting posture. Animals in the 16 ppm
- 3 group exhibited jerky respiration and eyelid closure. Body weight gain was initially decreased in
- 4 the three highest concentration groups; this effect had resolved in surviving animals by day 14
- 5 post-exposure. Four hour LC_{50} values of 13 ppm and 18 ppm were calculated for males and
- 6 females, respectively. A combined male and female LC_{05} value of 15 ppm was also calculated.
- 7 It should be noted that the LC_{50} values calculated from this study appear to be inconsistent with 8 the other available data (see Table II 6). Data are summarized in Table II 4
- 8 the other available data (see Table II-6). Data are summarized in Table II-4.
- 9

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 pp	m`		

*BASF, 1980

10

11

Death occurred in 12/12 rats exposed to 37,500 ppm methyl chloroformate vapor at 20°C 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.

16

Death occurred in 11/12, 5/6, and 6/6 rats exposed to an "atmosphere enriched or
saturated" with methyl chloroformate vapor at 20°C for 3, 10, and 30 minutes, respectively
(BASF, 1978). 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 20°C 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 LD₅₀ 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 LD₅₀ value of 894 mg/kg was reported for male and female Sprague-Dawley rats combined (BASF, 1981c). In another study, a dermal LD₅₀ of >2 mL/kg was reported for male rats (WARF Institute, Inc., 1972).

1 2

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.

3 4 5

6

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 RD₅₀ of 52.4 ppm was calculated. Results are

- 14 summarized in Table II-5.
- 15

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

16 17 18

19

20

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

21 II.2.2. Repeated-Exposure

22

23 In an inhalation range-finding study, groups of five male and five female Sprague-Dawley 24 rats were exposed to 0, 1.9, 6.2, or 19.5 ppm methyl chloroformate 6 hours/day for 5 days (HRC, 25 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. 26 27 In the 19.5 ppm group, males sneezed and had noisy nasal breathing in between exposures. 28 Decreased body weight was accompanied by decreased food and water consumption in rats 29 exposed to 19.5 ppm. Animals were necropsied three days post-exposure. Lungs failed to 30 collapse in 1/5 males and 3/5 females in the 6.2 ppm group and 5/5 females in the 19.5 ppm 31 group. Petechial bleeding was noted in the lungs of 1/5 males in the 6.2 ppm group and 5/5 males 32 and 1/5 females in the 19.5 ppm group. Lung weight was increased in all high-concentration

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 females; organ weights were not examined in males due to experimental error during necropsy.

2 Inflammatory and erosive mucous membrane lesions were noted in the nose, larynx, and trachea,

3 and bronchiolitis and pneumonia were noted in high-concentration rats. Focal epithelial

- 4 hyperplasia of the nasal mucosa was noted in the 6.2 and 19.5 ppm groups. Comparison of
- 5 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.
- 7 8

9 In a repeated-exposure study, groups of five male and five female Sprague-Dawley rats 10 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 11 12 8.8 ppm during the final week of exposure. Clinical signs, observed only at 8.8 ppm, included 13 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 14 15 volume, increased hemoglobin concentration, increased red cell count, increased neutrophil 16 count, increased total protein, decreased albumin, increased globulin, decreased albumin/globulin 17 ratio, and increased cholesterol were observed at 8.8 ppm as well. In addition, uncollapsed lungs, 18 lung congestion, enlarged tracheobronchial and medistinal lymph nodes, and increased lung 19 weight were observed at necropsy in rats exposed to 8.8 ppm. Histopathological lesions of the 20 nasal turbinates were observed at 3.1 and 8.8 ppm, while lesions were observed in the larynx of 21 animals exposed to 1.01, 3.1, and 8.8 ppm methyl chloroformate.

22

Groups of ten male and ten female Wistar rats were exposed to 0, 0.40, 2.15, 3.98, or 23 24 7.83 ppm methyl chloroformate 6 hours/day, 5 days/week for 3, 10, 20, or 65 exposures (90-day 25 study with interim necropsies after 3, 14, and 28 study days; satellite groups also contained 10 26 rats/sex/concentration) (BASF, 1999). In addition to observation for clinical signs and complete 27 necropsy, cell proliferation measurements were performed in four female rats per group. 5-28 Bromo-2'-deoxyuridine (BrdU) was administered to these females via subcutaneously implanted 29 minipumps. Pumps remained in the animals for 8 hours or 3 days for evaluation of cell 30 proliferation in nasal cavity and laryngeal epithelia. Four male rats in the 7.83 ppm group died; 31 deaths occurred after 24, 32, 36, and 41 exposures. Clinical signs were noted only in high-32 concentration animals and included rubbing of snout, sneezing, nasal crusts in the animals that 33 subsequently died, as well as abnormal respiration, and general morbidity. Decreased body 34 weight and body weight gain were noted in males in the 3.98 and 7.83 ppm groups sacrificed 35 after three exposures and at study termination. At necropsy, gross effects were observed only in 36 the 7.83 ppm group and included red foci in the lungs. Animals in the high concentration group, 37 except for those sacrificed after three exposures, exhibited increased lung weight. Concentration 38 and duration-related histological effects were limited to the respiratory tract and occurred in 39 2.15, 3.98, and 7.83 ppm animals at all sacrifice times. Nasal and laryngeal squamous cell 40 metaplasia were noted at 2.15, 3.98, and 7.83 ppm. Focal epithelial hyperplasia and squamous 41 cell metaplasia and hyperplasia of the trachea and lungs were noted at 3.98 and 7.83 ppm. No 42 histopathology was noted in the 0.40 ppm group. Cell proliferation was increased at 2.15 ppm 43 after 20 and 65 days, and at 3.98 and 7.83 ppm after 10, 20, and 65 days. The significant

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

- increases involved respiratory and transitional cell epithelium of the nose and in the ciliated and
 squamous epithelium of the larvnx. No cell proliferation was noted at 0.40 ppm.
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4 Groups of four male and four female Alderly Park SPF rats were exposed to 1 ppm 5 (fifteen 6-hour exposures, 5 ppm (fifteen 6-hr exposures), or 20 ppm (fifteen 6-hr exposures) 6 methyl chloroformate vapor in isopropanol (Gage, 1970). The vapor concentrations were 7 produced by injecting liquid at a known rate into a metered stream of air with a controlled fluid-8 feed atomizer. No effects were observed at 1 ppm. Nasal irritation and lethargy were noted at 5 9 ppm, and nasal irritation, respiratory difficulty, weight loss, lethargy, and poor condition were 10 observed at 20 ppm. Distended lungs and lung hemorrhage, and kidney congestion were noted at 11 autopsy in the 20 ppm group. No further details were provided.

- 1213 II.2.3. Developmental/Reproductive Toxicity
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Developmental and reproductive studies regarding animal exposure to methyl chloroformate were not available.

18 **II.2.4.** Genotoxicity19

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).

26 II.2.5. Carcinogenicity

Animal carcinogenicity data were not located.

30 **II.2.6. Summary**

31 32 Animal toxicity data include both acute and repeated-exposure inhalation studies. Rat 1-33 hr LC_{50} values were relatively consistent between studies as follows: 163 ppm for male and 34 female Charles River rats (Bio-Test Laboratories, Inc., 1975), 92-123 ppm and 100 ppm for male 35 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 36 37 reported to be 51-53 ppm (Hoechst, 1986) and 15 ppm (BASF, 1980); however, the 15 ppm 38 value is an outlier when compared to other available data. Signs of toxicity included body 39 weight loss, weakness and lethargy, respiratory distress, hematological effects consistent with 40 decreased oxygen availability (assumed secondary to pulmonary congestion and edema), and 41 bronchiolitis, fibrosis, and pulmonary edema. A 30-min RD_{50} of 47.2 ppm (nominal 42 concentration) methyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 43 1982). Methyl chloroformate did not induce mutations in an Ames bacterial reverse mutation 44 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 1
- concerning developmental/reproductive toxicity or carcinogenicity of methyl chloroformate were
- 2 3 located in the available literature. Animal data are summarized in Table II-6.
- 4

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
	·	Acı	ite Exposure	-
Rat	37,500	3 min	12/12 dead	BASF, 1978
Rat	735 (nominal)	20 min	10/10 dead	WARF Institute, Inc., 1972
Rat	26	1 hr	No effects	Fisher et al., 1981
Rat	74 (nominal)	1 hr	BMCL ₀₅	Bio-Test Labs, Inc., 1975
Rat-male	88	1 hr	LC ₅₀	Vernot et al., 1977
Rat-male	92-123	1 hr	LC ₅₀	Fisher et al., 1981
Rat-female	100	1 hr	LC ₅₀	Fisher et al., 1981
Rat-female	103	1 hr	LC ₅₀	Vernot et al., 1977
Rat	163 (nominal)	1 hr	LC ₅₀	Bio-Test Labs Inc., 1975
Rat	2974 (nominal)	1 hr	10/10 dead	WARF Institute, Inc., 1972
Rat	15	4 hrs	LC ₅₀	BASF, 1980
Rat	42.4 ppm	4 hrs	BMCL ₀₅	Hoechst, 1986
Rat-male	51	4 hrs	LC ₅₀	Hoechst, 1986
Rat-female	53	4 hrs	LC ₅₀	Hoechst, 1986
Mouse	52.4	30 minutes	RD ₅₀	Carpenter, 1982
		Repe	ated Exposure	
Rat	0.40	6 hr/d, 3 ds	No effects	BASF, 1999
Rat	2.15	6 hr/d, 3 ds	Histopathology	BASF, 1999
Rat	3.98	6 hr/d, 3 ds	Histopathology, decreased body weight	BASF, 1999
Rat	7.83	6 hr/d, 3 ds	Clinical signs, histopathology, decreased body weight	BASF, 1999
Rat	1.9	6 hr/d, 5 ds	No effects	HRC, 1992
Rat	6.2	6 hr/d, 5 ds	Clinical signs consistent with irritation, focal epithelia hyperplasia; petechial lung bleeding	HRC, 1992
Rat	19.5	6 hr/d, 5 ds	Clinical signs consistent with irritation, focal epithelia hyperplasia; inflammatory and erosive mucous membrane changes, petechial lung bleeding, increased lung	HRC, 1992

	Concentration	Exposure		
Species	(ppm)	Duration	Effect	Reference
			weight; pneumonia	
Rat	0.40	6 hr/d, 5 ds/week, 2 wks	No effects	BASF, 1999
Rat	2.15	6 hr/d, 5 ds/wk, 2 wks	Histopathology	BASF, 1999
Rat	3.98	6 hr/d, 5 ds/wk, 2 wks	Histopathology, cell proliferation	BASF, 1999
Rat	7.83	6 hr/d, 5 ds/wk, 2 wks	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF, 1999
Rat	1	6 hr, 15 exposures	No effects	Gage, 1970
Rat	5	6 hr, 15 exposures	Nasal irritation, lethargy	Gage, 1970
Rat	20	6 hr, 15 exposures	Nasal irritation, respiratory difficulty, lethargy, lung pathology, kidney congestion	Gage, 1970
Rat	0.13	6 hr/d, 5 ds/wk, 4 wks	No effects	BASF, 1993
Rat	0.38	6 hr/d, 5 ds/wk, 4 wks	No effects	BASF, 1993
Rat	0.40	6 hr/d, 5 ds/wk, 4 wks	No effects	BASF, 1999
Rat	1.01	6 hr/d, 5 ds/wk, 4 wks	Larynx lesions	BASF, 1993
Rat	2.15	6 hr/d, 5 ds/wk, 4 weeks	Histopathology, cell proliferation	BASF, 1999
Rat	3.1	6 hr/d, 5 ds/wk, 4 wks	Nasal turbinate histopathology; larynx lesions	BASF, 1993
Rat	3.98	6 hr/d, 5 ds/wk, 4 wks	Histopathology, cell proliferation	BASF, 1999
Rat	7.83	6 hr/d, 5 ds/wk, 4 wks	Clinical signs, histopathology, cell proliferation, increased lung weight	BASF, 1999
Rat	8.8	6 hr/d, 5 ds/wk, 4 wks	3/10 deaths in final week of exposure; clinical signs; decreased BW; hematological effects; lung congestion; increased lung weight; nasal turbinate	BASF, 1993

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

ТА	BLE II-6. Summar	y of Inhalation Dat	a of Animals Exposed to Methyl	TABLE II-6. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate					
Species	Concentration (ppm)			Reference					
			histopathology; larynx lesions						
Rat	0.40	6 hr/d, 5 ds/wk, 13 wks	No effects	BASF, 1999					
Rat	2.15	6 hr/d, 5 ds/wk, 13 wks	Histopathology, cell proliferation	BASF, 1999					
Rat	3.98	6 hr/d, 5 ds/wk, 13 wks	Histopathology, cell proliferation, decreased body weight	BASF, 1999					
Rat	7.83	6 hr/d, 5 ds/wk, 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).

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TABLE II-7. AEGL-1 Values for Methyl Chloroformate							
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr							
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

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

1 **II.4. DATA ANALYSIS AND AEGL-2**

2 **II.4.1.** Human Data Relevant to AEGL-2 3

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.

9 **II.4.2** Animal Data Relevant to AEGL-2

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

13 **II.4.3** Derivation of AEGL-2

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15 No acute inhalation data consistent with the definition of AEGL-2 with both 16 concentration and duration information were available. Therefore, the AEGL-2 values for 17 methyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is 18 considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is 19 justified based on the steep concentration curve with regard to lethality (4-hour rat LC_{50} : 51-53 20 ppm, 0% mortality in rats exposed to 45 ppm and 80% mortality in rats exposed to 57 ppm for 4 21 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 22 23 chloroformate are presented in Table II-8, and the calculations for these AEGL-2 values are 24 presented in Appendix II-A. 25

TABLE II-8. AEGL-2 Values for Methyl Chloroformate								
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr							
AEGL-2	4.0 ppm (16 mg/m ³)	2.8 ppm (11 mg/m ³)	2.2 ppm (8.6 mg/m ³)	1.4 ppm (5.5 mg/m ³)	0.70 ppm (2.7 mg/m ³)			

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28 These values are considered protective because rats showed no deaths and only nasal 29 turbinate histopathology and larynx lesions when repeatedly exposed to 3.1 ppm, and showed 30 only larynx lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

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33 **II.5. DATA ANALYSIS AND AEGL-3**

34 II.5.1. Human Data Relevant to AEGL-3 35

36 Human lethality data were anecdotal and lacked reliable concentration and time 37 information. Thus, those reports were not appropriate for establishing the AEGL-3 values. 38

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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II.5.2. Animal Data Relevant to AEGL-3

3 Rat 1-hr LC₅₀ values were as follows: 163 ppm for male and female Charles River rats 4 (Bio-Test Laboratories, In., 1975), 92-123 ppm and 100 ppm for male and female Fischer 344 5 rats, respectively (Fisher et al., 1981), and 88 ppm and 103 ppm for male and female Sprague 6 Dawley rats, respectively (Vernot et al., 1977). Exposure of male and female Fischer 344 rats to 7 26 ppm methyl chloroformate for 1 hour resulted in no deaths (Fisher et al., 1981). Four hour 8 LC_{50} values of 51 ppm and 53 ppm were calculated for male and female Wistar rats, 9 respectively; a combined male and female BMCL₀₅ value of 42.4 ppm and combined male and 10 female BMC $_{01}$ value of 47.8 ppm were also calculated (Hoechst, 1986).

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II.5.3. Derivation of AEGL-3

14 The calculated 4-hr BMCL₀₅ value in rats (42.4 ppm) (Hoechst, 1986) will be used as the 15 point-of-departure for methyl chloroformate AEGL-3 values. This concentration is considered a 16 threshold for lethality and is supported by the fact that no deaths were observed in rats exposed 17 to 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 18 each will be applied because methyl chloroformate is highly reactive and clinical signs are likely 19 caused by a direct chemical effect on the tissues; this type of effect is not expected to vary 20 greatly between species or among individuals. Thus, the total uncertainty factor is 10. The 21 concentration-exposure time relationship for many irritant and systemically-acting vapors and 22 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et 23 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 24 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when 25 extrapolating to shorter time points (10-min, 30-min and 1-hr) and n = 1 when extrapolating to 26 longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-27 hr LC₅₀ study (Bio-Test, 1975); utilizing the BMCL₀₅ from this study yields a 10-min AEGL-3 28 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst 29 (1986). The AEGL-3 values for methyl chloroformate are presented in Table II-9, and the 30 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-Min 30-Min 1-Hr 4-Hr 8-Hr						
AEGL-3	12 ppm (47 mg/m ³)	8.5 ppm (33 mg/m ³)	6.7 ppm (26 mg/m ³)	4.2 ppm (16 mg/m ³)	2.1 ppm (8.2 mg/m ³)	

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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).

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 II.6. SUMMARY OF AEGLS

2 II.6.1. AEGL Values and Toxicity Endpoints

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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.

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TABLE II-10. Summary of AEGL Values For Methyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	4.0 ppm (16 mg/m ³)	2.8 ppm (11 mg/m ³)	2.2 ppm (8.6 mg/m ³)	1.4 ppm (5.5 mg/m ³)	0.70 ppm (2.7 mg/m ³)	
AEGL-3 (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)	

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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11 **II.6.2.** Other Exposure Criteria12

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

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16 II.6.3. Data Adequacy and Research Needs

Human data are limited to anecdotal reports. Animal data include acute and repeatedexposure rat inhalation studies and a mouse RD₅₀ study. Support provided by the repeatedexposure studies adds to confidence in the derived AEGL values.

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Methyl Chloroformate

1	APPENDIX II-A: TIME SCALING CALCULATIONS FOR
2	METHYL CHLOROFORMATE
3	
4	DERIVATION OF AEGL-1 VALUES FOR METHYL CHLOROFORMATE
5	
6	Data are insufficient for derivation of AEGL-1 values; therefore, AEGL-1 values are Not
7	Recommended.

1	DERIVATI	ON OF AEGL-2 VALUES FOR METHYL CHLOROFORMATE
2 3 4	Key study: Hoechst,	1986
5	Toxicity Endpoint: 1	/3 of the AEGL-3 values
6		10 2 40
8	<u>10-min AEGL-2</u> :	$12 \text{ ppm} \div 3 = 4.0 \text{ ppm}$
8 9 10	<u>30-min AEGL-2</u> :	8.5 ppm \div 3 = 2.8 ppm
11	<u>1-hr AEGL-2</u> :	$6.7 \text{ ppm} \div 3 = 2.2 \text{ ppm}$
12		
13	<u>4-hr AEGL-2</u> :	$4.2 \text{ ppm} \div 3 = 1.4 \text{ ppm}$
14 15	<u>8-hr AEGL-2:</u>	2.1 ppm \div 3 = 0.70 ppm

1					
2 3	Key study: Hoechst, 1986				
4 5 6	Toxicity Endpoint: Calculat	ted BMCL ₀₅ (42.4 ppm) from a 4-hour exposure in rats.			
7 8 9 10	Scaling:	$\frac{10\text{-min, } 30\text{-min, and } 1\text{-hour}}{C^3 \text{ x } t = k}$ (42.4 ppm) ³ x 4 hr = 304900 ppm·hr			
11 12 13 14	<u>8-hours</u>	$C^{1} \ge t = k$ (42.4 ppm) ¹ \times 4 hr = 170 ppm·hr			
15 16 17 18	Uncertainty Factors:	3 for interspecies variability3 for intraspecies variability			
19 20 21 22 23	<u>10-min AEGL-3</u>	$C^{3} \ge 0.167 \text{ hr} = 304900 \text{ ppm} \cdot \text{hr}$ $C^{3} = 1825748 \text{ ppm}$ C = 122 ppm 10-min AEGL-3 = 122/10 = 12 ppm			
24 25 26 27 28 29	<u>30-min AEGL-3</u>	$C^{3} \ge 0.5 \text{ hr} = 304900 \text{ ppm} \cdot \text{hr}$ $C^{3} = 609800 \text{ ppm}$ C = 84.8 ppm 30-min AEGL-3 = 84.8/10 = 8.5 ppm			
 30 31 32 33 34 35 	<u>1-hr AEGL-3</u>	$C^{3} \ge 1 \text{ hr} = 304900 \text{ ppm} \cdot \text{hr}$ $C^{3} = 304900 \text{ ppm}$ C = 67.3 ppm 1-hr AEGL-3 = 67.3/10 = 6.7 ppm			
36 37	4-hr AEGL-3	4-hr AEGL-3 = $42.4/10 = 4.2$ ppm			
38 39 40 41 42	<u>8-hr AEGL-3</u>	$C^{1} \ge 8 \text{ hr} = 170 \text{ ppm} \cdot \text{hr}$ $C^{1} = 21.2 \text{ ppm}$ C = 21.2 ppm 8-hr AEGL-3 = 21/10 = 2.1 ppm			

APPENDIX II-B: DERIVATION SUMMARY FOR METHYL CHLOROFORMATE ACUTE EXPOSURE GUIDELINES FOR METHYL CHLOROFORMATE DERIVATION SUMMARY

	AEGL-1 VALUES FOR METHYL CHLOROFORMATE							
10-Min	30-Min	1-Hr	4-Hr	8-Hr				
NR	NR	NR	NR	NR				
Reference: NA								
Test Species/Stra	in/Number: NA							
Exposure Route/	Concentrations/I	Durations : NA						
Effects: NA								
Endpoint/Concer	ntration/Rational	e: NA						
Interspecies: Intraspecies:	Uncertainty Factors/Rationale: Interspecies: NA Intraspecies: NA (Alarie method requires no additional UF)							
Modifying Factor	1							
Animal to Huma		ustment: NA						
Time Scaling: NA								
Data quality and research needs: Data were insufficient for derivation of AEGL-1 values. AEGL-1 values are not recommended.								

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

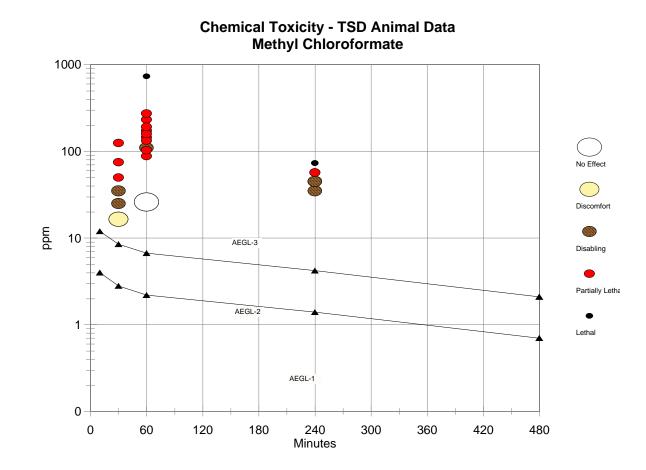
AEGL-2 VALUES FOR METHYL CHLOROFORMATE						
10-Minute	30-Min	1-Hr	4-Hr	8-Hr		
4.0 ppm	2.8 ppm	2.2 ppm	1.4 ppm	0.70 ppm		
Key Reference: Hoechst. 1986. Chlore						
	esearch Toxicology. R			Langer, K.H. Hoechst		
Test Species/Strain/Nu	mber: See AEGL-3 De	rivation summary tabl	e			
Exposure Route/Conc	entrations/Durations	: See AEGL-3 Derivat	tion summary table			
Effects: See AEGL-3 I	Derivation summary tal	ble				
inability to escape hour rat LC ₅₀ : 51- ppm for 4 hours (I clinically normal a	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))					
Uncertainty Factors/H		3 Derivation summary	table			
Modifying Factor: NA						
Animal to Human Do	Ŭ					
Time Scaling: See AE	GL-3 Derivation sumn	nary table				
exposed to 3.1 pp		nasal turbinate histopa	athology and larynx l	lesions when repeatedly		

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-Min	30-Min	1-Hr	4-Hr	8-Hr
12 ppm	8.5 ppm	6.7 ppm	4.2 ppm	2.1 ppm
Key Reference:				
female SPF Wista	proformic acid methyl estar rats. 4-hour LC_{50} . Hour seearch Toxicology. Re	ollander, H., Weigla	nd, W, Mayer, D., and	
Test Species/Strain/	Sex/Number: Rats/Wist	tar/5/sex/group		
Exposure Route/Con	ncentrations/Durations	Rats/Inhalation/4	hours	
	on/Rationale: Calculated or 1 hour exposure in rate		fter a 4 hr-exposure/ 42.	4 ppm/Estimated
Male and Female Male and Female Concentration Ma 35 ppm 45 ppm 57 ppm	$BMC_{01} = 47.8$ ale Mortality $0/5 \qquad 0$ $0/5 \qquad 0$	Mortality)/5)/5 3/5		
73 ppm		5/5		
	3:			
Modifying Factor: N	NA			
Animal to Human D	osimetric Adjustment:	Insufficient data		
n = 1 when extra justified based o	= k, where n=3 when ext apolating to longer time p n a 1-hr LC_{50} study (Bio of 13 ppm, which suppor	points (8-hours). T p-Test, 1975); utilizi	ime scaling from 4-houing the BMCL ₀₅ from the	rs to 10-minutes is his study yields a 10-mir
endpoint for AE ppm 6 hours/day	esearch Needs: Many ra GL-3. These values are v, 5 days/week for 4 wee dly (6 hours/day, 5 days/	considered protecti ks (BASF, 1999), a	ve because no rats died and no rats died until w	when exposed to 7.8

1 2

APPENDIX II-C: CATEGORY PLOT FOR METHYL CHLOROFORMATE



1

2 3 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

APPENDIX II-D: BENCHMARK CONCENTRATION CALCULATION FOR METHYL CHLOROFORMATE

BMDS MODEL RUN

5	~~~~~~~	~~~~~~~		~~~~~~	~~~~~~~	$\sim\sim\sim\sim\sim\sim$	
6	The form of the pro	bability function is	:				
7	P[response] = Ba						
8		l) * CumNorm(Inter	cept+Slope*Log	(Dose)),			
9		n(.) is the cumulativ			1		
10	Dependent varial						
11	Independent vari						
12	Slope parameter						
13	1 1						
14	Total number of	observations = 4					
15		records with missin	g values = 0				
16		er of iterations $= 25$					
17		n Convergence has		08			
18		ergence has been set					
19		0					
20	User has chosen the	e log transformed m	odel				
21							
22	Default Initial (and	Specified) Paramet	er Values				
23	background =	0					
24		-20.4973					
25	*	5.16963					
26	1						
27	Asymptotic Correla	ation Matrix of Para	meter Estimates				
28				e been estima	ted at a boundary	point, or have been specified	
29		not appear in the co			5		
30	<i>,</i>	11		,			
31	intercept						
32	intercept 1						
33	1						
34	Para	ameter Estimates					
35							
36	Variable	Estimate St	d . Err .				
37	Background	0	NA				
38	Intercept	-71.9357 0.4	149759				
39	Slope	18	NA				
40	1						
41	NA - Indicates that	this parameter has	hit a bound impli	ed by some i	inequality constra	int and thus has no standard	
42	error.	1	1	5	1 5		
43							
44							
45	Analysis of Devia	nce Table					
46	v						
47	Model	Log(likelihood)	Deviance	Test DF	P-value		
48	Full model	-5.00402					
49	Fitted model	-5.00722	0.00639048	3	0.9999		
50	Reduced model	-27.5256	45.0431	3	<.0001		
51							

AIC:12.0144

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					
Dose	EstProb.	Expected	Scaled Observed	Size	Residual			
35.0000	0.0000	0.000	0	10	-1.008e-007			
45.0000	0.0003	0.003	0	10	-0.0564			
57.0000	0.7993	7.993	8	10	0.005272			
73.0000	1.0000	10.000	10	10	0.0007765			
Chi-square =	0.00 DF = 3	P-valu	e = 1.0000					
Benchmark D Specified effe Risk Type Confidence le BMD = 49 BMDL = 4	= Extra risk evel = 0.95 0.6524							
		Ρ	robit Model w	ith 0.95	Confidence L	evel		
	Probit -							
ted	.8			/				
on At	-							
-ractic	.4		т					
	.2							
	0	BMDL	BN	/ID				
	35	40	45 50	5	5 60	65	70	7
	35	40	45 50	5 dose		65	70	7

CHAPTER III. ETHYL CHLOROFORMATE

1	T	ABLE OF CONTENTS: CHAPTER III: ETHYL CHLOROFORMA	ТЕ
2	LIST OF TA	ABLES: ETHYL CHLOROFORMATE	III-4
3	EXECUTIV	'E SUMMARY: ETHYL CHLOROFORMATE	III-5
4	III.1. HUI	MAN TOXICITY DATA	III-6
5	III.1.1.	Acute Lethality	III-6
6 7	III.1.2. III.1.2.	Non-lethal Toxicity 1. Case Report	
8	III.1.3.	Developmental/Reproductive Toxicity	III-7
9	III.1.4.	Genotoxicity	III-7
10	III.1.5.	Carcinogenicity	III-7
11	III.1.6.	Summary	III-7
12	III.2. ANI	IMAL TOXICITY DATA	III-7
13 14 15	III.2.1. III.2.1. III.2.1.		III-7
16	III.2.2.	Developmental/Reproductive Toxicity	III-9
17	III.2.3.	Genotoxicity	III-9
18	III.2.4.	Carcinogenicity	III-9
19	III.2.5.	Summary	III-10
20	III.3. DAT	TA ANALYSIS AND AEGL-1	III-10
21	III.3.1.	Human Data Relevant to AEGL-1	III-10
22	III.3.2.	Animal Data Relevant to AEGL-1	III-10
23	III.3.3.	Derivation of AEGL-1	III-11
24	III.4. DA	TA ANALYSIS AND AEGL-2	III-11
25	III.4.1.	Human Data Relevant to AEGL-2	III-11
26	III.4.2.	Animal Data Relevant to AEGL-2	III-11
27	III.4.3.	Derivation of AEGL-2	III-11

1	III.5. DA	TA ANALYSIS AND AEGL-3 III-11
2	III.5.1.	Human Data Relevant to AEGL-3
3	III.5.2.	Animal Data Relevant to AEGL-3
4	III.5.3.	Derivation of AEGL-3III-12
5	III.6. SU	MMARY OF AEGLSIII-12
6	III.6.1.	AEGL Values and Toxicity Endpoints
7	III.6.2.	Comparison with Other Standards and GuidelinesIII-13
8	III.6.3.	Data Quality and Research Needs
9	III.7. RE	FERENCES
10	APPENDIX	III-A: DERIVATION OF AEGL VALUES FOR ETHYL CHLOROFORMATEIII-15
11	APPENDIX	III-B: DERIVATION SUMMARY FOR ETHYL CHLOROFORMATEIII-19
12 13	APPENDIX	III-C: CATEGORY PLOT FOR ETHYL CHLOROFORMATEIII-22

1 2		LIST OF TABLES: ETHYL CHLOROFORMATE	
$\frac{2}{3}$	TABLE III-S 1.	Summary of AEGL Values For Ethyl Chloroformate	III-6
4	TABLE III-1.	Exposure of Male Swiss-Webster Mice to Ethyl Chloroformate for 30 minutes*	III-9
5	TABLE III-2.	Summary of Acute Inhalation Data of Animals Exposed to Ethyl Chloroformate	III-10
6	TABLE III-3.	AEGL-1 Values for Ethyl Chloroformate	III-11
7	TABLE III-4.	AEGL-2 Values for Ethyl Chloroformate	III-11
8	TABLE III-5.	AEGL-3 Values for Ethyl Chloroformate	III-12
9	TABLE III-6.	Summary of AEGL Values for Ethyl Chloroformate	III-13

1 2

EXECUTIVE SUMMARY: ETHYL CHLOROFORMATE

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

6 No acute inhalation data consistent with the definition of AEGL-2 with both 7 concentration and duration parameters were available. Therefore, the AEGL-2 values for ethyl 8 chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an 9 estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on 10 the steep concentration curve with regard to lethality (1-hour rat LC_{50} : 189-200 ppm; rats 11 exposed to 47 ppm for 1-hr were clinically normal and had no mortality; Fisher et al., 1981).

11

13 One-third of the most conservative 1-hr LC₅₀ value in rats (145 ppm x 1/3 = 48 ppm) 14 (Vernot et al., 1977) was used as the point-of-departure for ethyl chloroformate AEGL-3 values. 15 This concentration is considered a threshold for lethality and is supported by the fact that no 16 deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and 17 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 18 19 effect is not expected to vary greatly between species or among individuals. Furthermore, inter-20 and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were 21 calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl 22 chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting 23 AEGL values were considered protective when compared with chemical-specific, repeated-24 exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-25 exposure time relationship for many irritant and systemically-acting vapors and gases may be 26 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 27 28 chemical-specific scaling exponent, temporal scaling was performed using n=3 when 29 extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to 30 longer time points (4-hours and 8-hours).

The calculated values are listed in the table below.

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TABLE III-S 1. Summary of AEGL Values For Ethyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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/m ³)	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.

References:

- 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.

17 III.1. HUMAN TOXICITY DATA

18 III.1.1. Acute Lethality

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

23 III.1.2. Non-lethal Toxicity

24 III.1.2.1. Case Report

25

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

31 thigh. He showered in a domestic shower, and developed ocular irritation and cough,

32 presumably because the warmth/humidity of the shower room produced ethyl chloroformate

33 fumes from the discarded clothing. Symptoms then subsided until 3.5 hours after the incident

34 when he experienced chest tightness and difficulty breathing. He was slightly cyanotic and had

1 audible crepitations at the base of his right lung; a reddened area was visible on the right thigh.

2 He was then hospitalized and subsequently developed pulmonary edema. He received medical

3 treatment and symptoms resolved over the next few days, with no long-term effects.

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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.

15 III.1.5. Carcinogenicity

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

20 III.1.6. Summary

21

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.

28 III.2. ANIMAL TOXICITY DATA

29 III.2.1. Acute Lethality

30 III.2.1.1. Rats

31

27

32 Groups of ten male Sprague Dawley rats were exposed to 365 or 730 ppm (nominal 33 concentrations) ethyl chloroformate for 1 hour (WARF Institute, Inc, 1978). A "semi-portable" 34 exposure chamber containing an exhaust fan for adjustable air flow was utilized. Ethyl 35 chloroformate was administered into the incoming air stream just before it entered the chamber 36 port, and exposure concentrations were calculated by dividing the total amount sprayed into the 37 chamber by the total cubic feet of air circulated through the chamber. Within one minute, and 38 throughout the 1-hour exposure period, animals in both groups had closed eyes and were 39 gasping. Animals in the 730 ppm group were in a semi-conscious state from 10-minutes into the 40 exposure through the end of the exposure period; all animals in the 730 ppm group died between 41 one and two hours post-exposure. All animals in the 365 ppm group died within 24-hours post-42 exposure. Hemorrhage in all lung lobes and hemorrhage in the trachea were noted during gross 43 necropsy.

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 Groups of five male and five female Fischer 344 rats were exposed to 0, 47, 153, 180, 2 245, or 270 ppm ethyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber. 3 followed by a 14-day observation period (Fisher et al., 1981). Ethyl chloroformate chamber 4 concentrations were monitored by real time variable pathlength infrared photospectrometry. The 5 LC₅₀ values were 189 (164-216) ppm for male rats, and 200 (173-232) ppm for female rats at 14 6 days post-exposure. Controls and rats in the 47 ppm group were clinically normal and showed 7 no treatment-related effects at necropsy. Body weight gain was decreased for surviving males 8 and females in the 153 and 180 ppm groups at day 7 and at termination. All rats in the 245 and 9 270 ppm groups died prior to scheduled sacrifice. Average relative lung weight of animals in the 10 245 and 270 ppm groups was approximately three-times greater than that of controls, and 11 corroborating lesions indicative of acute alveolar hemorrhage were noted. Relative lung weight 12 was also increased (magnitude not specified) in the 153 and 180 ppm groups. Red lung 13 coloration was noted in one male and one female in the 153 ppm group, and two females and one 14 male in the 180 ppm group. 15 16 Vernot et al. (1977) reported a 1-hour LC₅₀ of 145 (140-150) ppm for male Sprague-Dawley 17 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 18 19 analytically determined. No further experimental details were available. 20 21 Death occurred in 9/10 rats exposed to 200 ppm ethyl chloroformate for 1 hour (BASF, 22 1970a). Clinical signs included mucous membrane irritation and gasping. Lung congestion and 23 edema were noted at necropsy. 24 25 Death occurred in 11/12 rats exposed to an "atmosphere enriched or saturated" with ethyl chloroformate vapor at 20°C for 3 minutes. (BASF, 1970b). Clinical signs included vigorous 26 27 escape behavior, extremely severe mucous membrane irritation, and gasping. Lung congestion, 28 edema, and emphysema were noted at necropsy. 29 30 Groups of four male and four female Alderly Park SPF rats were exposed to 1 ppm 31 (twenty 6-hour exposures), 5 ppm (twenty 6-hr exposures), or 20 ppm (ten 6-hr exposures) ethyl 32 chloroformate vapor in isopropanol (Gage, 1970). The vapor concentrations were produced by 33 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.

38

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).

1 **III.2.1.2.** Mice

2

3 Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice 4 were exposed head only to concentrations of 0, 25, 50, 100, or 200 ppm ethyl chloroformate 5 aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 6 minute recovery period, while respiratory rates were monitored continuously. Undiluted ethyl 7 chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump 8 at a known rate. Aerosol was directed into a 6 L stainless steel chamber which was continuously 9 evacuated at 18.3 L/min. An RD₅₀ of 77.5 ± 5.4 ppm was calculated. Results are summarized in

- 10 Table III-1.
- 11

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			
*Carpenter, 1982						

*Carpenter, 1982

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14 **III.2.2.** Developmental/Reproductive Toxicity

16 Studies concerning the developmental/reproductive toxicity of ethyl chloroformate were 17 not located.

19 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).

25 **III.2.4.** Carcinogenicity

26 27 Groups of 50 male Sprague-Dawley rats were administered 1.5, 3.0, or 6.0 ppm ethyl 28 chloroformate by inhalation 6 hours/day, 5 days/week for a total of 30 exposures (Sellakumar et 29 al., 1987). There was no treatment-related effect on life span. A single (1/50) animal in the 6.0 30 ppm group developed a squamous cell carcinoma of the nasal mucosa; the time to tumor 31 appearance was 700 days. No nasal tumors were noted at 1.5 or 3.0 ppm.

32

33 Van Duuren et al. (1987) investigated the carcinogenicity of ethyl chloroformate in 34 female ICR/Ha Swiss mice by dermal and subcutaneous administration. Groups of 30 to 50 mice 35 received dermal applications of 3.0, 4.3, or 5.5 mg ethyl chloroformate in acetone three 36 times/week for 18-22 months. Tumor incidence was 0/50, 1/3 0, and 0/50, for the 3.0, 4.3, and 37 5.5 mg dose groups, respectively. In a dermal initiation-promotion assay, mice were

38 administered a single 5.5 mg dose of ethyl chloroformate, followed 2 weeks later by thrice

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 weekly applications of phorbol mysterate acetate (as a promoter) for 18-22 months. Tumors

2 were noted in 6/50 animals (4 papillomas, 2 squamous cell carcinomas), suggesting that ethyl

3 chloroformate may be active as a tumor promoter. In a subcutaneous injection study, mice were

4 injected in the left flank once weekly with 0.3 or 1.1 mg ethyl chloroformate in 0.1 mL

5 tricaprylin for 18-22 months. Tumor incidence was 1/50 for the 0.3 mg group (squamous cell

6 carcinoma) and 0/50 in the 1.1 mg group.

7

8 III.2.5. Summary

9

10 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

12 Fischer 344 rats, respectively (Fisher et al., 1981), and 145 ppm and 170 ppm for male and

13 female sprague Dawley rats, respectively (Vernot et al., 1977). Signs of toxicity included

14 decreased body weight gain, respiratory distress, increased lung weight and pulmonary edema.

15 A 30-min RD₅₀ of 77.5 ppm (nominal concentration) ethyl chloroformate was reported for male

16 Swiss-Webster mice (Carpenter, 1982). No data concerning developmental/reproductive toxicity

17 were located in the available literature. Ethyl chloroformate was negative in the Ames assay.

18 Carcinogenicity data (Van Duuren et al., 1987) suggest that ethyl chloroformate may be a tumor

19 promoter by the dermal route. Animal data are summarized in Table III-2.

20

T	TABLE III-2. Summary of Acute Inhalation Data of Animals Exposed to Ethyl Chloroformate							
Species	Concentration (ppm)	Exposure Duration	Effect	Reference				
Rat	47	1 hr	No effects	Fisher et al., 1981				
Rat-male	145	1 hr	LC_{50}	Vernot et al., 1977				
Rat-female	170	1 hr	LC_{50}	Vernot et al., 1977				
Rat-male	189	1 hr	LC_{50}	Fisher et al., 1981				
Rat-female	200	1 hr	LC_{50}	Fisher et al., 1981				
Rat	245	1 hr	10/10 dead	Fisher et al., 1981				
Rat	270	1 hr	10/10 dead	Fisher et al., 1981				
Rat	365 (nominal)	1 hr	10/10 dead	WARF Institute, Inc., 1978				
Rat	730 (nominal)	1 hr	10/10 dead	WARF Institute, Inc, 1978				
Mouse	77.5 (nominal)	30 min	RD ₅₀	Carpenter, 1982				

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22

23 III.3. DATA ANALYSIS AND AEGL-1

24 III.3.1. Human Data Relevant to AEGL-1

25 26

27

30

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).

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TABLE III-3. AEGL-1 Values for Ethyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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.

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9 III.4. DATA ANALYSIS AND AEGL-2

10 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.
- 15 III.4.2. Animal Data Relevant to AEGL-2
 - No animal data consistent with the definition of AEGL-2 were available.

19 III.4.3. Derivation of AEGL-2

20

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 with regard to lethality (1-hour rat LC₅₀: 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

- 28 these AEGL-2 values are presented in Appendix III-A.
- 29

TABLE III-4. AEGL-2 Values for Ethyl Chloroformate						
Classification 10-Min 30-Min 1-Hr 4-Hr 8-H				8-Hr		
AEGL-2	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)	

30 31

32 III.5. DATA ANALYSIS AND AEGL-3

33 III.5.1. Human Data Relevant to AEGL-3

- 34 35
- No human data consistent with the definition of AEGL-3 were available.

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

III.5.2. Animal Data Relevant to AEGL-3

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).

9 III.5.3. Derivation of AEGL-3

10 11

12

13 14 One-third of the most conservative 1-hr LC_{50} value in rats (145 ppm x 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

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

17 type of effect is not expected to vary greatly between species or among individuals.

18 Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-

19 3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3),

20 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

24 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et

25 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically

26 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

28 longer time points (4-hours and 8-hours The AEGL-3 values for ethyl chloroformate are

29 presented in Table III-5, and the calculations for these AEGL-3 values are presented in 30 Appendix III-A.

30 Appe 31

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

32

33 34

4 III.6. SUMMARY OF AEGLS

35 III.6.1. AEGL Values and Toxicity Endpoints

36

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-min	30-min	1-hr	4-hr	8-hr
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/m ³)	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.

III.7. REFERENCES

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1	
2	APPENDIX III-A: DERIVATION OF AEGL VALUES FOR
3	ETHYL CHLOROFORMATE
4	
5	DERIVATION OF AEGL-1 VALUES FOR ETHYL CHLOROFORMATE
6	
7	Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate.

1	DERIVATION OF AEGL-2 VALUES FOR ETHYL CHLOROFORMATE							
2 3	Vay study: Varnat a							
3 4	Key study: Vernot et al., 1977							
5	Toxicity Endpoint: 1/3 of the AEGL-3 values							
6 7	10-min AEGL-2:	8.8 nnm + 3 = 2.0 nnm						
8	<u>10-IIIII ALOL-2</u> .	8.8 ppm \div 3 = 2.9 ppm						
9	<u>30-min AEGL-2</u> :	$6.1 \text{ ppm} \div 3 = 2.0 \text{ ppm}$						
10	1 hr AECL 2	4.9 mm + 2 = 1.6 mm						
11 12	<u>1-hr AEGL-2</u> :	$4.8 \text{ ppm} \div 3 = 1.6 \text{ ppm}$						
13	4-hr AEGL-2:	$1.2 \text{ ppm} \div 3 = 0.40 \text{ ppm}$						
14								
15	<u>8-hr AEGL-2:</u>	$0.60 \text{ ppm} \div 3 = 0.20 \text{ ppm}$						

1	DERIVATION	OF AEGL-3 VALUES FOR ETHYL CHLOROFORMATE
23	Key study: Vernot et al.,	1977
4 5	Toxicity Endpoint: Estim	nated LC_{01} (1/3 the LC_{50}) from a 1-hour exposure in male rats.
6 7 8	LC50 = 145 ppm; 1/3 x	145 ppm = 48.3 ppm (point of departure)
9	Scaling:	
10 11	10-minutes and 30-minut	tes
12 13 14 15		$C^{3} \ge t = k$ (48.3 ppm) ³ \times 1 hr = 112769 ppm·hr
13 16 17 18 19	<u>4-hours and 8-hours:</u>	$C^{1} \ge t = k$ (48.3 ppm) ¹ \times 1 hr = 48.3 ppm·hr
20 21 22	Uncertainty Factors:	3 for interspecies variability3 for intraspecies variability
23 24 25 26 27 28	<u>10-min AEGL-3</u> :	$C^{3} \ge 0.167 \text{ hr} = 112769 \text{ ppm-hr}$ $C^{3} = 675263 \text{ ppm}$ C = 87.7 ppm 10-min AEGL-3 = 87.7/10 = 8.8 ppm
29 30 31 32 33 34 35	<u>30-min AEGL-3</u> :	$C^{3} \ge 0.5 \text{ hr} = 112769 \text{ ppm-hr}$ $C^{3} = 225538 \text{ ppm}$ C = 60.9 ppm 30-min AEGL-3 = 60.9/10 = 6.1 ppm
36 37 38	<u>1-hr AEGL-3</u> :	1-hr AEGL-3 = 48.3/10 = 4.8 ppm
38 39 40 41 42 43 44	<u>4-hr AEGL-3:</u>	$C^{1} x 4 hr = 48.3 ppm hr$ $C^{1} = 12 ppm$ C = 12 ppm 4-hr AEGL-3 = 12/10 = 1.2 ppm

1	<u>8-hr AEGL-3:</u>	
2		$C^1 \ge 8 hr = 48.3 ppm hr$
3		$C^1 = 6.0 \text{ ppm}$
4		C = 6.0 ppm
5		8-hr AEGL-3 = $6.0/10 = 0.60$ ppm

APPENDIX III-B: DERIVATION SUMMARY FOR ETHYL CHLOROFORMATE

ACUTE EXPOSURE GUIDELINES FOR ETHYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR ETHYL CHLOROFORMATE				
10-Min	30-Min	1-Hr	4-Hr	8-Hr
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Stra	in/Number: NA			
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: NA				
Uncertainty Factors/Rationale: Interspecies = NA Intraspecies = NA (Alarie method requires no additional UF)				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA	Time Scaling: NA			
Data quality and research needs: Data were insufficient for derivation of AEGL-1 values. AEGL-1 values are not recommended.				

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-2 VALUES FOR ETHYL CHLOROFORMATE				
10-Min	30-Min	1-Hr	4-Hr	8-Hr
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 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/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 D	Derivation summary tal	ble		
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/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 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

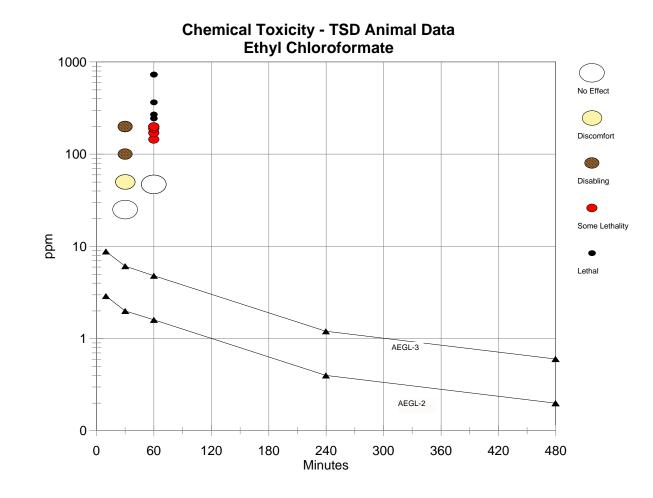
1

	AEGL-3 VALUE	S FOR ETHYL C	HLOROFORMATE	
10-Min	30-Min	1-Hr	4-Hr	8-Hr
8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm
				d skin corrosion data for armacol. 42: 417-424.
Test Species/Strain/Sez	x/Number: Sprague-I	Dawley rats/ males		
Exposure Route/Conce (1/3 the 1-hour male			hour AEGL-3) (1/3 x 145 pj	pm = 48.3 ppm)
Endpoint/Concentration		ted LC_{01} in rats afte	r a 1 hr-exposure/ 48.2	3 ppm/Estimated threshold
Effects: Male rat LC ₅₀ =	145 ppm; female rat	$LC_{50} = 170 \text{ ppm}$		
 Interspecies = 3: Intraspecies = 3: 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. Total UF = 10. 				
Modifying Factor: NA				
Animal to Human Dos	imetric Adjustment:	Insufficient data		
	where n=3 when ext ating to longer time p			ites and 30-minutes) and
Data Quality and Rese endpoint for AEGL		acute lethality stud	ies with consistent res	sults. Appropriate

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 III-C: CATEGORY PLOT FOR ETHYL CHLOROFORMATE



CHAPTER IV: PROPYL CHLOROFORMATE

1	TABLE OF CONTENTS: CHAPTER IV: PROPYL CHLOR(OFORMATE
2	LIST OF TABLES: PROPYL CHLOROFORMATE	IV-4
3	EXECUTIVE SUMMARY: PROPYL CHLOROFORMATE	IV-5
4	IV.1. HUMAN TOXICITY DATA	IV-6
5	IV.1.1. Acute Lethality	IV-6
6	IV.1.2. Non-lethal Toxicity	IV-6
7	IV.1.3. Developmental/Reproductive Toxicity	IV-6
8	IV.1.4. Genotoxicity	IV-6
9	IV.1.5. Carcinogenicity	IV-6
10	IV.1.6. Summary	IV-6
11	IV.2. ANIMAL TOXICITY DATA	IV-7
12	IV.2.1. Acute Lethality	IV-7
13 14	IV.2.1.1. Rats IV.2.1.2. Mice	
14	IV.2.1.2. Milee	
16	IV.2.2.1 Robits	
17	IV.2.3. Developmental/Reproductive Toxicity	IV-9
18	IV.2.4. Genotoxicity	IV-9
19	IV.2.5. Carcinogenicity	IV-9
20	IV.2.6. Summary	IV-9
21	IV.3. DATA ANALYSIS AND AEGL-1	IV-9
22	IV.3.1. Human Data Relevant to AEGL-1	IV-9
23	IV.3.2. Animal Data Relevant to AEGL-1	IV-9
24	IV.3.3. Derivation of AEGL-1	IV-9
25	IV.4. DATA ANALYSIS AND AEGL-2	IV-10
26	IV.4.1. Human Data Relevant to AEGL-2	IV-10
27	IV.4.2. Animal Data Relevant to AEGL-2	IV-10
28	IV.4.3. Derivation of AEGL-2	IV-10
29	IV.5. DATA ANALYSIS AND AEGL-3	IV-10
30	IV.5.1. Human Data Relevant to AEGL-3	IV-10

1	IV.5.2.	Animal Data Relevant to AEGL-3	IV-10
2	IV.5.3.	Derivation of AEGL-3	. IV - 11
3	IV.6. SU	MMARY OF AEGLS	IV-11
4	IV.6.1.	AEGL Values and Toxicity Endpoints	. IV-11
5	IV.6.2.	Comparison with Other Standards and Guidelines	IV-12
6	IV.6.3.	Data Quality and Research Needs	. IV-12
7	IV.7. RE	FERENCES	. IV-12
8	APPENDIX	K IV-A: DERIVATION OF AEGL VALUES FOR PROPYL CHLOROFORMATE	. IV-13
9	APPENDIX	K IV-B: DERIVATION SUMMARY FOR PROPYL CHLOROFORMATE AEGLS	. IV-17
10	APPENDIX	X IV-C: CATEGORY PLOT FOR PROPYL CHLOROFORMATE	IV-20
11 12 13	APPENDIX	K IV-D: BENCHMARK CONCENTRATION CALCULATION FOR PROPYL CHLOROFORMATE	. IV-21

1 2		LIST OF TABLES: PROPYL CHLOROFORMATE	
3	TABLE IV-S 1	. Summary of AEGL Values For Propyl Chloroformate IV	V-5
4	TABLE IV-1.	Exposure of Albino Rats to Propyl Chloroformate 1 hour	V -7
5	TABLE IV-2.	Exposure of Male Swiss-Webster Mice to Propyl Chloroformate for 30 minutes IV	V-8
6	TABLE IV-3.	AEGL-1 Values for Propyl Chloroformate IV-	-10
7	TABLE IV-4.	AEGL-2 Values for Propyl Chloroformate IV-	-10
8	TABLE IV-5.	AEGL-3 Values for Propyl Chloroformate IV-	-11
9	TABLE IV-6.	Summary of AEGL Values for Propyl Chloroformate IV-	-11

1 2 3

EXECUTIVE SUMMARY: PROPYL CHLOROFORMATE

3 Data were insufficient for derivation of AEGL-1 values for propyl chloroformate. Therefore,
 4 AEGL-1 values are not recommended.
 5

6 No acute inhalation data consistent with the definition of AEGL-2 with both concentration 7 and duration information were available. Therefore, the AEGL-2 values for propyl chloroformate 8 were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a 9 threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep 10 concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 11 333 ppm; 10/10 at 1000 ppm; Bio-Test, 1970).

12

13 The calculated 1-hour rat BMCL₀₅ of 216 ppm (Bio-Test Laboratories, Inc., 1970) was used 14 for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were 15 applied because propyl chloroformate is highly reactive and clinical signs are likely caused by a 16 direct chemical effect on the tissues; this type of effect is not expected to vary greatly between 17 species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each 18 were also applied when AEGL-3 values were calculated for the structural analogs, methyl 19 chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate 20 (Section VII.5.3), and these resulting AEGL values were considered protective when compared with 21 chemical-specific, repeated-exposure data for these analogs. A modifying factor of 2 was also 22 applied because the key study reported nominal, not analytical, concentrations and there are no 23 confirmatory studies. Thus, the total uncertainty/modifying factor is 20. The concentration-24 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 25 26 obtain conservative and protective AEGL values in the absence of an empirically derived chemical-27 specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter 28 time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-29 hours and 8-hours).

- 29 30
- 31
- 32

The calculated values are listed in the table below.

	TABLE IV-S 1. Summary of AEGL Values For Propyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	Endpoint (Reference)	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data	
AEGL-2 (Disabling)	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/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/m ³)	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)	

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

1

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

IV.1. HUMAN TOXICITY DATA

IV.1.1. Acute Lethality

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

IV.1.2. Non-lethal Toxicity

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

IV.1.3. Developmental/Reproductive Toxicity

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

29 IV.1.4. Genotoxicity

30

31 Genotoxicity studies regarding acute human exposure to propyl chloroformate were not 32 available. 33

34 **IV.1.5.** Carcinogenicity

35 36 Carcinogenicity studies regarding human exposure to propyl chloroformate were not 37 available.

38

39 IV.1.6. Summary

40 41

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Data concerning human exposure to propyl chloroformate are not available.

1 IV.2. ANIMAL TOXICITY DATA

2 **IV.2.1.** Acute Lethality

3 **IV.2.1.1. Rats**

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5 Groups of five male and five female young adult Charles River albino rats (avg. wt. 6 320 g) were exposed to nominal concentrations of 249, 333, 1000, 3077, or 21,538 ppm propyl 7 chloroformate vapor for one hour (Bio-Test Laboratories, Inc., 1970). Vapor was generated by 8 bubbling clean, dry air through undiluted propyl chloroformate. The resulting vapor was mixed 9 with additional dry air to obtain the desired vapor concentration. The test atmosphere was then 10 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 11 12 dividing the total weight of the propyl chloroformate vaporized by the total volume of air used during each inhalation exposure. No adverse effects were observed in the 249 ppm group during 13 14 exposure. Bloody nasal discharge and dyspnea were observed in the 333 ppm group toward the 15 end of the exposure period, while hyperactivity, clear nasal discharge, dyspnea, and salivation 16 were observed in the 1000, 3077, and 21,538 ppm groups. No adverse effects on body weight 17 were observed in any animals that survived the 14-day observation period; however, necropsy 18 revealed slight to moderate hyperemia in these animals. In animals that did not survive the 19 14-day observation period, necropsy revealed moderate to severe lung hyperemia. A 1-hour 20 LC_{50} of 410 ppm, BMCL₀₅ of 216 ppm, and BMC₀₁ of 229 ppm were calculated. Data are summarized in Table IV-1. 21

22

ŗ	TABLE IV-1. Ex	posure of Albino Rat	s 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

- 23 24

25 Death occurred in 3/10 rats exposed to 200 ppm propyl chloroformate for 1 hour (BASF, 26 1970a). Clinical signs included restlessness, mucous membrane irritation, and dyspnea. Acute 27 lung emphysema was noted at necropsy.

Propyl 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

Death occurred in 12/12 rats exposed to an "atmosphere enriched or saturated" with
propyl chloroformate vapor at 20°C 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 LD₅₀ value of 650 mg/kg was reported for Charles River albino rats (Bio-Test
Laboratories, Inc., 1970). Oral LD₅₀ values of 1212 mg/kg (BASF, 1980) and 872 mg/kg were
reported for Sprague-Dawley rats (BASF, 1970c).

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11 **IV.2.1.2. Mice**

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13 Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice 14 were exposed head only to concentrations of 0, 25, 50, 75, or 100 ppm propyl chloroformate 15 aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 16 minute recovery period, while respiratory rates were monitored continuously. Undiluted propyl 17 chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump 18 at a known rate. Aerosol was directed into a 6 L stainless steel chamber which was continuously 19 evacuated at 18.3 L/min. An RD₅₀ of 83.5 ± 2.17 ppm was calculated. Results are summarized 20 in Table IV-2.

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TABLE IV-2. Exposure of Male Swiss-Webster 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

24 IV.2.2. Nonlethal Toxicity

25 IV.2.2.1. Rabbits

26

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.

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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 **IV.2.3.** Developmental/Reproductive Toxicity 2

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.

17 IV.2.6. Summary

18 19 Animal toxicity data are limited. A 30-min RD₅₀ of 83.5 ppm (nominal concentration) 20 propyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). A 1-hr LC_{50} 21 of 410 ppm, BMCL₀₅ of 216 ppm, and BMC₀₁ of 229 ppm were calculated for Charles River albino rats (Bio-Test Laboratories, Inc., 1970). Propyl chloroformate is severely irritating to the 22 23 skin and eyes of albino rabbits (Bio-Test Laboratories, Inc., 1970). The compound was negative 24 in a Salmonella mutagenicity reversion assay. No data concerning developmental/reproductive 25 toxicity or carcinogenicity for exposure to propyl chloroformate were located in the available 26 literature.

28 **IV.3. DATA ANALYSIS AND AEGL-1**

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- IV.3.1. Human Data Relevant to AEGL-1 30
- 31 32

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

33 IV.3.2. Animal Data Relevant to AEGL-1

34 35

36

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

- 37 **IV.3.3.** Derivation of AEGL-1
- 38 39

AEGL-1 values for propyl chloroformate are not recommended due to insufficient data 40 (Table IV-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 IV-3. AEGL-1 Values for Propyl Chloroformate						
Classification10-Min30-Min1-Hr4-Hr8-Hr						
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

IV.4. DATA ANALYSIS AND AEGL-2

IV.4.1. Human Data Relevant to AEGL-2

No human data were available.

IV.4.2. Animal Data Relevant to AEGL-2

No robust animal data were available.

IV.4.3. Derivation of AEGL-2

14 No acute inhalation data consistent with the definition of AEGL-2 with both 15 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 16 considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is 17 18 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., 19 1970). The AEGL-2 values for propyl chloroformate are presented in Table IV-4, and the 20 21 calculations for these AEGL-2 values are presented in Appendix IV-A.

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TABLE IV-4. AEGL-2 Values for Propyl Chloroformate						
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr						
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/m ³)	0.47 ppm (2.4 mg/m ³)	

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26 IV.5. DATA ANALYSIS AND AEGL-3

IV.5.1. Human Data Relevant to AEGL-3

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

31 IV.5.2. Animal Data Relevant to AEGL-3

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A 1-hour rat LC₅₀ of 410 ppm and BMCL₀₅ of 216 ppm were calculated (Bio-Test
 Laboratories, Inc., 1970). No deaths were noted at 249 ppm.

1 **IV.5.3.** Derivation of AEGL-3

3 The calculated 1-hour rat BMCL₀₅ of 216 ppm (Bio-Test Laboratories, Inc., 1970) will be 4 used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will 5 be applied because propyl chloroformate is highly reactive and clinical signs are likely caused 6 by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly 7 between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors 8 of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, 9 methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl 10 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 11 12 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. 13 The concentration-exposure time relationship for many irritant and systemically-acting vapors 14 15 and gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten 16 Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an 17 empirically derived chemical-specific scaling exponent, temporal scaling was performed using 18 n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n=1 when 19 extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for propyl 20 chloroformate are presented in Table IV-5, and the calculations for these AEGL-3 values are 21 presented in Appendix IV-A.

22

TABLE IV-5. AEGL-3 Values for Propyl Chloroformate						
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr						
AEGL-3	20 ppm (100 mg/m ³)	14 ppm (70 mg/m ³)	11 ppm (55 mg/m ³)	2.7 ppm (14 mg/m ³)	1.4 ppm (7.0 mg/m ³)	

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IV.6. SUMMARY OF AEGLS

26 IV.6.1. AEGL Values and Toxicity Endpoints

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 2 and AEGL 2 values were based on a 1 hour PMCL in rate.

30 3, and AEGL-3 values were based on a 1-hour BMCL $_{05}$ in rats.

³¹

Т	TABLE IV-6. Summary of AEGL Values for Propyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	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/m ³)	0.47 ppm (2.4 mg/m ³)	
AEGL-3 (Lethal)	20 ppm (100 mg/m ³)	14 ppm (70 mg/m ³)	11 ppm (55 mg/m ³)	2.7 ppm (14 mg/m ³)	1.4 ppm (7.0 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.

1 2 **IV.6.2.** Comparison with Other Standards and Guidelines 3 4 No extant values were located for propyl chloroformate. 5 6 IV.6.3. **Data Quality and Research Needs** 7 8 Data are extremely limited. Human data do not exist and animal data are limited to rat acute 9 lethality studies and one mouse RD₅₀ study. The limited data set necessitated the application of a 10 modifying factor for AEGL value derivation. 11 12 **IV.7. REFERENCES** 13 14 BASF. 1970a. Report on the study of the acute inhalation of chloroformic acid propyl ester in rats. 15 Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, 16 Ludwigshafen, Germany. February 3, 1970. 17 18 BASF. 1970b. Report on the study of the acute inhalation hazard of chloroformic acid propyl ester in 19 rats (inhalation hazard test). Unpublished report, BASF Aktiengesellschaft, Experimental 20 Toxicology and Ecology, Ludwigshafen, Germany. February 3, 1970. 21 22 BASF. 1970c. Report on the study of the acute oral toxicity of chloroformic acid propyl ester in rats. 23 Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, 24 Ludwigshafen, Germany. February 3, 1970. 25 26 BASF. 1980. Report on the study of the acute oral toxicity. Unpublished report, BASF 27 Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. December 28 11, 1990. 29 30 BASF. 1988. Report on the study of chloroformic acid propyl ester in the Ames test (preincubation test 31 with Salmonella typhimurium) Unpublished Report. Project No. 40M0523/874090. September 32 7, 1988, on behalf of BG Chemie. 33 34 Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG 35 Industries, Inc. IBT No. A8345. OTS0570701. 36 37 Carpenter, C.P. 1982. Ethyl chloroformate, n-propyl chloroformate, Isobutyl chloroformate, Sec-butyl 38 chloroformate. Sensory Irritation. Report by Mellon Institute. Report to PPG Industries, Inc., 39 Chemicals Division. Report No. 82-49S. 40 41 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure 42 Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC. 43 44 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship 45 of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

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

DERIVATION	OF AEGL-2 VALUES FOR PROPYL CHLOROFORMATE				
Key study: Bio-Test Laboratories, Inc., 1970					
Toxicity Endpoint: 1/3 of the AEGL-3 values					
<u>10-min AEGL-2</u> :	20 ppm \div 3 = 6.7 ppm				
<u>30-min AEGL-2</u> :	14 ppm \div 3 = 4.7 ppm				
<u>1-hr AEGL-2</u> :	11 ppm \div 3 = 3.7 ppm				
<u>4-hr AEGL-2</u> :	2.7 ppm \div 3 = 0.90 ppm				
<u>8-hr AEGL-2:</u>	$1.4 \text{ ppm} \div 3 = 0.47 \text{ ppm}$				
	Key study: Bio-Test Lab Toxicity Endpoint: 1/3 of <u>10-min AEGL-2</u> : <u>30-min AEGL-2</u> : <u>1-hr AEGL-2</u> : <u>4-hr AEGL-2</u> :				

1	DERIVATION O	F AEGL-3 VALUES FOR PROPYL CHLOROFORMATE
2 3 4	Key study: Bio-Test Laborat	cories, Inc., 1970 ed BMCL ₀₅ (216 ppm) from a 1-hour exposure in rats.
4 5	Toxicity Enupoint. Calculate	a BMCL ₀₅ (210 ppm) nom a 1-nour exposure in fats.
6	Scaling:	
7	10-minutes and 30-minutes	
8		$C^3 x t = k$
9		$(216 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 10077696 \text{ ppm} \cdot \text{hr}$
10	4.1 1.0.1	
11	4-hours and 8-hours	
12		$C^{1} \mathbf{x} t = k$
13 14		$(216 \text{ ppm})^1 \text{ x } 1 \text{ hr} = 216 \text{ ppm} \cdot \text{hr}$
14	Uncertainty Factors:	
16	<u>oncontainty ractors</u> .	
17		3 for interspecies variability
18		3 for intraspecies variability
19		
20	Modifying Factor:	
21		2 for sparse data base and use of key study with nominal
22 23		concentrations
23 24	<u>10-min AEGL-3:</u>	
25	<u>to min riede 5</u> .	$C^3 \ge 0.167 \text{ hr} = 10,077,696 \text{ ppm} \cdot \text{hr}$
26		$C^3 = 60345485 \text{ ppm}$
27		C = 392 ppm
28		10-min AEGL-3 = 392/20 = 20 ppm
29		
30	<u>30-min AEGL-3</u>	-3
31		$C^3 \ge 0.5 \text{ hr} = 10,077,696 \text{ ppm} \cdot \text{hr}$
32 33		$C^3 = 20155392 \text{ ppm}$
33 34		C = 272 ppm 30-min AEGL-3 = 272/20 = 14 ppm
35		50 mm ALGE 5 272/20 14 ppm
36	<u>1-hr AEGL-3</u>	
37		1-hr AEGL-3 = 216/20 = 11 ppm
38		
39	4-hr AEGL-3	1
40		$C^1 \times 4 \text{ hr} = 216 \text{ ppm} \cdot \text{hr}$
41		$C^1 = 54 \text{ ppm}$
42 43		C = 54 ppm 4-hr AEGL-3 = 54/20 = 2.7 ppm
43 44		4-m ADOL- 5 = 54/20 = 2.7 ppm
77		

1	8-hr AEGL-3	
2		$C^1 \ge 8 hr = 216 ppm hr$
3		$C^1 = 27 \text{ ppm}$
4		C = 27 ppm
5		8-hr AEGL-3 = $27/20 = 1.4$ ppm

6 7

APPENDIX IV-B: DERIVATION SUMMARY FOR PROPYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR PROPYL CHLOROFORMATE DERIVATION SUMMARY

	AEGL-1 VALUES FOR PROPYL CHLOROFORMATE								
10-Min	10-Min 30-Min 1-Hr 4-Hr 8-Hr								
NR	NR	NR	NR	NR					
Reference: NA									
Test Species/Stra	in/Number: NA								
Exposure Route/	Concentrations /	Durations: NA							
Effects: NA	Effects: NA								
Endpoint/Concer	ntration/Rationa	le: NA							
Uncertainty Facto	ors/Rationale: N	4							
Modifying Factor	r: NA								
Animal to Huma	Animal to Human Dosimetric Adjustment: NA								
Time Scaling: NA									
- ·		AEGL-1 values are r	ot recommended for pro	Data quality and research needs: AEGL-1 values are not recommended for propyl chloroformate. Data are insufficient to derive 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

AEGL-2 VALUES FOR PROPYL CHLOROFORMATE									
10-Min 30-Min 1-Hr 4-Hr 8-Hr									
6.7 ppm	4.7 ppm	3.7 ppm	0.90 ppm	0.47 ppm					
Key Reference:	Key Reference:								
Bio-Test Laboratories,	Inc. 1970. Acute toxi	icity studies on n-propy	yl chloroformate. R	Report to PPG Industries,					
Inc. IBT No. A8345.									
Test Species/Strain/N	umber: See AEGL-3 l	Derivation summary ta	ble						
Exposure Route/Conc	entrations/Durations	: See AEGL-3 Derivat	tion summary table						
Effects: See AEGL-3 I	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/F	Rationale: See AEGL-	3 Derivation summary	table						
Modifying Factor: NA	A								
Animal to Human Dosimetric Adjustment: NA									
Time Scaling: See AE	GL-3 Derivation summ	nary table							
Data quality and research	arch needs: See AEG	L-3 Derivation summa	ry 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

1

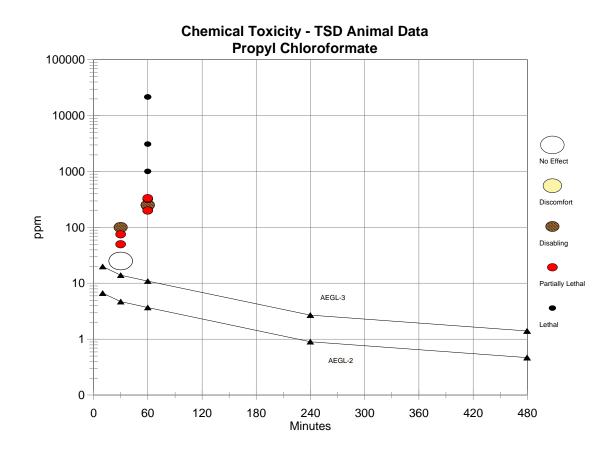
	AEGL-3 VALUES	S FOR PROPYL C	HLUKUFUKMAT	Ľ		
10-Min 30-Min 1-Hr 4-Hr 8-Hr						
20 ppm	14 ppm	11 ppm	2.7 ppm	1.4 ppm		
Key Reference:	•	•				
Bio-Test Laboratories, I Inc. IBT No. A8345.	Inc. 1970. Acute toxi	icity studies on n-pro	opyl chloroformate.	Report to PPG Industries,		
Test Species/Strain/Se	x/Number: Albino ra	ts/ 5/sex/group				
Exposure Route/Conce (Calculated BMCL ₀₅	entrations/Durations of 216 ppm was the p					
Endpoint/Concentration death for 1 hour expo		$_{405}$ in rats after a 1 hr	-exposure/ 216 ppm/	Estimated threshold for		
Effects: LC ₅₀ =410 ppm	n; BMC ₀₁ = 229 ppm;	$BMCL_{05} = 216 ppm$				
the tissues; this ty Furthermore, inte were calculated for (Section V.5.3), a	pe of effect is not exp r- and intraspecies und or the structural analog nd n-butyl chloroform	bected to vary greatly certainty factors of 3 gs, methyl chloroform nate (Section VII.5.3	between species or each were also appl mate (Section II.5.3)), and these resultin	ied when AEGL-3 values , isopropyl chloroformate		
Modifying Factor: 2: S reported	-		nominal, not analyti	cal, concentrations		
Animal to Human Dos	Ŷ					
	, where n=3 when ext ting to longer time po			utes and 30-minutes) and		
Data Quality and Rese						

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

APPENDIX IV-C: CATEGORY PLOT FOR PROPYL 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

APPENDIX IV-D: BENCHMARK CONCENTRATION CALCULATION FOR PROPYL CHLOROFORMATE

BMDS MODEL RUN

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

Dependent variable = Mean

Independent variable = Dose

2 Slope parameter is not restricted

Total number of observations = 3

5 Total number of records with missing values = 0

- Maximum number of iterations = 250
- 7 Relative Function Convergence has been set to: 1e-008
- B Parameter Convergence has been set to: 1e-008

0 User has chosen the log transformed model

Default Initial (and Specified) Parameter Values

background = 0intercept = -14.8454

slope = 2.39641

Asymptotic Correlation Matrix of Parameter Estimates

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

	Intercept	Slope
Intercept	NA	NĂ
Slope	NA	NA

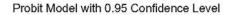
NA - This parameter's variance has been estimated at zero.

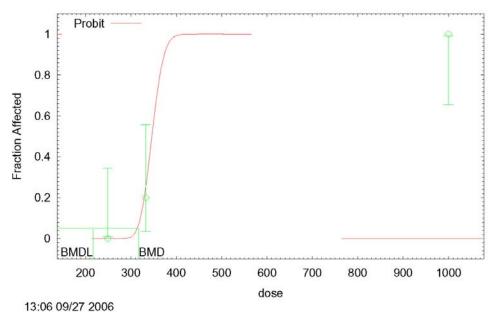
Par	ameter Estimates	5
Variable	Estimate	Std. Err
Background	0	NA
Intercept	-99.4462	20016.9
Slope	16.977	3446.36
*		

5 NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard 6 error.

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

$\frac{1}{2}$		Ana	alysis of Devi	ance Table		
2 3 4 5	Model	Log(like	,	Deviance	Test DF	P-value
4	Full model	-5.00		- (2052 000		0.0000
	Fitted model	-5.00		7.62052e-008	1	0.9998
6	Reduced mode	el -20.1	904	30.3727	2	<.0001
7	AIC: 14.008					
8 9						
			Goodness	of Fit		
10				Scaled		
11	Dose	EstProb.	Expected	Observed	Size	Residual
12						
13	249.0000	0.0000	0.000	0	10	-0.0001952
14	333.0000	0.2000	2.000	2	10	4.115e-007
15	1000.0000	1.0000	10.000	10	10	0
16	Chi-square $= 0$	D.00 DF =	1 P-value =	= 0.9998		
17	-					
18						
19	Benchmark Do	ose Computatio	n			
20		1				
21	Specified effec	t = 0.05				
22	Risk Type = I					
23	Confidence lev					
24	BMD = 317.61					
25		216.399				
26						
20						





CHAPTER V: ISOPROPYL CHLOROFORMATE

1	T	ABLE OF CONTENTS: CHAPTER V: ISOPROPYL CHLOROFOR	MATE
2	LIST OF	TABLES: ISOPROPYL CHLOROFORMATE	V-4
3	EXECUT	IVE SUMMARY: ISOPROPYL CHLOROFORMATE	V-5
4	V.1. HU	MAN TOXICITY DATA	V-6
5	V.1.1.	Acute Lethality	V-6
6	V.1.2.	Non-lethal Toxicity	V-6
7	V.1.3.	Developmental/Reproductive Toxicity	V-6
8	V.1.4.	Genotoxicity	V-6
9	V.1.5.	Carcinogenicity	V-6
10	V.1.6.	Summary	V-6
11	V.2. AN	IMAL TOXICITY DATA	V-6
12 13 14	V.2.	Acute Lethality 1.1. Rats 1.2. Mice	V-6
15	V.2.2	Nonlethal Toxicity	V-9
16	V.2.3.	Developmental/Reproductive Toxicity	V-10
17	V.2.4.	Genotoxicity	V-10
18	V.2.5	Carcinogenicity	V-10
19	V.2.6.	Summary	V-10
20	V.3. DA	TA ANALYSIS AND AEGL-1	V-11
21	V.3.1.	Human Data Relevant to AEGL-1	V-11
22	V.3.2.	Animal Data Relevant to AEGL-1	V-12
23	V.3.3.	Derivation of AEGL-1	V-12
24	V.4. DA	TA ANALYSIS AND AEGL-2	V-12
25	V.4.1.	Human Data Relevant to AEGL-2	V-12
26	V.4.2.	Animal Data Relevant to AEGL-2	V-12
27	V.4.3.	Derivation of AEGL-2	V-12

1	V.5. DATA ANALYSIS AND AEGL-3V-13
2	V.5.1. Human Data Relevant to AEGL-3V-13
3	V.5.2. Animal Data Relevant to AEGL-3V-13
4	V.5.3. Derivation of AEGL-3V-13
5	V.6. SUMMARY OF AEGLSV-13
6	V.6.1. AEGL Values and Toxicity EndpointsV-13
7	V.6.2. Comparison with Other Standards and GuidelinesV-14
8	V.6.3. Data Quality and Research NeedsV-15
9	V.7. REFERENCESV-15
10	APPENDIX V-A: DERIVATION OF AEGL VALUES FOR ISOPROPYL CHLOROFORMATEV-17
11	APPENDIX V-B: DERIVATION SUMMARY FOR ISOPROPYL CHLOROFORMATE AEGL V-21
12 13	APPENDIX V-C: CATEGORY PLOT FOR ISOPROPYL CHLOROFORMATEV-24

1		LIST OF TABLES: ISOPROPYL CHLOROFORMATE	
2 3	TABLE V-S 1.	Summary of AEGL Values For Isopropyl Chloroformate	V-5
4	TABLE V- 1.	Exposure of Albino Rats to Isopropyl Chloroformate for up to 1 hour	
5	TABLE V-2.	Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 30 minutes	
6	TABLE V-3.	Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 15 minutes	V-9
7	TABLE V-4.	Summary of Inhalation Data of Animals Exposed to Isopropyl Chloroformate	V-11
8	TABLE V-5.	AEGL-1 Values for Isopropyl Chloroformate	V-12
9	TABLE V-6.	AEGL-2 Values for Isopropyl Chloroformate	V-12
10	TABLE V-7.	AEGL-3 Values for Isopropyl Chloroformate	V-13
11	TABLE V-8.	Summary of AEGL Values for Isopropyl Chloroformate	V-14
12	TABLE V-9.	Extant Standards and Guidelines for Isopropyl Chloroformate	V-14
13			

1 2 3

EXECUTIVE SUMMARY: ISOPROPYL CHLOROFORMATE

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

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).

10 11

One-third of the 1-hr LC₅₀ value in rats (300 ppm x 1/3 = 100 ppm) (Bio Test

12 Laboratories, Inc., 1970) was used as the point-of-departure for isopropyl chloroformate AEGL-

13 3 values. This concentration is considered an estimated threshold for lethality. Interspecies and

14 intraspecies uncertainty factors of 3 each were applied because isopropyl chloroformate is highly

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

16 effect is not expected to vary greatly between species or among individuals. Thus, the total 17 uncertainty factor is 10. The concentration-exposure time relationship for many irritant and

18 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

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-

22 minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

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	TABLE V-S 1. Summary of AEGL Values For Isopropyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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/m ³)	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/m ³)	2.5 ppm (13 mg/m ³)	1.3 ppm (6.5 mg/m ³)	Estimated lethality threshold in the rat after a 1-hr 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.
- 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.

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2	
3	V.1. HUMAN TOXICITY DATA
4	V.1.1. Acute Lethality
5	
6	Information concerning death in humans following inhalation exposure to isopropyl
7	chloroformate is not available.
8	
9	V.1.2. Non-lethal Toxicity
10	Short tame tools monifie industrial hypigns monitoring for igomory lablan formate was
11 12	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
12	employee exposure during tank truck unloading operations. Exposures were considered
13	potential because, due to the acute toxicity of isopropyl chloroformate, employees wore full-face
14	supplied-air respirators, neoprene gloves, rubber boots, and neoprene clothing. Four personal
16	monitoring results ranged from 0.2 ppm to 5.6 ppm for the sampled activity (20-40 minutes).
17	Two area sample results were 0.06 ppm and 1.7 ppm.
18	Two area sample results were 0.00 ppm and 1.7 ppm.
19	V.1.3. Developmental/Reproductive Toxicity
20	villet Developmentalisteproductive remety
21	Developmental/reproductive studies regarding acute human exposure to isopropyl
22	chloroformate were not available.
23	
24	V.1.4. Genotoxicity
25	•
26	Genotoxicity studies regarding acute human exposure to isopropyl chloroformate were
27	not available.
28	
29	V.1.5. Carcinogenicity
30	
31	Carcinogenicity studies regarding human exposure to isopropyl chloroformate were not
32	available.
33	
34	V.1.6. Summary
35	
36	No reports regarding lethal toxicity, developmental/reproductive toxicity, genotoxicity,
37	or carcinogenicity were available. One industrial hygiene report was available; however, worker
38	exposures were considered "potential" due to protective clothing.
39	
40	V.2. ANIMAL TOXICITY DATA
41	V.2.1. Acute Lethality
42	V.2.1.1. Rats
43	
44	Groups of five male and five female young adult Charles River albino rats were exposed
45	to nominal concentrations of 300, 1640, or 15,600 ppm isopropyl chloroformate vapor for up to

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 one hour (Bio-Test Laboratories, Inc., 1970). Vapor was generated by bubbling clean, dry air
- 2 through undiluted isopropyl chloroformate (8-10 °C) in a water bath. The resulting vapor was
- 3 mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was
- 4 then introduced into the top of a 70 L Plexiglass inhalation chamber, dispersed by a baffle plate,
- 5 and exhausted at the bottom of the chamber. Average nominal concentrations were calculated by 6 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
- 8 gasping for breath within 15 minutes after the initiation of exposure and exhibited convulsions
- 9 and salivation. Low-concentration animals exhibited gasping and slight salivation. Necropsy of
- 10 animals that died revealed moderate to severe lung hyperemia. Rats that survived the 14-day
- 11 observation period exhibited no gross abnormalities at necropsy. The 1-hour LC₅₀ was
- 12 determined to be 300 ppm. Data are summarized in Table V-1.
- 13

TABLE V-1. Exposure of Albino Rats to Isopropyl Chloroformate for up to 1 hour*				
Nominal	Exposure Duration			
Concentration (ppm)	(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

14 15

16 Death occurred in 0/12 rats exposed to 200 ppm isopropyl chloroformate vapor for 1 hour 17 (BASF, 1968a). Clinical signs included slight mucosal irritation. No abnormalities were noted 18 at necropsy.

19

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.

24

25 In a repeated-exposure study (Collins and Proctor, 1984), groups of 4 male and 4 female 26 Sprague-Dawley rats were exposed to 0, 25, 50, or 100 ppm isopropyl chloroformate (analytical 27 concentrations) 6 hr/day for 5 days. Three high-concentration males died after 2, 4, and 5 days 28 of treatment, respectively, and three high-concentration females died after 3, 3, and 4 days of 29 treatment, respectively. Clinical observations on the day prior to death included lethargy, 30 labored breathing, staining around the muzzle, muscular weakness, and low body temperature. 31 At necropsy, uncollapsed lungs, fluid-filled tracheas, and red discoloration of various tissues 32 (associated with lack of exsanguination) were observed. This study is described in more detail in 33 Section V.2.2. 34

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).

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 The vapor concentrations were produced by injecting liquid at a known rate into a metered

2 stream of air with a controlled fluid-feed atomizer. No effects were observed at 5 ppm, nasal 3 irritation was observed at 20 ppm, respiratory difficulty, weight loss, and one death with lung 4 however a stream of a stream of the strea

hemorrhage were observed at 50 ppm, and two male rats died at 200 ppm. No further details
were provided.

6

7 In an acute oral toxicity study (Bio-Test Laboratories, Inc., 1971), Charles River albino 8 rats (2/sex/dose) were administered 118.5, 177.8, 266.7, or 400 mg/kg isopropyl chloroformate 9 by gavage and observed up to 14 days. There were no deaths at the low dose, 2/4 animals died at 10 177.8 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 11 12 were observed following dosing. Hemorrhages were observed in the stomachs of animals that 13 died during the study. An LD₅₀ of 177.8 mg/kg was calculated. An approximate oral LD₅₀ of 14 800 mm³ was reported in rats (BASF, 1968c).

16 **V.2.1.2. Mice**

17

15

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.

22 Undiluted isopropyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc

23 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.

25 Data are summarized in Table V-2.

26

TABLE V-2. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 30 minutes*						
Concentration (ppm)	Mortality within 24 hr.					
50	320/260	19	1/4			
75	225/150	33	3/4			
100	260/110	58	4/4			
200	275/55	80	4/4			
500	_	100	4/4 (died in exposure)			

Carpenter, 1982

27 28

29 In another study (Anderson, 1984), groups of four male Swiss-Webster mice were 30 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 31 syringe drive into a Pitt #1 generator. The glass exposure chamber and had a capacity of 2.2 L, 32 33 and air flow was 8.8 L/min. Baseline respiratory rates of each mouse were recorded for 10 34 minutes before exposure. Respiratory rates were recorded at 5 and 10 minutes into the 15 minute 35 exposure period, and percent respiratory depression was calculated from these values. Lung 36 weights were obtained at necropsy following death from exposure or scheduled sacrifice. In this 37 study, the RD₅₀ is calculated to be 375 ppm, and a 15-min. LC_{50} is estimated to be between 283

- 1 and 345 ppm. Concentration-related increases in lung weight, indicative of pulmonary edema,
- 2 were observed in treated animals compared to controls. Data are summarized in Table V-3.
- 3

TABLE V-3. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 15 minutes*							
Concentration (ppm)			% Decrease in Respiratory Rate		Mean Lung wt.	Lung/Body wt. Ratio (x100)	Mortality Within
Nominal	Analytical	5 Min	10 Min	Average	(g)	Katio (x100)	24 hr.
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

6

7 8 As briefly described in Section V.2.1.1, Collins and Proctor (1984) exposed groups of 9 4 male and 4 female Sprague-Dawley rats to 0, 25, 50, or 100 ppm isopropyl chloroformate 10 vapor 6 hr/day for 5 days. Isopropyl chloroformate vapor was generated using a sintered glass 11 bubbler supplied with pre-dried compressed air. Chamber concentrations were achieved by 12 adjusting the rate of air flow through the generator. The exposure chambers were 600 L 13 stainless-steel and glass whole body chambers. Actual test concentrations were determined 14 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 15 16 of air passing through the chamber. Mean daily chamber concentrations were 25, 50, and 100 17 ppm and corresponding measured concentrations were 22, 42, and 86 ppm, respectively. The 18 study authors' attribute these differences to the low accuracy of the orifice plate system used to 19 measure flow rate through the chamber. Three high-concentration males and three high-20 concentration females died during the exposure period. Clinical observations on the day prior to 21 death included lethargy, labored breathing, staining around the muzzle, muscular weakness, and 22 low body temperature. Treatment-related body weight loss was observed post-exposure in mid-23 and high concentration males and females and decreased body weight gain was observed in low-24 concentration males. Concentration-related increases (p<0.02) in lung weight were observed in 25 all treatment groups when compared to controls. In animals surviving to the end of the study, 26 enlarged bronchial lymph nodes were observed at necropsy in several animals in all 27 concentration groups. Focal alveolar edema and bronchiolitis were observed in several mid-28 concentration and all high-concentration animals. Peribronchiolar mononuclear cell infiltrate 29 was observed in low- and mid-concentration animals and is assumed to have preceded the 30 bronchiolitis observed in the high-concentration animals. Animals from all three treatment 31 groups exhibited focal pulmonary emphysema. 32

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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

V.2.3. Developmental/Reproductive Toxicity 2

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).

12 V.2.5 Carcinogenicity 13

Animal carcinogenicity data for isopropyl chloroformate were not available.

16 V.2.6. Summary

18 Animal toxicity data are limited. A 30-min RD₅₀ of 104 ppm (nominal concentration) 19 isopropyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982), while a 20 15-minute RD₅₀ of 375 ppm (analytical concentration) and estimated 15-min LC₅₀ of 283 to 21 345 ppm were determined for male Swiss-Webster mice (Anderson, 1984). A 1-hr LC_{50} of 300

22 ppm was calculated for Charles River albino rats (Bio-Test Laboratories, Inc., 1970). Repeated

23 exposure to 100 ppm isopropyl chloroformate resulted in death in Sprague-Dawley rats, while

24 lower concentrations resulted in body weight loss, increased lung weight, and bronchiolitis.

25 Increased lung weight and edema were consistently observed in decedents in most studies.

- 26 Isopropyl chloroformate was negative in the Ames assay. No data concerning
- 27 developmental/reproductive toxicity or carcinogenicity from exposure to isopropyl
- 28 chloroformate were located in the available literature. Animal inhalation data are summarized in 29 Table V-4.
- 30

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 V-4. Summary of Inhalation Data of Animals Exposed to Isopropyl Chloroformate						
	Concentration	Exposure				
Species	(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 hr	0/12 dead	BASF, 1968a		
Rat	300 (nominal)	1 hr	LC ₅₀	Bio Test Labs, Inc., 1970		
Rat	200	5 hrs	2/8 dead	Gage, 1970		
Mouse	283-345	15 min	LC ₅₀	Anderson, 1984		
Mouse	375	15 min	RD ₅₀	Anderson, 1984		
Mouse	104	30 min	RD ₅₀	Carpenter, 1982		
		Re	peated Exposure			
Rat	20	6 hr/d, 20 d	Nasal irritation	Gage, 1970		
Rat	50	6 hr/d, 11 d	Respiratory difficulty, weight loss, lung hemorrhage, 1/8 dead	Gage, 1970		
Rat	22	6 hr/d, 5 d	Decreased body weight gain, increased lung weight, enlarged bronchial lymph nodes, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema	Collins & Proctor, 1984		
Rat	42	6 hr/d, 5 d	Body weight loss, increased lung weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema	Collins & Proctor, 1984		
Rat	86	6 hr/d, 5 d	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 d treatment 3/4 females dead: deaths after 3, 3, and 5 d treatment	Collins & Proctor, 1984		

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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.

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.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).

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TABLE V-5. AEGL-1 Values for Isopropyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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

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V.4. DATA ANALYSIS AND AEGL-2

V.4.1. Human Data Relevant to AEGL-2

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

V.4.2. Animal Data Relevant to AEGL-2

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

V.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 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.

30

TABLE V-6. AEGL-2 Values for Isopropyl Chloroformate					
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr				8-Hr	
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm (4.2 mg/m ³)	0.43 ppm (2.2 mg/m ³)
ALGL-2	(30 mg/m^3)	(22 mg/m^3)	(17 mg/m^3)	(4.2 mg/m^3)	(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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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.5. **DATA ANALYSIS AND AEGL-3** 2

V.5.1. Human Data Relevant to AEGL-3

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

V.5.2. Animal Data Relevant to AEGL-3

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).

V.5.3. Derivation of AEGL-3

12 13 One-third of the 1-hr LC₅₀ value in rats (300 ppm x 1/3 = 100 ppm) (Bio-Test 14 Laboratories, Inc., 1970) will be used as the point-of-departure for isopropyl chloroformate 15 AEGL-3 values. This concentration is considered an estimated threshold for lethality and is 16 supported by the fact that 0/12 rats died when exposed to approximately 200 ppm for 1 hour 17 (BASF, 1968a). Interspecies and intraspecies uncertainty factors of 3 each will be applied 18 because isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct 19 chemical effect on the tissues; this type of effect is not expected to vary greatly between species 20 or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time 21 relationship for many irritant and systemically-acting vapors and gases may be described by 22 $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain 23 conservative and protective AEGL values in the absence of an empirically derived chemical-24 specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to 25 shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time 26 points (4-hours and 8-hours The AEGL-3 values for isopropyl chloroformate are presented in 27 Table V-7, and the calculations for these AEGL-3 values are presented in Appendix V-A.

28

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

29

30 The derived AEGL-3 values are considered protective because no deaths were noted in 31 rats exposed to 42 ppm isopropyl chloroformate 6 hours/day for 5 days (Collins and Proctor, 32 1984).

33

34 **V.6**. **SUMMARY OF AEGLS**

35 V.6.1. AEGL Values and Toxicity Endpoints 36

37 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 38 39 by dividing AEGL-3 values by 3, and AEGL-3 values were based on an estimated 1-hour 40 lethality threshold in rats. 41

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

TABLE V-8. Summary of AEGL Values for Isopropyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	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/m ³)	0.43 ppm (2.2 mg/m ³)
AEGL-3 (Lethal)	18 ppm (90 mg/m ³)	13 ppm (65 mg/m ³)	10 ppm (50 mg/m ³)	2.5 ppm (13 mg/m ³)	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

The following standards were located for isopropyl chloroformate.

TABLE V-9. Extant Standards and Guidelines for Isopropyl Chloroformate					
		Exposure Duration			
Guideline	10 Min	30 Min	1 Hr	4 Hrs	8 Hrs
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm
AEGL-3	18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm
ERPG-1 ^a	Insufficient Data				
ERPG-2 ^a	5 ppm				
ERPG-3 ^a	20 ppm				
Dutch MAC ^b					1 ppm

⁷ 8 9

^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

defined objectionable odor. No ERPG-1 for isopropyl chloroformate is derived because of insufficient data.

for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly

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.

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.6.3. Data Quality and Research Needs

Animal data are limited to acute and repeated-exposure rat inhalation studies and a two mouse RD_{50} studies. The support provided by the repeated-exposure studies adds to confidence in the derived AEGL values.

V.7. REFERENCES

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3 4	Toxicology Research Laboratory, Midland, MI.
5	NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute
6	Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
7	
8	SDU Uitgevers Nationale MAC List, 2000. (under the auspices of the Ministry of Social Affairs and
9	Employment), The Hague, The Netherlands.
10	
11	ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship
12	of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

APPENDIX V-A: DERIVATION OF AEGL VALUES FOR ISOPROPYL CHLOROFORMATE DERIVATION OF AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE AEGL-1 values are not recommended for isopropyl chloroformate due to insufficient data.

1	Derivation of AEGL	-2 Values for Isopropyl Chloroformate
2		
3		
4	Key study: Bio-Test I	Laboratories, Inc., 1970
5		
6	Toxicity Endpoint: 1/	3 of the AEGL-3 values
7		
8	10-min AEGL-2:	$18 \text{ ppm} \div 3 = 6.0 \text{ ppm}$
9		
10	30-min AEGL-2:	13 ppm \div 3 = 4.3 ppm
11		
12	<u>1-hr AEGL-2</u> :	$10 \text{ ppm} \div 3 = 3.3 \text{ ppm}$
13		
14	4-hr AEGL-2:	2.5 ppm \div 3 = 0.83 ppm
15		
16	8-hr AEGL-2:	$1.3 \text{ ppm} \div 3 = 0.43 \text{ ppm}$

1	DERIVATION OF AEC	GL-3 VALUES FOR ISOPROPYL CHLOROFORMATE						
2 3	Key study: Bio-Test Laborator	ries, Inc., 1970						
4 5	Toxicity Endpoint: Estimated LC_{01} (1/3 the LC_{50}) from a 1-hour exposure in male rats.							
6 7 8	LC50 = 300 ppm; 1/3 x 300 pp	pm = 100 ppm (point of departure)						
9 10 11	Scaling: <u>10-minutes and 30-minutes</u>	$C^3 \ge t = k$						
12 13		$(100 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr}$						
14 15 16 17	<u>4-hours and 8-hours</u>	$C^{1} \ge t = k$ $(100 \text{ ppm})^{1} \ge 1 \text{ hr} = 100 \text{ ppm} \cdot \text{hr}$						
18 19 20 21	Uncertainty Factors:	3 for interspecies variability3 for intraspecies variability						
22 23 24 25 26	<u>10-min AEGL-3</u> :	$C^{3} \ge 0.167 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr}$ $C^{3} = 5988024 \text{ ppm}$ C = 182 ppm 10-min AEGL-3 = 182/10 = 18 ppm						
27 28 29 30 31 32 33	<u>30-min AEGL-3</u>	$C^{3} \ge 0.5 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr}$ $C^{3} = 2,000,000 \text{ ppm}$ C = 126 ppm 30-min AEGL-3 = 126/10 = 13 ppm						
34 35 36	1-hr AEGL-3	1-hr AEGL-3 = $100/10 = 10 \text{ ppm}$						
37 38 39 40 41	<u>4-hr AEGL-3</u>	$C^{1} x 4 hr = 100 ppm hr$ $C^{1} = 25 ppm$ C = 25 ppm 4-hr AEGL-3 = 25/10 = 2.5 ppm						
42 43 44	8-hr AEGL-3	$C^1 \ge 8 hr = 100 ppm hr$						

1	$C^1 = 12.5 \text{ ppm}$
2	C = 12.5 ppm
3	8-hr AEGL-3 = $12.5/10 = 1.3$ 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

APPENDIX V-B: DERIVATION SUMMARY FOR ISOPROPYL CHLOROFORMATE AEGL

ACUTE EXPOSURE GUIDELINES FOR PROPYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE										
10-Min	10-Min 30-Min 1-Hr 4-Hr 8-Hr									
NR	NR NR NR NR									
Reference: NA										
Test Species/Stra	in/Number: NA									
Exposure Route/	Concentrations/	Durations: NA								
Effects: NA	Effects: NA									
Endpoint/Concentration/Rationale: NA										
Uncertainty Factors/Rationale:										
Interspecies										
Intraspecies										
(Alarie method r	equires no addit	ional UF)								
Modifying Factor	r: NA									
Animal to Human Dosimetric Adjustment: NA										
Time Scaling: NA										
	research needs: ient for deriving v		ot recommended for is	sopropyl chloroformate. Data						

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-2 VALUES FOR ISOPROPYL CHLOROFORMATE								
10-Min	30-Min	1-Hr	4-Hr	8-Hr				
6.0 ppm	6.0 ppm 4.3 ppm 3.3 ppm 0.83 ppm 0.43 ppm							
Key Reference:	Key Reference:							
Bio-Test Laboratories,	Inc. 1970. Acute vap	or inhalation toxicity s	tudy with IPCF in	albino rats. Report to PPG				
Industries, Inc. IBT N	o. N9129.							
Test Species/Strain/N	umber: See AEGL-3	Derivation summary ta	ble					
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table								
Effects: See AEGL-3 Derivation summary table								
Endpoint/Concentrat	ion/Rationale: 3-fold	reduction of AEGL-3	values. Considered	threshold for the inability to				
escape.								
Modifying Factor: N	A							
Animal to Human Do	simetric Adjustment	:NA						
Time Scaling: See AE	EGL-3 Derivation sum	nary table						
				re considered protective r 20 days (Gage, 1970).				

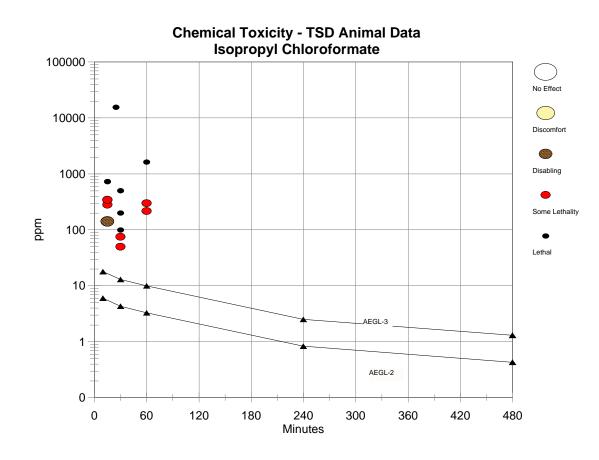
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

AEGL-3 VALUES FOR ISOPROPYL CHLOROFORMATE								
10-Min	30-Min	1-Hr	4-Hr	8-Hr				
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 Indu	stries, Inc. IBT No. 1	N9129.						
Test Species/Strain/Sex	/Number: Albino rat	ts/ 5/sex/group						
Exposure Route/Conce	ntrations/Durations	: Rats/Inhalation/1 h	our					
$(1/3 \text{ the 1-hour rat } LC_{50})$	was the point-of-depa	arture for AEGL-3) ($1/3 \ge 300 \text{ ppm} = 100$	ppm)				
Endpoint/Concentratio	n/Rationale: 1/3 the	1-hour rat LC ₅₀ / 10	0 ppm/Estimated three	shold for death for 1 hour				
exposure in rats								
Effects: LC ₅₀ =300 ppm								
Uncertainty Factors/Ra	ationale:							
Interspecies = 3:								
Intraspecies = 3:								
Isopropyl chloroformate								
tissues; this type of effect	et is not expected to v	ary greatly between	species or among indi	viduals.				
Modifying Factor: NA								
Animal to Human Dosi	metric Adjustment:	Insufficient data						
Time Scaling: $c^n x t = k$,	where n=3 when ext	rapolating to shorter	time points (10-minu	tes and 30-minutes) and $n =$				
	ng to longer time poin							
Data Quality and Resea	arch Needs: Sparse a	cute toxicity data se	t, with repeated-expos	sure studies available for				
support. Values are	e considered protectiv	ve because no deaths	were noted in rats exp	posed to 42 ppm, 6 hours/day				
for 5 days (Collins	and Prostor 1094)							

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 V-C: CATEGORY PLOT FOR ISOPROPYL CHLOROFORMATE



CHAPTER VI: ALLYL CHLOROFORMATE

1]	TABLE OF CONTENTS: CHAPTER VI: ALLYL CHLOROFORM	ATE
2	LIST OF T	ABLES: ALLYL CHLOROFORMATE	VI-4
3	EXECUTI	VE SUMMARY: ALLYL CHLOROFORMATE	VI-5
4	VI.1. HU	JMAN TOXICITY DATA	VI-6
5	V.1.1.	Acute Lethality	VI-6
6	V.1.2.	Non-lethal Toxicity	VI-6
7	V.1.3.	Developmental/Reproductive Toxicity	VI-6
8	V.1.4.	Genotoxicity	VI-6
9	V.1.5.	Carcinogenicity	VI-6
10	V.1.6.	Summary	VI-6
11	VI.2. AN	NIMAL TOXICITY DATA	VI-6
12	VI.2.1.	Acute Lethality	VI-6
13	VI.2.1	1.1. Rats	VI-6
14	VI.2.2	Developmental/Reproductive Toxicity	VI-7
15	VI.2.3.	Genotoxicity	VI-7
16	VI.2.4.	Carcinogenicity	VI-7
17	VI.2.5.	Summary	VI-8
18	VI.3. D.	ATA ANALYSIS AND AEGL-1	VI-8
19	VI.3.1.	Human Data Relevant to AEGL-1	VI-8
20	VI.3.2.	Animal Data Relevant to AEGL-1	VI-8
21	VI.3.3.	Derivation of AEGL-1	VI-8
22	VI.4. DA	ATA ANALYSIS AND AEGL-2	VI-8
23	VI.4.1.	Human Data Relevant to AEGL-2	VI-8
24	VI.4.2.	Animal Data Relevant to AEGL-2	VI-8
25	VI.4.3	Derivation of AEGL-2	VI-8

1	VI.5. DA	TA ANALYSIS AND AEGL-3
2	VI.5.1.	Human Data Relevant to AEGL-3VI-9
3	VI.5.2.	Animal Data Relevant to AEGL-3VI-9
4	VI.5.3.	Derivation of AEGL-3 VI-9
5	VI.6. SU	MMARY OF AEGLS
6	VI.6.1.	AEGL Values and Toxicity Endpoints
7	VI.6.2.	Comparison with Other Standards and Guidelines
8	VI.6.3.	Data Quality and Research Needs
9	VI.7. RE	FERENCES
10	APPENDIX	VI-A:DERIVATION OF AEGL VALUES FOR ALLYL CHLOROFORMATE VI-11
11	APPENDIX	VI-B: DERIVATION SUMMARY FOR ALLYL CHLOROFORMATE AEGLS VI-15
12	APPENDIX	VI-C: CATEGORY PLOT FOR ALLYL CHLOROFORMATE VI-18
13 14 15		X VI-D: BENCHMARK CONCENTRATION CALCULATION FOR ILOROFORMATE

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		LIST OF TABLES: ALLYL CHLOROFORMATE	
2 3	TABLE VI-S 1.	Summary of AEGL Values For Allyl Chloroformate	VI-5
4	TABLE VI-1.	Exposure of Sprague Dawley Rats to Allyl Chloroformate 1 hour	VI-7
5	TABLE VI-2.	AEGL-1 Values for Allyl Chloroformate	VI-8
6	TABLE VI-3.	AEGL-2 Values for Allyl Chloroformate	VI-9
7	TABLE VI-4.	AEGL-3 Values for Allyl Chloroformate	VI-9
8	TABLE VI-5.	Summary of AEGL Values for Allyl Chloroformate	VI-10
0			

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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5

EXECUTIVE SUMMARY: ALLYL CHLOROFORMATE

Data were insufficient for the derivation of AEGL-1 values for allyl chloroformate. 4 Therefore, AEGL-1 values are not recommended for allvl chloroformate.

6 No acute inhalation data consistent with the definition of AEGL-2 with both 7 concentration and duration information were available. Therefore, the AEGL-2 values for allyl 8 chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an 9 estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on 10 the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 33.7 11 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm; Stillmeadow, 1970).

12

13 The calculated 1-hour rat BMCL₀₅ of 21 ppm (Stillmeadow Inc., 1987) was used for 14 deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied 15 because allyl chloroformate is highly reactive and clinical signs are likely caused by a direct 16 chemical effect on the tissues; this type of effect is not expected to vary greatly between species 17 or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were 18 also applied when AEGL-3 values were calculated for the structural analogs, methyl 19 chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl 20 chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective 21 when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the 22 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, 23 24 ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL 25 values in the absence of an empirically derived chemical-specific scaling exponent, temporal 26 scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-27 minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

28

TABLE VI-S 1. Summary of AEGL Values For Allyl Chloroformate								
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr Endpoint (Referen						Endpoint (Reference)		
AEGL-1	NR	NR	NR	NR	NR	Insufficient data		
(Nondisabling)								
AEGL-2	1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm		1/3 the AEGL-3 values		
(Disabling)	(6.4 mg/m^3)	(4.3 mg/m^3)	(3.4 mg/m^3)	(0.88 mg/m^3)	(0.44 mg/m^3)	(Stillmeadow Inc., 1987)		
AEGL-3	3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm	1-hour rat BMCL ₀₅		
(Lethality)	(19 mg/m^3)	(13 mg/m^3)	(10 mg/m^3)	(2.6 mg/m^3)	(1.3 mg/m^3)	(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.

29 30

31 References

32

33 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure 34 Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.

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 - 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.

VI.1. HUMAN TOXICITY DATA

V.1.1. Acute Lethality

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

- 15 V.1.2. Non-lethal Toxicity
 - Information concerning non-lethal toxicity in humans following inhalation exposure to allyl chloroformate is not available.
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V.1.3. Developmental/Reproductive Toxicity

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

25 V.1.4. Genotoxicity

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

30 V.1.5. Carcinogenicity

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

35 V.1.6. Summary

36

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

39

40 VI.2. ANIMAL TOXICITY DATA

- 41 VI.2.1. Acute Lethality
- 42 VI.2.1.1. Rats
- 43
- 44 Groups of five male and five female Sprague Dawley rats were exposed to 33.7, 65.0,
- 45 77.7, 134.5, 175.7, or 233.3 ppm allyl chloroformate for 1 hour, followed by a 14-day
- 46 observation period (Stillmeadow Inc., 1987). Animals were exposed in a 200 liter stainless steel

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

- 1 dymanic flow inhalation chamber. The aerosol was generated by aspirating the allyl
- 2 chloroformate through a pressure operated spray nozzle. The concentrated aerosol was then
- 3 diluted with dried, filtered air and drawn into the exposure chamber. Air flow was maintained
- 4 through the use of a calibrated critical orifice, and air flow was recorded at 30 minute intervals
- 5 during the exposure period. The concentration of allyl chloroformate in the exposure
- 6 atmosphere was determined analytically at 30 and 60 minutes via gas chromatography. Clinical
- 7 signs were noted in all exposure groups and included decreased activity, body tremors,
- 8 constricted pupils, diarrhea, emaciation, epistaxis, gasping, lacrimation, nasal discharge,
- 9 piloerection, polyuria, ptosis, respiratory gurgle, and salivation. Nine of the ten rats exposed to
- 10 33.7 ppm gained weight over the 14 day observation period, and the tenth animal retained a
- 11 constant weight. All eight of the rats exposed to higher concentrations and surviving the 14-day
- 12 observation period lost weight. Gross necropsy findings included discoloration of the lungs,
- 13 pulmonary edema, clear fluid in the thoracic cavity, gas distended gastrointestinal tract, and
- 14 discoloration of gastrointestinal tract contents. An LC_{50} of 65.1 ppm, a BMCL₀₅ of 21 ppm, and
- 15 a BMC_{01} of 25.7 ppm were calculated. Data are summarized in Table VI-1.
- 16

TABLE VI-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	LC ₅₀						
BMCL ₀₅	21 ppm						
BMC ₀₁			25.7 ppm				

*Stillmeadow Inc., 1987

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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.

- 28 29 **VI.2.4.** (
- 30

VI.2.4. Carcinogenicity

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

¹⁷ 18

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.2.5. Summary

3 Animal toxicity data are limited to one well-conducted rat lethality study, yielding an 4 LC₅₀ of 65.1 ppm, a BMCL₀₅ of 21 ppm, and a BMC₀₁ of 25.7 ppm and showing clinical signs 5 consistent with severe irrritation. No reproductive/developmental toxicity data, genotoxicity 6 data, or carcinogenicity data were located. 7

8 VI.3. DATA ANALYSIS AND AEGL-1 9

VI.3.1. Human Data Relevant to AEGL-1 10

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

13 VI.3.2. Animal Data Relevant to AEGL-1

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

17 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).

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TABLE VI-2. AEGL-1 Values for Allyl Chloroformate								
Classification	Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr							
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.

> 32 33

34

22 23

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

35 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 36 37 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 38 39

(1-hour rat mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm;

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

- 1 Stillmeadow Inc., 1987). The AEGL-2 values for allyl chloroformate are presented in Table VI-
- 2 3, and the calculations for these AEGL-2 values are presented in Appendix VI-A.
- 3

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

4 5

6

7

8 9

10 11

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14

15

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.

VI.5.2. Animal Data Relevant to AEGL-3

A 1-hour rat LC_{50} of 65.1 ppm and a BMCL₀₅ of 21 ppm were calculated (Stillmeadow Inc., 1987).

16 VI.5.3. Derivation of AEGL-3

17 18 The calculated 1-hour rat BMCL₀₅ of 21 ppm (Stillmeadow Inc., 1987) will be used for 19 deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be 20 applied because allyl chloroformate is highly reactive and clinical signs are likely caused by a 21 direct chemical effect on the tissues; this type of effect is not expected to vary greatly between 22 species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each 23 were also applied when AEGL-3 values were calculated for the structural analogs, methyl 24 chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl 25 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 26 uncertainty factor is 10. The concentration-exposure time relationship for many irritant and 27 systemically-acting vapors and gases may be described by $c^n x t = k$, where the exponent, n, 28 29 ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL 30 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 30-31 32 minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-33 3 values for allyl chloroformate are presented in Table VI-4, and the calculations for these 34 AEGL-3 values are presented in Appendix VI-A.

35

TABLE VI-4. AEGL-3 Values for Allyl Chloroformate							
Classification10-Min30-Min1-Hr4-Hr8-Hr							
AEGL-3	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)		

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 VI.6. SUMMARY OF AEGLS

2 VI.6.1. AEGL Values and Toxicity Endpoints

3 4

5

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

6 three-fold reduction of AEGL-3 values. AEGL-3 values were based on the BMCL₀₅ from a 1-7 hour rat study.

8

TABLE VI-5. Summary of AEGL Values for Allyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	
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/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)	

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

9

VI.6.2. Comparison with Other Standards and Guidelines

No other extant values were located for allyl chloroformate.

VI.6.3. Data Quality and Research Needs

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.

VI.7. REFERENCES

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

APPENDIX VI-A:DERIVATION OF AEGL VALUES FOR ALLYL CHLOROFORMATE DERIVATION OF AEGL-1 VALUES FOR ALLYL CHLOROFORMATE AEGL-1 values for allyl chloroformate are not recommended.

1	DERIVATION	OF AEGL-2 VALUES FOR ALLYL CHLOROFORMATE
2		
3		
4	Key study: Stillmeadow	Inc., 1987
5		
6	Toxicity Endpoint: 1/3 of	f the AEGL-3 values
7		
8		
9	<u>10-min AEGL-2</u> :	$3.8 \text{ ppm} \div 3 = 1.3 \text{ ppm}$
10		
11	<u>30-min AEGL-2</u> :	$2.6 \text{ ppm} \div 3 = 0.87 \text{ ppm}$
12		
13	<u>1-hr AEGL-2</u> :	2.1 ppm \div 3 = 0.70 ppm
14		
15	<u>4-hr AEGL-2</u> :	$0.53 \text{ ppm} \div 3 = 0.18 \text{ ppm}$
16		
17	<u>8-hr AEGL-2:</u>	$0.26 \text{ ppm} \div 3 = 0.090 \text{ ppm}$

1 2 3	DERIVATION OF	AEGL-3 VALUES FOR ALLYL CHLOROFORMATE
4 5	Key study: Stillmeadow Inc., 19	987
5 6 7	Toxicity Endpoint: 1-hour rat B	SMCL ₀₅ (21 ppm)
7 8 9	Scaling:	
10 11	<u>10-min and 30-min</u>	$C^3 \ge t = k$
12 13		$(21 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 9261 \text{ ppm} \cdot \text{hr}$
14 15 16 17	<u>4-hrs and 8-hrs</u>	$C^{1} \ge t = k$ $(21 \text{ ppm})^{1} \ge 1 \text{ hr} = 21 \text{ ppm} \cdot \text{hr}$
18 19 20 21	Uncertainty Factors:	3 for interspecies variability3 for intraspecies variability
22 23 24 25 26 27	<u>10-min AEGL-3</u> :	$C^{3} \ge 0.167 \text{ hr} = 9261 \text{ ppm} \cdot \text{hr}$ $C^{3} = 55455 \text{ ppm}$ C = 38 ppm 10-min AEGL-3 = 38/10 = 3.8 ppm
28 29 30 31 32 33	<u>30-min AEGL-3</u>	$C^{3} \ge 0.5 \text{ hr} = 9261 \text{ ppm} \cdot \text{hr}$ $C^{3} = 18522 \text{ ppm}$ C = 26.4 ppm 30-min AEGL-3 = 26.4/10 = 2.6 ppm
33 34 35 36	<u>1-hr AEGL-3</u>	1-hr AEGL-3 = $21/10 = 2.1$ ppm
 37 38 39 40 41 42 	4-hr AEGL-3	$C^{1} x 4 hr = 21 ppm hr$ $C^{1} = 5.25 ppm$ C = 5.25 ppm 4-hr AEGL-3 = 5.25/10 = 0.53 ppm

1	<u>8-hr AEGL-3</u>	
2		$C^1 \ge 8$ hr = 21 ppm·hr
3		$C^1 = 2.63 \text{ ppm}^2$
4		C = 2.63 ppm
5		8-hr AEGL-3 = $2.63/10 = 0.26$ ppm
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

APPENDIX VI-B: DERIVATION SUMMARY FOR ALLYL
CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR PROPYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR ALLYL CHLOROFORMATE								
10 min	10 min 30 Min 1 Hr 4 Hour 8 Hour							
NR	NR	NR	NR	NR				
Key Reference: Chen	nical-specific data wer	e insufficient for derivin	g AEGL-1 values.					
Test Species/Strain/N	Number:							
Exposure Route/Con	centrations/Duration	s:						
Effects:								
Endpoint/Concentra	tion/Rationale:							
Uncertainty Factors /	Rationale:							
Modifying Factor:								
Animal to Human D	osimetric Adjustment	:						
Time Scaling:								
		mical-specific data were	e available for derivatio	n of AEGL-1 values				
for allyl chloroforr	nate.							

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-2 VALUES FOR ALLYL CHLOROFORMATE							
10-Min	30-Min	1-Hr	4-Hr	8-Hr			
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.090 ppm			
Key Reference:							
Stillmeadow Inc. 1987 Testing Laboratory. H IL. February 19, 1987.	ouston, TX. Project N	5 5		, U			
Test Species/Strain/N	umber: See AEGL-3	Derivation summary ta	ble				
Exposure Route/Conc	entrations/Durations	: See AEGL-3 Derivat	ion summary table				
Effects: See AEGL-3 I	Derivation summary ta	ble					
2 1	his approach is justifie		oncentration curve	with regard to lethality			
Uncertainty Factors/H	Rationale: See AEGL-	3 Derivation summary	table				
Modifying Factor: N	A						
Animal to Human Do	simetric Adjustment:	NA					
Time Scaling: See AE	GL-3 Derivation summ	nary table					
Data quality and rese	arch needs: See AEG	L-3 Derivation summa	ry 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

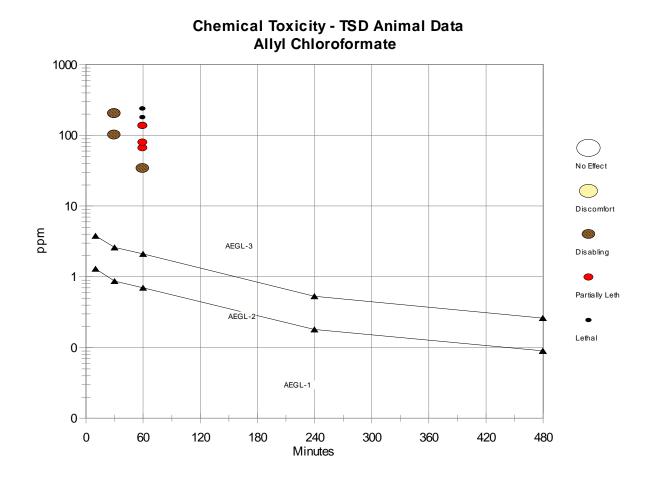
1

	AEGL-3 VALUE	S FOR ALLYL CH	ILOROFORMATE	
10-Min	30-Min	1-Hr	4-Hr	8-Hr
3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm
Key Reference:				
Stillmeadow Inc. 1987				
Testing Laboratory. He	ouston, TX. Project N	lo. 4438-86. Report	Submitted to PPG In	ndustries, Inc., Chicago, IL.
February 19, 1987. O	ГS0536028.			
Test Species/Strain/Se	x/Number: Sprague I	Dawley rats/ 5/sex/gi	oup	
Exposure Route/Conc	entrations/Durations	: Rats/Inhalation/1 h	lour	
(Calculated BMCL ₀₅ of	21 ppm was the point	-of-departure for AI	EGL-3)	
Endpoint/Concentrati	on/Rationale: BMCL	L_{05} in rats after a 1 hi	-exposure/ 21 ppm/I	Estimated threshold for
death for 1 hour exp	osure in rats			
Effects : LC ₅₀ =65.1 ppr	m; $BMC_{01} = 25.7 \text{ ppm}$; $BMCL_{05} = 21 ppn$	1	
Uncertainty Factors/R	ationale:			
Interspecies = 3:				
Intraspecies = 3:				
Allyl chloroformate is h				
				dividuals. Furthermore,
				values were calculated for
the structural analogs, n				
butyl chloroformate (Se				red protective when
compared with chemica	· · ·	posure data for thes	e analogs.	
Modifying Factor: NA				
Animal to Human Dos	· · · · · · · · · · · · · · · · · · ·			
				utes and 30-minutes) and
	ating to longer time p		-hours).	
Data Quality and Rese	earch Needs: Sparse d	lata set.		

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 VI-C: CATEGORY PLOT FOR 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

1

APPENDIX VI-D: BENCHMARK CONCENTRATION CALCULATION FOR ALLYL CHLOROFORMATE

BMDS MODEL RUN

The form of the probability function is: P[response] = Background+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function Dependent variable = Mean Independent variable = Dose Slope parameter is not restricted Total number of observations = 6Total number of records with missing values = 0Maximum number of iterations = 250Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 User has chosen the log transformed model Default Initial (and Specified) Parameter Values background = 0intercept = -7.2918slope = 1.72308Asymptotic Correlation Matrix of Parameter Estimates (*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix) Intercept slope Intercept 1 -1 1 Slope -1 **Parameter Estimates** Variable Estimate Std. Err. Background 0 NA Intercept -10.3866 2.68182 Slope 2.48392 0.621724 NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

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

Analysis of Deviance Table					
Model	Log(likelihood)	Deviance	Test DF	P-value	
Full model Fitted model	-16.0896	2.46858	4	0.6503	
Reduced model	-36 6519	2.40838 41 1245	4	<.0001	

AIC: 38.6478

Boodness of Fit	
Joouness of 1 in	

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

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

Benchmark Dose Computation

Specified effect = 0.05

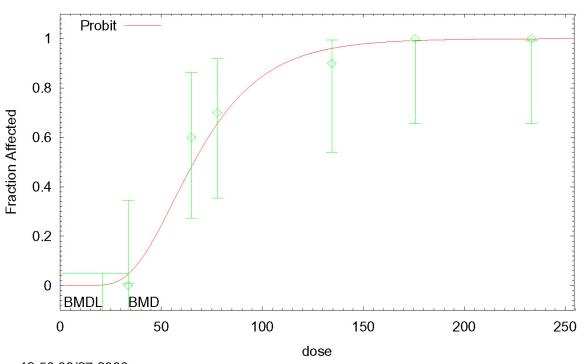
Risk Type = Extra risk

Confidence level = 0.95

BMD = 33.7621

BMDL = 21.098

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



Probit Model with 0.95 Confidence Level

12:56 09/27 2006

CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE 3

1TABLE OF CONTENTS : CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL2CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

3 4	LIST OF TABLES: CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE	VII-4
5 6	EXECUTIVE SUMMARY: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFO sec-BUTYL CHLOROFORMATE	
7	VII.1. HUMAN TOXICITY DATA	VII-6
8	VII.1.1. Acute Lethality	VII-6
9	VII.1.2. Non-lethal Toxicity	VII-6
10	VII.1.3. Developmental/Reproductive Toxicity	VII-6
11	VII.1.4. Genotoxicity	VII-6
12	VII.1.5. Carcinogenicity	VII-6
13	VII.1.6. Summary	VII-7
14	VII.2. ANIMAL TOXICITY DATA	VII-7
15	VII.2.1. Acute Lethality	VII-7
16	VII.2.2. Non-lethal Toxicity	
17	VII.2.3. Developmental/Reproductive Toxicity	
18	VII.2.4. Genotoxicity	VII-9
19	VII.2.5. Carcinogenicity	
20	VII.2.6. Summary	VII-9
21	VII.3. DATA ANALYSIS AND AEGL-1	VII-9
22	VII.3.1. Human Data Relevant to AEGL-1	
23	VII.3.2. Animal Data Relevant to AEGL-1	VII-9
24	VII.3.3. Derivation of AEGL-1	VII-9
25	VII.4. DATA ANALYSIS AND AEGL-2	VII-10
26	VII.4.1. Human Data Relevant to AEGL-2	VII-10
27	VII.4.2. Animal Data Relevant to AEGL-2	VII-10
28	VII.4.3. Derivation of AEGL-2	VII-10
29	VII.5. DATA ANALYSIS AND AEGL-3	VII-11
30	VII.5.1. Human Data Relevant to AEGL-	VII-11
	n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-2	

1	VII.5.2.	Animal Data Relevant to AEGL-3 VII-11
2	VII.5.3.	Derivation of AEGL-3
3	VII.6. S	UMMARY OF AEGLSVII-12
4	VII.6.1.	AEGL Values and Toxicity Endpoints
5	VII.6.2.	Comparison with Other Standards and Guidelines
6	VII.6.3	Data Quality and Research Needs
7	II.7. REF	FERENCES
8 9		VII-A: DERIVATION OF AEGL VALUES FOR n-BUTYL CHLOROFORMATE, CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE
10 11		VII-B: DERIVATION SUMMARY FOR n-BUTYL CHLOROFORMATE, ISOBUTYL ORMATE, and sec-BUTYL CHLOROFORMATE AEGLS
12 13		VII-C: CATEGORY PLOT FOR n-BUTYL CHLOROFORMATE, ISOBUTYL DRMATE, AND sec-BUTYL CHLOROFORMATE

LIST OF TABLES: CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

3			
4	TABLE VII-S 1.	Summary of AEGL Values for n-Butyl Chloroformate	.VII-5
5	TABLE VII-S 2.	Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate	.VII-6
6	TABLE VII-1.	Exposure of Male Swiss-Webster Mice to Isobutyl Chloroformate for 30 minutes	.VII-8
7	TABLE VII-2.	Exposure of Male Swiss-Webster Mice to sec-butyl Chloroformate for 30 minutes	.VII-8
8 9	TABLE VII- 3.	AEGL-1 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec Butyl Chloroformate	VII-10
10	TABLE VII-4.	AEGL-2 Values for n-Butyl Chloroformate	VII-10
11	TABLE VII-5.	AEGL-2 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate	VII-11
12	TABLE VII-6.	AEGL-3 Values for n-Butyl Chloroformate	VII-11
13	TABLE VII-7.	AEGL-3 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate	VII-12
14	TABLE VII-8.	Summary of AEGL Values for n-butyl Chloroformate	VII-12
15	TABLE VII-9.	Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate	VII-13

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	EXECUTIVE SUMMARY: n-BUTYL CHLOROFORMATE, ISOBUTYL
2	CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE
3	
3 4	
4 5	Data ware insufficient for the derivation of AECL 1 values for n butyl chloroformate
5 6	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.
	Therefore, AEGL-1 values are not recommended for n-butyl chloroformate.
7	No coute inholotion data consistant with the definition of AECL 2 with both
8 9	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
10	chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an
11 12	estimate of a threshold for irreversible effects (NRC, 2001). The resulting values are considered
12	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)
14	5 days (HRC 1990).
15	One third of the concentration where 1/10 rate diad after a 1 hr evenequire to a hutul
16 17	One-third of the concentration where $4/10$ rats died after a 1-hr exposure to n-butyl chloroformeta (200 mm v $1/2 = 66.7$ mm) (DASE 1070) was used as the point of departure for
17	chloroformate (200 ppm x $1/3 = 66.7$ ppm) (BASF, 1970) was used as the point-of-departure for n butul chloroformate AECL 2 values. This concentration is considered on estimated, threshold
18 19	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-
19 20	butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical
20 21	effect on the tissues; this type of effect is not expected to vary greatly between species or among
21 22	individuals. Thus, the total uncertainty factor was 10. The concentration-exposure time
22	relationship for many irritant and systemically-acting vapors and gases may be described by $c^n x$
23 24	t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain
24 25	conservative and protective AEGL values in the absence of an empirically derived chemical-
23 26	specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to
20 27	shorter time points (10-minutes and 30-minutes) and $n = 1$ when extrapolating to longer time
28	points (4-hours and 8-hours). The resulting values are considered protective because no rats died
28 29	when exposed to 5.1 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC
30	1990), and when exposed to 28.4 ppm 6 hours.day for 5 days (HRC 1990).
31	1770), and when exposed to 20.4 ppm o nours day for 5 days (fine 1770).
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	TABLE VII-S 1. Summary of AEGL Values for n-Butyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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/m ³)	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.

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1 Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or

2 AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl

3 chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and

4 mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar

5 toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD₅₀ values are 97 ppm for isobutyl

6 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.

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TABLE VII-S 2. Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate						
Classification	10-Min	30-Minute	1-Hr	4-Hr	8-Hr	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 ppm (10 mg/m ³)	By analogy to n-butyl chloroformate

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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.

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VII.1.2. Non-lethal Toxicity

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

23 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.

28 VII.1.4. Genotoxicity29

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

33 VII.1.5. Carcinogenicity34

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

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.1.6. Summary

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

VII.2. ANIMAL TOXICITY DATA

VII.2.1. Acute Lethality

10 <u>n-Butyl Chloroformate</u>

Death occurred in 4/10 rats exposed to 200 ppm n-butyl chloroformate for 1 hour (BASF,
 12 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 20°C. (BASF, 16 1970). Clinical signs included vigorous escape behavior, severe mucous membrane irritation, and gasping. Lung congestion and edema with hydrothorax were noted at necropsy.

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Oral LD₅₀ values of 1325 mg/kg (administered in 10% aqueous tragacanth gum emulsion) and 20 2120 mg/kg (administered in 20% aqueous tragacanth gum emulsion) were reported for rats (BASF, 21 1970). An oral LD₅₀ of 2610 mg/kg was reported for male and female Sprague-Dawley rats when n-22 butyl chloroformate was administered in olive oil (BASF, 1980). 23

24 VII.2.2. Non-lethal Toxicity

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26 <u>n-Butyl Chloroformate</u>

27 In an inhalation range-finding study, groups of five male and five female Sprague-Dawley 28 rats were exposed to 0, 2.9, 9.9, or 28.4 ppm n-butyl chloroformate 6 hours/day for 5 days (HRC, 29 1990). None of the rats died. There was a concentration-related decrease in food consumption in all 30 treatment groups. Clinical signs in the 9.9 and 28.4 ppm groups included concentration-dependent 31 sneezing, rubbing the snout with paws, closed or partially closed eyes, rapid breathing, licking the 32 inside of the mouth, and sniffing and noisy respiration between exposures. High-concentration rats 33 also exhibited prone position, lack of reaction to acoustic stimuli, and hypoactivity (after the first 34 exposure). Body weight loss was noted in high-concentration males throughout the study; whereas, 35 high-concentration females showed initial body weight loss, followed by decreased body weight 36 gain. Lung weights were increased in high-concentration males and females and in mid-37 concentration females.

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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

45 effects were reported.

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 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

7 chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a

8 known rate. Aerosol was directed into a 6 L stainless steel chamber which was continuously 9 evacuated at 18.3 L/min. An RD₅₀ of 97.0 \pm 5.82 ppm was calculated. Results are summarized in

9 evacuated at 18.5 L/min. An KD₅₀ of 97.0 \pm 5.82 ppm was calculated. Results are summarized in 10 Table VII-1.

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TABLE VII-1. Exposure of Male Swiss-Webster Mice to Isobutyl Chloroformate for 30 minutes*						
Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs			
25	265/20	25	0/4			
50	260/155	40	0/4			
100	310/155	50	0/4			
150	290/145	50	0/4			
200	295/85	71	0/4			

*Carpenter, 1982

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14 sec-Butyl Chloroformate

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Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice 16 17 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 18 19 recovery period, while respiratory rates were monitored continuously. Undiluted sec-butyl 20 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 21 22 evacuated at 18.3 L/min. An RD₅₀ of 117 ± 1.64 ppm was calculated. Results are summarized in 23 Table VII-2.

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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

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 VII.2.3. Developmental/Reproductive Toxicity 2

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.

15 VII.2.5. Carcinogenicity

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

20 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 n-butyl chloroformate, isobutyl chloroformate, or sec butyl chloroformate.

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31 VII.3. DATA ANALYSIS AND AEGL-1

32 VII.3.1. Human Data Relevant to AEGL-133

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

36 VII.3.2. Animal Data Relevant to AEGL-1 37

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

- 3940 VII.3.3. Derivation of AEGL-1
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42 Data are insufficient for the derivation of AEGL-1 values for n-butyl chloroformate,
 43 isobutyl chloroformate, or sec-butyl chloroformate. Therefore, AEGL-1 values are not

44 recommended (Table VII-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 VII-3. AEGL-1 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec Butyl Chloroformate						
Classification10-Min30-Min1-Hr4-Hr8-Hr						
AEGL-1	NR	NR				

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

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

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

VII.4.2. Animal Data Relevant to AEGL-2

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

12 VII.4.3. Derivation of AEGL-2

14 <u>n-Butyl Chloroformate</u>

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 nbutyl 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.

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TABLE VII- 4. AEGL-2 Values for n-Butyl Chloroformate						
Classification10-Min30-Min1-Hr4-Hr8-Hr						
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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These 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).

27 28

Isobutyl Chloroformate and sec-Butyl Chloroformate

29 Chemical-specific data were insufficient for the derivation of AEGL-2, values for

30 isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-

31 butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest

32 that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982)

33 (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for

34 sec-butyl chloroformate). Thus, the , AEGL-2 values for n-butyl chloroformate were adopted as

1 surrogates for isobutyl chloroformate and sec-butyl chloroformate. The AEGL-2 values for

- 2 isobutyl chloroformate and sec-butyl chloroformate are presented in Table VII-5.
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TABLE VII-5. AEGL-2 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate							
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr						
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.

VII.5.2. Animal Data Relevant to AEGL-3

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

16 VII.5.3. Derivation of AEGL-3

18 <u>n-Butyl Chloroformate</u>

19 20

20 One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl 21 chloroformate (200 ppm x 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 22 23 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 24 25 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 26 27 relationship for many irritant and systemically-acting vapors and gases may be described by cⁿ x 28 t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain 29 conservative and protective AEGL values in the absence of an empirically derived chemical-30 specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to 31 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 32 33 Table VII-6, and the calculations for these AEGL-3 values are presented in Appendix VII-A.

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TABLE VII-6. AEGL-3 Values for n-Butyl Chloroformate							
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr						
AEGL-3	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)		

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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).

6 Isobutyl Chloroformate and sec-Butyl Chloroformate

7 Chemical-specific data were insufficient for the derivation of AEGL-3, values for 8 isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-9 butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest 10 that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) 11 (male Swiss-Webster mouse RD₅₀ 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 12 13 surrogates for isobutyl chloroformate and sec-butyl chloroformate. The AEGL-3 values for 14 isobutyl chloroformate and sec-butyl chloroformate are presented in Table VII-7. 15

TABLE VII-7.AEGL-3 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate								
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr							
AEGL-3	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)			

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17 VII.6. SUMMARY OF AEGLS

18 VII.6.1. AEGL Values and Toxicity Endpoints

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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.

24 25

	TABLE VII-8. Summary of AEGL Values for n-butyl Chloroformate						
Classification10-Min30-Min1-Hr4-Hr8-1							
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/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)		

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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28 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

30 chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and

1 mouse RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar

2 toxicity. Thus, the AEGL-1, AEGL-2, and AEGL-3 values for n-butyl chloroformate were

3 adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.

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TABLE VII-9. Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate							
Classification	4-Hr	8-Hr					
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/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)		

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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VII.6.2. Comparison with Other Standards and Guidelines

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 9 The Dutch MAC for n-butyl chloroformate is 1 ppm [MAC (Maximaal Aanvaarde
 10 Concentratie) (Maximal Accepted Concentration)], is defined analogous to the ACGIH-TLV11 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).

No extant values were located for isobutyl chloroformate or sec-butyl chloroformate.

8 VII.6.3 Data Quality and Research Needs

No human data are available and animal data are sparse.

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1	APPENDIX VII-A: DERIVATION OF AEGL VALUES FOR n-BUTYL
2	CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and Sec-BUTYL
3	CHLOROFORMATE
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6	Derivation Of AEGL-1 Values For N-Butyl Chloroformate, Isobutyl Chloroformate,
7	and Sec-Butyl Chloroformate
8	
9	AEGL-1 values for n-butyl chloroformate, isobutyl chloroformate, and sec-butyl chloroformate
10	are not recommended.

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

AEGL-2 values for n-butyl chloroformate were adopted as AEGL-2 values
 chloroformate and sec-butyl chloroformate.

1 2 3	Derivation of AEGL-3 Values	for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec- Butyl Chloroformate
3 1	Kowatudan DASE 1070	
4 5	Key study: BASF, 1970 Toxicity Endpoint: 1-hour rat letha	lity thrachold actimate
6	Toxicity Endpoint. T-nour fat letna	ity threshold estimate
7	Scaling: 10-minutes and 30-minutes	,
8	Seaming. 10-minutes and 50-minutes	$C^3 \mathbf{x} t = k$
9		$(66.7 \text{ ppm})^3 \text{ x } 1 \text{ hr} = 296,741 \text{ ppm} \cdot \text{hr}$
10		(00.7 ppm) x 1 m 250,7 11 ppm m
11	4-hours and 8-hours	
12	- nouis und o nouis	$C^1 \mathbf{x} t = k$
13		$(66.7 \text{ ppm})^1 \text{ x } 1 \text{ hr} = 66.7 \text{ ppm} \cdot \text{hr}$
14		(con, pp)
15	Uncertainty Factors:	
16	2	3 for interspecies variability
17		3 for intraspecies variability
18		
19	<u>10-min AEGL-3</u> :	
20		$C^3 \ge 0.167 \text{ hr} = 296,741 \text{ ppm} \cdot \text{hr}$
21		$C^3 = 1,776,892 \text{ ppm}$
22		C = 121 ppm
23		10-min AEGL-3 = 121/10 = 12 ppm
24		
25	<u>30-min AEGL-3</u>	
26 27		$C^{3} \ge 0.5 \text{ hr} = 296,741 \text{ ppm} \cdot \text{hr}$ $C^{3} = 593482 \text{ ppm}$
27		C = 595482 ppm C = 84.0 ppm
28 29		30-min AEGL-3 = 84.0/10 = 8.4 ppm
30		30-IIIII ALOL-3 – 84.0/10 – 8.4 ppin
31	<u>1-hr AEGL-3</u>	
32	<u>1 in ALGE 5</u>	1-hr AEGL-3 = 66.7/10 = 6.7 ppm
33		
34	4-hr AEGL-3	
35		$C^1 \times 4 hr = 66.7 ppm hr$
36		$C^1 = 16.8 \text{ ppm}$
37		C = 16.8 ppm
38		4-hr AEGL-3 = 16.8/10 = 1.7 ppm
39		
40	<u>8-hr AEGL-3</u>	
41		$C^1 \ge 8$ hr = 66.7 ppm hr
42		$C^1 = 8.34 \text{ ppm}$
43		C = 8.34 ppm
44		8-hr AEGL-3 = $8.34/10 = 0.83$ ppm
45		
46 47	Isobutyl Chloroformate and sec-	
47 48	butyl chloroformate.	formate adopted as AEGL-3 values for isobutyl chloroformate and sec-
40	outyr chioroformate.	

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APPENDIX VII-B: DERIVATION SUMMARY FOR n-BUTYL CHLOROFORMATE,
ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR N-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES for n-BUTYL CHLOROFORMATE							
10 min	30 min	1 hr	4 hr	8 hr			
NR	NR	NR	NR	NR			
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.							
Test Species/Strain/N	Number:						
Exposure Route/Concentrations/Durations:							
Effects:							
Endpoint/Concentra	tion/Rationale:						
Uncertainty Factors /	Rationale:						
Modifying Factor:							
Animal to Human D	osimetric Adjustment						
Time Scaling:							
Data Quality and Research Needs: No chemical-specific data were available for derivation of AEGL-1 values for n-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

AEGL-1 VALUES for ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE							
10 min	30 min	1 hr	4 hr	8 hr			
NR	NR	NR	NR	NR			
Key Reference:	Key Reference:						
Test Species/Strain/N	Number:						
Exposure Route/Con	centrations/Duration	s:					
Effects:	Effects:						
Endpoint/Concentra	tion/Rationale:						
Uncertainty Factors/	Uncertainty Factors/Rationale:						
Modifying Factor:	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. No data were available to derive values 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 Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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AEGL-2 VALUES FOR n-BUTYL CHLOROFORMATE										
10-Min	30-Min	1-Hr	4-Hr	8-Hr						
4.0 ppm	4.0 ppm 2.8 ppm 2.2 ppm 0.57 ppm 0.28 ppm									
Key Reference:			·							
BASF. 1970. BASF A Gewerbetoxikologi	G, Gewerbehygienisch sche Vorprufung. Un			orokohlensaureester-						
Test Species/Strain/N	umber: See AEGL-3 I	Derivation summary ta	ible							
Exposure Route/Conc	entrations/Durations	: See AEGL-3 Deriva	tion summary table							
Effects: See AEGL-3 I	Derivation summary tal	ble								
Endpoint/Concentration to escape.	ion/Rationale: 3-fold	reduction of AEGL-3	values. Considered t	hreshold for the inability						
Uncertainty Factors/I	Rationale: See AEGL-	3 Derivation summary	/ table							
Modifying Factor: N.	A									
Animal to Human Do	simetric Adjustment:	NA								
Time Scaling: See AE	Time Scaling: See AEGL-3 Derivation summary table									
		loroformate for 6 hour	s/day, 5 days/week f	cause rats showed no for 4 weeks (HRC 1990),						

1

AEGL-2 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE					
10-Min	30-Min	1-Hr	4-Hr	8-Hr	
4.0 ppm	2.8 ppm	2.2 ppm	0.57 ppm	0.28 ppm	
Key Reference:					
	n-butyl chloroformate. oformate and sec-butyl		ate AEGL-2 values add	opted as AEGL-2 values	
Test Species/Strain/N	umber:				
Exposure Route/Cond	centrations/Durations	:			
Effects:					
Endpoint/Concentrat	ion/Rationale:				
Uncertainty Factors/I	Rationale:				
Modifying Factor: N.	A				
Animal to Human Dosimetric Adjustment: NA					
Time Scaling:					
AEGL-2 values for i sec-butyl chloroform isobutyl chloroforma Webster mouse RD ₅₀	sobutyl chloroformate nate are structural analo nte and sec-butyl chloro values are 97 ppm for	and sec-butyl chlorof ogs of n-butyl chlorof oformate are of simila isobutyl chloroform	Formate. However, isolormate and mouse RD ar toxicity (Carpenter, 1 ate and 117 ppm for se		

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

1

AEGL-3 VALUES FOR n-BUTYL CHLOROFORMATE						
10-Min	30-Min	1-Hr	4-Hr	8-Hr		
12 ppm	8.4 ppm	6.7 ppm	1.7 ppm	0.83 ppm		
Key Reference:						
BASF. 1970. BASF AC Gewerbetoxikologis	6, Gewerbehygienisch che Vorprufung. Unj			lorokohlensaureester-		
Test Species/Strain/Sex	/Number: Sprague I	Dawley rats/ 5/sex/gr	oup			
Exposure Route/Conce (1/3 the concentration	entrations/Durations ion causing death in 4			EGL-3)		
Endpoint/Concentration 66.7 ppm; Estimated t				after a 1 hr-exposure;		
Effects:						
				direct chemical effect on mong individuals.		
Modifying Factor: NA						
Animal to Human Dos	imetric Adjustment:	Insufficient data				
Time Scaling: $c^n x t = k$, n = 1 when extrapolat				utes and 30-minutes) and		
	to 5.1 ppm n-butyl ch	loroformate for 6 ho		e because rats showed no k for 4 weeks, and when		

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-3 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE					
10-Min 30-Min 1-Hr 4-Hr 8-Hr					
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/Number:

Exposure Route/Concentrations/Durations:

Effects:

Endpoint/Concentration/Rationale:

Uncertainty Factors/Rationale:

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

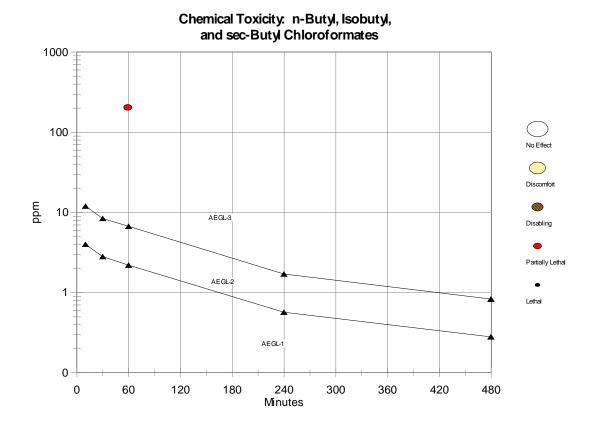
Time Scaling:

Data quality and research needs: Sparse data set. 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 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-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.

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APPENDIX VII-C: CATEGORY PLOT FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, AND sec-BUTYL CHLOROFORMATE



CHAPTER VIII: BENZYL CHLOROFORMATE

TABLE OF CONTENTS: CHAPTER VIII: BENZYL CHLOROFORMATE

2	LIST OF TA	ABLES: BENZYL CHLOROFORMATE	VIII-4
3	EXECUTIV	E SUMMARY: BENZYL CHLOROFORMATE	VIII-5
4	VIII.1. H	IUMAN TOXICITY DATA	VIII-6
5	VIII.1.1.	Acute Lethality	VIII-6
6	VIII.1.2.	Non-lethal Toxicity	VIII-6
7	VIII.1.3.	Developmental/Reproductive Toxicity	VIII-6
8	VIII.1.4.	Genotoxicity	VIII-6
9	VIII.1.5.	Carcinogenicity	VIII-6
10	VIII.1.6.	Summary	VIII-6
11	VIII.2. A	NIMAL TOXICITY DATA	VIII-6
12	VIII.2.1.	Acute Lethality	VIII-6
13	VIII.2.2.	Non-lethal Toxicity	VIII-7
14	VIII.2.3.	Developmental/Reproductive Toxicity	VIII-7
15	VIII.2.4.	Genotoxicity	VIII-7
16	VIII.2.5.	Carcinogenicity	VIII-7
17	VIII.2.6.	Summary	VIII-8
18	VIII.3. I	DATA ANALYSIS AND AEGL-1	VIII-8
19	VIII.3.1.	Human Data Relevant to AEGL-1	VIII-8
20	VIII.3.2.	Animal Data Relevant to AEGL-1	VIII-8
21	V.III.3.3.	Derivation of AEGL-1	VIII-8
22	VIII.4. I	DATA ANALYSIS AND AEGL-2	VIII-8
23	VIII.4.1.	Human Data Relevant to AEGL-2	VIII-8
24	VIII.4.2.	Animal Data Relevant to AEGL-2	VIII-8
25	VIII.4.3.	Derivation of AEGL-2	VIII-8
26	VIII.5. D	OATA ANALYSIS AND AEGL-3	VIII-9
27	VIII.5.1.	Human Data Relevant to AEGL-3	VIII-9
28	VIII.5.2.	Animal Data Relevant to AEGL-3	VIII-9
29	VIII.5.3.	Derivation of AEGL-3	VIII-9

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	VIII.6. SUMMARY OF AEGLSVIII-10
2	VIII.6.1. AEGL Values and Toxicity EndpointsVIII-10
3	VIII.6.2. Comparison with Other Standards and GuidelinesVIII-10
4	VIII.6.3. Data Quality and Research Needs
5	VIII.7. REFERENCES
6	APPENDIX VIII-A: DERIVATION OF AEGL VALUES FOR BENZYL CHLOROFORMATE VIII-12
7	APPENDIX VIII-B: DERIVATION SUMMARY FOR BENZYL CHLOROFORMATE AEGLS.VIII-15
8	APPENDIX VIII-C: CATEGORY PLOT FOR BENZYL CHLOROFORMATE

LIST OF TABLES: CHAPTER VIII: BENZYL CHLOROFORMATE 1 2 3 4 TABLE VIII-1. 5 TABLE VIII-2. 6 TABLE VIII-3. 7 TABLE VIII-4. 8 Summary of AEGL Values for Benzyl Chloroformate 10 TABLE VIII-5.

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EXECUTIVE 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).

14 The experimental concentration causing no deaths in rats (18.6 ppm) after a 4-hour 15 exposure (BASF, 1990) was used as the point-of-departure for benzyl chloroformate AEGL-3 16 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because benzyl 17 chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect 18 on the tissues; this type of effect is not expected to vary greatly between species or among 19 individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied 20 when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section 21 II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), 22 and the resulting AEGL values were considered protective when compared with chemical-23 specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The 24 concentration-exposure time relationship for many irritant and systemically-acting vapors and 25 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et 26 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 27 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when 28 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to 29 longer time points (8-hours) The 30-minute AEGL-3 value was adopted as the 10-minute AEGL-30 3 value. 31

	TABLE VIII-S 1. Summary of AEGL Values For Benzyl Chloroformate							
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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)		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 15 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.

26 VIII.1.6. Summary 27

28 No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive toxicity, 29 genotoxicity, or carcinogenicity were available.

30 31 VIII.2. ANIMAL TOXICITY DATA

32 VIII.2.1. Acute Lethality

34 Groups of five male and five female SPF Wistar rats were exposed to 18.6 or 84.6 ppm 35 (analytical concentrations) benzyl chloroformate for 4-hours followed by a 14-day observation 36 period (BASF, 1990). The nose-only exposures were performed in a 55 L glass-steel system; 37 animals were restrained in tubes and noses projected into the chamber. Benzyl chloroformate 38 concentrations were measured hourly during exposure using gas chromatography. Clinical signs 39 noted during exposure included accelerated respiration and restlessness in the low-concentration 40 group and irregular respiration, reddish nasal discharge, and restlessness in the high-41 concentration group. Clinical signs during the post-exposure observation period included 42 accelerated respiration and ruffled fur in low-concentration rats and intermittent respiration, 43 respiratory sounds, reddish nasal discharge, aggressiveness (males only), ruffled fur, and 44 deteriorated general state. All clinical signs had resolved by day 2 post-exposure in the 18.6 45 ppm group and by day 5 post-exposure in survivors in the 84.6 ppm group. Body weight gain

- 1 was decreased in high-concentration animals of both sexes during the first week after exposure;
- 2 however animals surviving to study termination adjusted to normal body weight. There were no
- 3 gross treatment-related effects noted at necropsy in animals surviving to study termination.
- 4 Gross examination of animals that died during the study showed lung emphysema with
- 5 hyperemia and tympanism of the intestinal tract. An approximate LC_{50} of 85 ppm was reported
- 6 for male and female rats combined. Mortality data are summarized in Table VIII-1.
- 7

TABLE VIII-1. Mortality in Rats Exposed to Benzyl Chloroformate for 4 hours*						
Cumulative lethality on day	18.6 p	pm	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	0/10)	5/	10		

*BASF, 1990.

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10 Death occurred in 0/12, 1/6, and 4/6 rats exposed to an "atmosphere enriched or 11 saturated" with benzyl chloroformate vapor at 20°C for 1, 3, and 8 hours, respectively (BASF, 12 1973). Clinical signs included vigorous escape behavior, mucous membrane irritation, and 13 dyspnea. Lung emphysema, dilation of the heart, and mottled liver were noted at necropsy.

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VIII.2.2. Non-lethal Toxicity

17 Information on non-lethal toxicity in animals following inhalation exposure to benzyl 18 chloroformate is not available.

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20 VIII.2.3. Developmental/Reproductive Toxicity 21

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

- 25 VIII.2.4. Genotoxicity
- 26

27 Benzyl chloroformate was negative in a reverse mutation assay in Salmonella 28 typhimuium strains TA 98, TA 100, TA1535, and TA 1537 in the presence and absence of S9 29 mix (Allen and Panfili, 1986). 30

31 VIII.2.5. Carcinogenicity

32 33

No information on the carcinogenicity of benzyl chloroformate was located.

1 VIII.2.6. Summary

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

9 VIII.3.1. Human Data Relevant to AEGL-1

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

13 VIII.3.2. Animal Data Relevant to AEGL-1

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

17 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).

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TABLE VIII-2. AEGL-1 Values for Benzyl Chloroformate					
Classification10-Min30-Min1-Hr4-Hr8-Hr					
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.

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- 24 VIII.4. DATA ANALYSIS AND AEGL-2
- 25 VIII.4.1. Human Data Relevant to AEGL-2
 - No human data consistent with the definition of AEGL-2 were available.
- 2829 VIII.4.2. Animal Data Relevant to AEGL-2
- 30 31

32

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

33 VIII.4.3. Derivation of AEGL-2

34

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

39 (4-hour rat mortality incidence: 0/10 at 18.6 ppm; 5/10 at 84.6 ppm BASF, 1990) and because

1 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.
- 3 4

TABLE VIII-3. AEGL-2 Values for Benzyl Chloroformate						
Classification 10-Min 30-Min 1-Hr 4-Hr 8-Hr						
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/m ³)	

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VIII.5. DATA ANALYSIS AND AEGL-3

VIII.5.1. Human Data Relevant to AEGL-3

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

VIII.5.2. Animal Data Relevant to AEGL-3

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).

17 VIII.5.3. Derivation of AEGL-318

19 The concentration causing no deaths in rats (18.6 ppm) after a 4-hour exposure (BASF, 20 1990) will be used as the point-of-departure for benzyl chloroformate AEGL-3 values. 21 Interspecies and intraspecies uncertainty factors of 3 each will be applied because benzyl 22 chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect 23 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 24 25 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), 26 27 and these resulting AEGL values were considered protective when compared with chemical-28 specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The 29 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 30 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 31 32 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when 33 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to 34 longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 35 value. The AEGL-3 values for benzyl chloroformate are presented in Table VIII-4, and the 36 calculations for these AEGL-3 values are presented in Appendix VIII-A.

TABLE VIII- 4. AEGL-3 Values for Benzyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr

AEGL-3 3.7 ppm 3.7 ppm 2.9 ppm (26 mg/m ³) (26 mg/m ³) (20 mg/m ³)) $\begin{array}{c} 1.9 \text{ ppm} \\ (13 \text{ mg/m}^3) \end{array} = \begin{array}{c} 0.93 \text{ ppm} \\ (6.5 \text{ mg/m}^3) \end{array}$
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VIII.6. SUMMARY OF AEGLS

VIII.6.1. AEGL Values and Toxicity Endpoints

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.

TABLE VIII-5. Summary of AEGL Values for Benzyl Chloroformate						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	1.2 ppm (8.7 mg/m ³)	1.2 ppm (8.7 mg/m ³)	0.97 ppm (6.7 mg/m ³)	0.63 ppm (4.3 mg/m ³)	0.31 ppm (2.2 mg/m ³)	
AEGL-3 (Lethal)	3.7 ppm (26 mg/m ³)	3.7 ppm (26 mg/m ³)	2.9 ppm (20 mg/m ³)	1.9 ppm (13 mg/m ³)	0.93 ppm (6.5 mg/m ³)	

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VIII.6.2. Comparison with Other Standards and Guidelines

- 14 15
- No extant values were located for benzyl chloroformate.
- 16 17

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18 VIII.6.3. Data Quality and Research Needs

20 No human toxicity data were available. The only animal toxicity data available were21 from two rat studies.

VIII.7. REFERENCES

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 Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 15, 1990.

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

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.

1	APPENDIX VIII-A: DERIVATION OF AEGL VALUES FOR BENZYL
2	CHLOROFORMATE
3	
4	DERIVATION OF AEGL-1 VALUES FOR BENZYL CHLOROFORMATE
5	
6	
7	AEGL-1 values for benzyl chloroformate are not recommended.

1		Derivation of AEGL-2 Values for Benzyl Chloroformate				
2						
3						
4	Key study: BASF,	1990				
5						
6	Toxicity Endpoint: 1/3 of the AEGL-3 values					
7						
8						
9	10-min AEGL-2:	$3.7 \text{ ppm} \div 3 = 1.2 \text{ ppm}$				
10						
11	30-min AEGL-2:	$3.7 \text{ ppm} \div 3 = 1.2 \text{ ppm}$				
12	<u></u> ,	en prese e en prese				
13	1-hr AEGL-2:	$2.9 \text{ ppm} \div 3 = 0.97 \text{ ppm}$				
14	<u>1 m / 12 02 2</u> .					
15	4-hr AEGL-2:	$1.9 \text{ ppm} \div 3 = 0.63 \text{ ppm}$				
16	<u>4-III ADOL-2</u> .	1.7 ppm \div 5 – 0.05 ppm				
		0.02 2 0.21				
17	<u>8-hr AEGL-2:</u>	$0.93 \text{ ppm} \div 3 = 0.31 \text{ ppm}$				

1	DERIVATION OF AEGL-3 VALUES FOR BENZYL CHLOROFORMATE				
2 3 4	Key study: BASF, 1990				
5 6	Toxicity Endpoint: Concen	tration causing no mortality in 4-hour rat study (18.6 ppm)			
7 8	Scaling:				
9	30-minutes and 1-hr				
10		$C^3 \ge t = k$			
11		$(18.6 \text{ ppm})^3 \text{ x 4 hr} = 25739 \text{ ppm} \cdot \text{hr}$			
12					
13	<u>8-hours</u>				
14		$C^1 \mathbf{x} t = k$			
15		$(18.6 \text{ ppm})^1 \text{ x 4 hr} = 74.4 \text{ ppm} \cdot \text{hr}$			
16					
17	Uncertainty Factors:				
18		3 for interspecies variability			
19		3 for intraspecies variability			
20					
21	<u>10-min AEGL-3</u> : 30-minut	e value adopted as 10-minute value = 3.7 ppm			
22 23	30-min AEGL-3				
23 24	<u>50-IIIIII AEGE-5</u>	$C^3 \ge 0.5 hr = 25739 ppm hr$			
24 25		$C^{3} = 51478 \text{ ppm}$			
23 26		C = 37.2 ppm			
20 27		30-min AEGL-3 = 37.2/10 = 3.7 ppm			
28		50-mm ALGE-5 57.2/10 5.7 ppm			
29	<u>1-hr AEGL-3</u>				
30	<u></u>	$C^3 \ge 1 hr = 25739 ppm hr$			
31		$C^3 = 25739 \text{ ppm}$			
32		C = 29.5 ppm			
33		1-hr AEGL-3 = $29/10 = 2.9$ ppm			
34		11			
35	4-hr AEGL-3				
36	4-hr AEGL-3 = 18.6/10	0 = 1.9 ppm			
37					
38	8-hr AEGL-3				
39		$C^1 \ge 8$ hr = 74.4 ppm hr			
40		$C^1 = 9.3 \text{ ppm}$			
41		C = 9.3 ppm			
42	8-hr AEGL-3 = $9.3/10$	= 0.93 ppm			

APPENDIX VIII-B: DERIVATION SUMMARY FOR BENZYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR BENZYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR BENZYL CHLOROFORMATE							
10 Min	10 Min 30 Min 1 Hr 4 Hr 8 Hr						
NR	NR	NR	NR	NR			
Key Reference: Cher	nical-specific data wer	e insufficient for derivir	ng AEGL-1 values.				
Test Species/Strain/N	Number:						
Exposure Route/Concentrations/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 benzyl chloro	for benzyl chloroformate.						

AEGL-2 VALUES FOR BENZYL CHLOROFORMATE					
10-Min 30-Min 1-Hr 4-Hr 8-Hr					
1.2 ppm 1.2 ppm 0.97 ppm 0.63 ppm 0.31 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/N	umber: See AEGL-3 I	Derivation summary ta	ble		
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 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).					
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table					
Modifying Factor: NA					
Animal to Human Dosimetric Adjustment: NA					
Time Scaling: See AE	Time Scaling: See AEGL-3 Derivation summary table				
Data quality and research needs: See AEGL-3 Derivation summary table.					

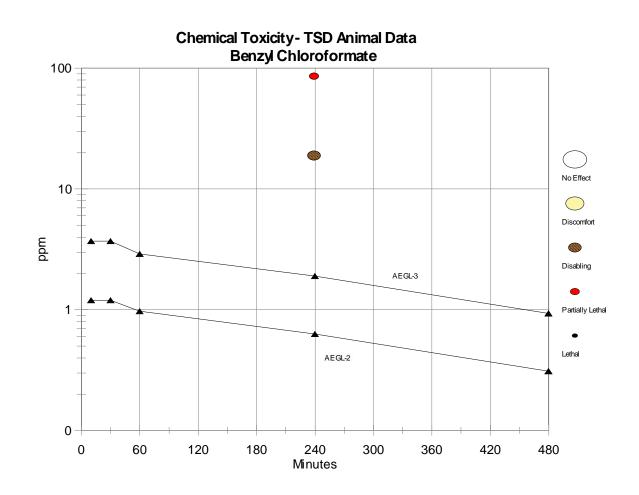
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	AEGL-3 VALUES	S FOR BENZYL C	HLOROFORMAT	Е
10-Min	30-Min	1-Hr	4-Hr	8-Hr
3.7 ppm	3.7 ppm	2.9 ppm	1.9 ppm	0.93 ppm
Key Reference: BASF. 1990. Study on exposure. Project No. 12				
Toxicology and Ecology				in, Experimental
Test Species/Strain/Sex	/Number: Sprague I	Dawley rats/ 5/sex/gr	roup	
Exposure Route/Conce (Concentration causing				GL-3)
Endpoint/Concentratio for 4 hour exposure		tration causing no n	nortality/18.6 ppm/E	stimated threshold for death
Effects : No mortality =	18.6 ppm; 5/10 dead =	= 84.6 ppm		
the structural analogs, m butyl chloroformate (Sec compared with chemical	highly reactive and c et is not expected to v neertainty factors of 3 ethyl chloroformate (etion VII.5.3), and th	ary greatly between each were also app Section II.5.3), isop ese resulting AEGL	species or among in lied when AEGL-3 v ropyl chloroformate values were conside	dividuals. Furthermore, values were calculated for (Section V.5.3), and n-
Modifying Factor: NA				
Animal to Human Dosi	metric Adjustment:	Insufficient data		
				nutes and 1-hour) and $n = 1$ adopted as the 10-minute
Data Quality and Resea	arch Needs: Sparse d	lata set.		

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APPENDIX VIII-C: CATEGORY PLOT FOR BENZYL CHLOROFORMATE



CHAPTER IX: PHENYL CHLOROFORMATE

1	T	ABLE OF CONTENTS: CHAPTER IX: PHENYL CHLOROFORM	ATE
2	LIST OF TA	ABLES CHAPTER IX: PHENYL CHLOROFORMATE	IX-4
3	EXECUTIV	/E SUMMARY: PHENYL CHLOROFORMATE	IX-5
4	IX.1. HU	MAN TOXICITY DATA	IX-6
5	IX.1.1.	Acute Lethality	IX-6
6	IX.1.2.	Non-lethal Toxicity	IX-6
7	IX.1.3.	Developmental/Reproductive Toxicity	IX-6
8	IX.1.4.	Genotoxicity	IX-6
9	IX.1.5.	Carcinogenicity	IX-6
10	IX.1.6.	Summary	IX-6
11	IX.2. AN	IMAL TOXICITY DATA	IX-6
12 13	IX.2.1. IX.2.1	Acute Lethality	
14	IX.2.2.	Non-lethal Toxicity	IX-9
15	IX.2.2		
16	IX.2.3.	Developmental/Reproductive Toxicity	
17	IX.2.4.	Genotoxicity	
18	IX.2.5.	Carcinogenicity	
19	IX.2.6.	Summary	IX-10
20	IX.3. DA	ATA ANALYSIS AND AEGL-1	IX-10
21	IX.3.1.	Human Data Relevant to AEGL-1	IX-10
22	IX.3.2.	Animal Data Relevant to AEGL-1	IX-10
23	IX.3.3.	Derivation of AEGL-1	IX-10
24	IX.4. DA	TA ANALYSIS AND AEGL-2	IX-10
25	IX.4.1.	Human Data Relevant to AEGL-2	IX-10
26	IX.4.2.	Animal Data Relevant to AEGL-2	IX-10
27	IX.4.3.	Derivation of AEGL-2	IX-11
28	IX.5. DA	TA ANALYSIS AND AEGL-3	IX-11
29	IX.5.1.	Human Data Relevant to AEGL-3	IX-11
30	IX.5.2.	Animal Data Relevant to AEGL-3	IX-11

1	IX.5.3.	Derivation of AEGL-3 IX-	·11
2	IX.6. SU	MMARY OF AEGLS IX-	·12
3	IX.6.1.	AEGL Values and Toxicity Endpoints IX-	·12
4	IX.6.2.	Comparison with Other Standards and Guidelines IX-	·12
5	IX.6.3.	Data Quality and Research Needs IX-	·12
6	IX.7. REI	FERENCES IX-	·13
7	APPENDIX	XIX-A: DERIVATION OF AEGL VALUES FOR PHENYL CHLOROFORMATE IX-	-14
8	APPENDIX	IX-B: DERIVATION SUMMARY FOR PHENYL CHLOROFORMATE AEGLS IX-	·17
9	APPENDIX	XIX-C: CATEGORY PLOT FOR PHENYL CHLOROFORMATE IX-	·20
10 11	APPENDIX	IX-D: BENCHMARK CONCENTRATION CALCULATION FOR PHENYL CHLOROFORMATE IX-	·21
12			

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LIST OF TABLES CHAPTER IX: PHENYL CHLOROFORMATE

3	TABLE IX-S 1.	Summary of AEGL Values For Phenyl Chloroformate	IX-5
4	TABLE IX-1.	Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours	IX-7
5	TABLE IX-2.	Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours	IX-8
6	TABLE IX-3.	Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours	IX-8
7	TABLE IX-4.	Exposure of Male Swiss-Webster Mice to Phenyl Chloroformate for 30 minutes	IX-9
8	TABLE IX-5.	AEGL-1 Values for Phenyl Chloroformate	IX-10
9	TABLE IX-6.	AEGL-2 Values for Phenyl Chloroformate	IX-11
10	TABLE IX-7.	AEGL-3 Values for Phenyl Chloroformate	IX-12
11	TABLE IX-8.	Summary of AEGL Values for Phenyl Chloroformate	IX-12

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EXECUTIVE 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).

13 14 The 4-hour rat BMCL₀₅ of 3.6 ppm from the combined BASF (1990) and Hoechst 15 (1989) studies was used as the point-of-departure for phenyl chloroformate AEGL-3 values. 16 Interspecies and intraspecies uncertainty factors of 3 each were applied because phenyl 17 chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect 18 on the tissues; this type of effect is not expected to vary greatly between species or among 19 individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied 20 when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section 21 II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), 22 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 23 24 concentration-exposure time relationship for many irritant and systemically-acting vapors and 25 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et 26 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 27 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when 28 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to 29 longer time points (8-hours) The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 30 value.

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	TABLE IX-S 1. Summary of AEGL Values For Phenyl Chloroformate					
Classification10-Min30-Min1-Hr4-Hr8-Hr				8-Hr	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)	0.060 ppm (0.38 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.

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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

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.

27 **IX.1.6.** Summary

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

- 32 IX.2. ANIMAL TOXICITY DATA
- 33 IX.2.1. Acute Lethality
- 34 IX.2.1.1. Rats
- 35

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 glasssteel 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

43 discharge, escape attempts, and decreased pain reflex in mid- and high-concentration animals.

44 Clinical signs during the post-exposure observation period included accelerated respiration,

45 respiratory sounds, reddish ocular and nasal discharge and aggressiveness in all exposure groups.

1 In addition, squatting position, urine-contaminated fur, high-stepping gait, and deteriorated 2 general state were noted in mid- and high-concentration animals, and piloerection was noted 3 only in high-concentration animals. All clinical signs in low-concentration animals had resolved 4 by day 3 post-exposure; clinical signs persisted through observation day 13 in mid- and high-5 concentration animals. Body weight gain was decreased (compared to historical controls) in 6 low-concentration males and females and in mid-concentration males during the first week after 7 exposure: however animals surviving to study termination adjusted to normal body weight. 8 Body weight gain of mid-concentration females and high-concentration males and females was 9 decreased during week one of the observation period; all animals in these groups died by week 2. 10 There were no gross treatment-related effects noted at necropsy in low-concentration males and 11 females surviving to study termination. One male rat in the mid-concentration group exhibited 12 small atelectatic areas in the lung. Gross examination of animals that died during the study 13 showed lung emphysema with hyperemia and pneumonia and necrotic foci and grey-brown 14 lobular periphery of the liver. Four-hour LC₅₀ values of 46.8 ppm, 15.8 ppm and 28 ppm (95% 15 CI: 16-48 ppm) were reported for male rats, female rats, male and female rats combined, 16 respectively. BMCL₀₅ and BMC₀₁ values were calculated and are presented in Table IX-1; 17 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

concentrations in the lower portionsummarized in Table IX-1.

20

TABLE IX-1. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*					
Males Females Combined Males and Fe					
15.6 ppm	0/5	2/5	2/10		
74.9 ppm	4/5	5/5	9/10		
159.3 ppm	5/5	5/5	10/10		
LC ₅₀	46.8 ppm	15.8 ppm	28 ppm		
BMCL ₀₅	7.45 ppm	0.49 ppm	3.2 ppm		
BMC ₀₁	45.8 ppm	8.99 ppm	41.5 ppm		

*BASF, 1990

21 22

23 Groups of five male and five female SPF Wistar rats were exposed to 1.76, 44.5, 97, 156 or 311 ppm 24 (analytical concentrations) phenyl chloroformate for 4-hours followed by a 14-day observation 25 period (Hoechst, 1989). The nose-only exposures were performed in a 60-L glass and stainless steel 26 exposure chamber operated under dynamic flow conditions. Phenyl chloroformate concentrations 27 were measured every 60 minutes during exposure using gas chromatography. Clinical signs noted in 28 all treatment-groups in a concentration-related manner included irregular respiration, gasping, 29 wheezing, staggered gait, squatting posture, ruffled fur, cyanosis, shivering, squinting, red ocular 30 discharge, salivation, red nasal discharge, and sneezing. Additionally, foamy nasal discharge and 31 corneal cloudiness were noted in the 156 and 311 ppm groups. Body weight gain was decreased in 32 both sexes after exposure, but animals surviving to study termination regained initial body weight. 33 Light beige-colored lungs with dark red foci on the lungs were noted at necropsy in animals 34 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 35

Phenyl Chloroformate

- 1 liver and adrenals, and light-colored spleen. Four hour LC₅₀ values of 38.9 ppm and 43 ppm were
- 2 calculated for males and females, respectively. Mortality data are summarized in Table IX-2.
- 3

TABLE	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

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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.

10 11

ТАВ	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

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.

- 5 Death occurred in 0/12, 4/6, 6/6, and 6/6 rats exposed to an "atmosphere enriched or 6 saturated" with phenyl chloroformate vapor at 20°C for 3 minutes, 10 minutes, 30, minutes, and 7 1 hour, respectively (BASF, 1970). Clinical signs included vigorous escape behavior, mucous 8 membrane irritation, and altered respiration. Lung edema was noted at necropsy.
- 10 IX.2.2. Non-lethal Toxicity

11 **IX.2.2.1. Mice**

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16 17 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.
- 21

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

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IX.2.3. Developmental/Reproductive Toxicity

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

29 **IX.2.4.** Genotoxicity 30

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

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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

IX.2.5. Carcinogenicity

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

IX.2.6. Summary

8 Animal data are limited for phenyl chloroformate. Two 4-hour rat inhalation studies 9 were available, yielding LC₅₀ 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, 10 1970). A 30-min RD₅₀ of 19.5 ppm phenyl chloroformate was reported for male Swiss-Webster 11 12 mice (Carpenter, 1982). No animal data regarding developmental/reproductive toxicity, 13 genotoxicity, or carcinogenicity were available. 14

15 **DATA ANALYSIS AND AEGL-1** IX.3.

16 IX.3.1. Human Data Relevant to AEGL-1

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

20 IX.3.2. Animal Data Relevant to AEGL-1

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

24 IX.3.3. Derivation of AEGL-1 25

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

27 28

26

TABLE IX-5. AEGL-1 Values for Phenyl Chloroformate					
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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.

29

30

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

- 32
- 33 34

35

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

36 IX.4.2. Animal Data Relevant to AEGL-2 37

38 No animal data consistent with the definition of AEGL-2 were available. 39

1 IX.4.3. Derivation of AEGL-2

2

3 No acute inhalation data consistent with the definition of AEGL-2 were available. 4 Therefore, the AEGL-2 values for phenyl chloroformate will be based upon a 3-fold reduction 5 in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 6 2001). This approach is justified based on the steep concentration curve with regard to lethality 7 (4-hour rat mortality incidence: 2/10 at 15.6 ppm; 7/10 at 44.5 ppm; 9/10 at 74.9 ppm; BASF, 8 1990; Hoechst, 1989), and because observed clinical signs resolved (were reversible) at 15.6 9 ppm (BASF, 1990). . The AEGL-2 values for phenyl chloroformate are presented in Table IX-6, 10 and the calculations for these AEGL-2 values are presented in Appendix IX-A.

11

	TABLE IX	K-6. AEGL-2 Valu	es for Phenyl Chl	oroformate	
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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)

12 13

17

18

20

14 IX.5. DATA ANALYSIS AND AEGL-3

15 IX.5.1. Human Data Relevant to AEGL-3 16

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

19 IX.5.2. Animal Data Relevant to AEGL-3

21 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 22 23 BMCL₀₅ value of 3.6 ppm was calculated for male and female rats when the BASF (1990) and 24 Hoechst (1989) studies were combined. 25

26 27

IX.5.3. Derivation of AEGL-3

28 The 4-hour rat BMCL₀₅ of 3.6 ppm from the combined BASF (1990) and Hoechst 29 (1989) studies will be used as the point-of-departure for phenyl chloroformate AEGL-3 values. 30 Interspecies and intraspecies uncertainty factors of 3 each will be applied because phenyl 31 chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect 32 on the tissues; this type of effect is not expected to vary greatly between species or among 33 individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied 34 when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section 35 II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), 36 and these resulting AEGL values were considered protective when compared with chemical-37 specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The 38 concentration-exposure time relationship for many irritant and systemically-acting vapors and 39 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 40

- 1 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when
- 2 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to
- 3 longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3
- 4 value. The AEGL-3 values for phenyl chloroformate are presented in Table IX-7, and the
- 5 calculations for these AEGL-3 values are presented in Appendix IX-A.
- 6

	TABLE IX	K-7. AEGL-3 Valu	ies for Phenyl Ch	loroformate	
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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)

7 8

9 IX.6. SUMMARY OF AEGLS

10 IX.6.1. AEGL Values and Toxicity Endpoints

- 11 12
- 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 BMCL₀₅ value.
- 16

	TABLE IX-8. Sun	nmary of AEGL V	alues for Phenyl	Chloroformate	
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr
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/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)

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

17 18

19 IX.6.2. Comparison with Other Standards and Guidelines

- 20
- 21
- 22

No extant values were located for phenyl chloroformate.

23 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 RD₅₀ study in male Swiss Webster mice.

IX.7. REFERENCES

1

5

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- 11 Carpenter, C.P. 1982. Methyl and Phenyl chloroformate. Sensory Irritation. Report by Mellon 12 Institute. Report to PPG Industries, Inc., Chemicals Division. Report No. 82-19S. 13

14 Hoechst. 1989. Chloroformic acid phenyl ester. Aerosol inhalation toxicity in male and female SPF 15 Wistar rats. 4-hour LC₅₀. Hofmann, T. Hoechst Pharmaceutical Research Toxicology. Report 16 No. 89.0761. April 26, 1989. 17

- 18 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure 19 Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC. 20
- 21 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship 22 of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

1	APPENDIX IX-A: DERIVATION OF AEGL VALUES FOR
2	PHENYL CHLOROFORMATE
3	
4	DERIVATION OF AEGL-1 VALUES FOR PHENYL CHLOROFORMATE
5	
6	AEGL-1 values for phenyl chloroformate are not recommended.

1	DERIVATION	OF AEGL-2 VALUES FOR PHENYL CHLOROFORMATE
2		
3		
4	Key studies: BASF, 1990); Hoechst, 1989
5		
6	Toxicity Endpoint: 1/3 of	f the AEGL-3 values
7		
8		
9	10-min AEGL-2:	$0.72 \text{ ppm} \div 3 = 0.24 \text{ ppm}$
10		
11	30-min AEGL-2:	$0.72 \text{ ppm} \div 3 = 0.24 \text{ ppm}$
12		
13	<u>1-hr AEGL-2</u> :	$0.57 \text{ ppm} \div 3 = 0.19 \text{ ppm}$
14		
15	4-hr AEGL-2:	$0.36 \text{ ppm} \div 3 = 0.12 \text{ ppm}$
16		
17	8-hr AEGL-2:	$0.18 \text{ ppm} \div 3 = 0.060 \text{ ppm}$
		rr - rr

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

APPENDIX IX-B: DERIVATION SUMMARY FOR PHENYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR PHENYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR PHENYL CHLOROFORMATE								
10 Min	30 Min	1 Hr	4 Hour	8 Hour				
NR	NR	NR	NR	NR				
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.								
Test Species/Strain/N	Number:							
Exposure Route/Con	centrations/Duration	s:						
Effects:								
Endpoint/Concentra	tion/Rationale:							
Uncertainty Factors /	Rationale:							
Modifying Factor:								
Animal to Human D	osimetric Adjustment							
Time Scaling:								
Data Quality and Research Needs: No chemical-specific data were available for derivation of AEGL-1 values for phenyl chloroformate.								

1

AEGL-2 VALUES FOR PHENYL CHLOROFORMATE						
10-Min 30-Min 1-Hr 4-Hr 8-Hr						
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/Rationale: See AEGL-3 Derivation summary table

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: See AEGL-3 Derivation summary table

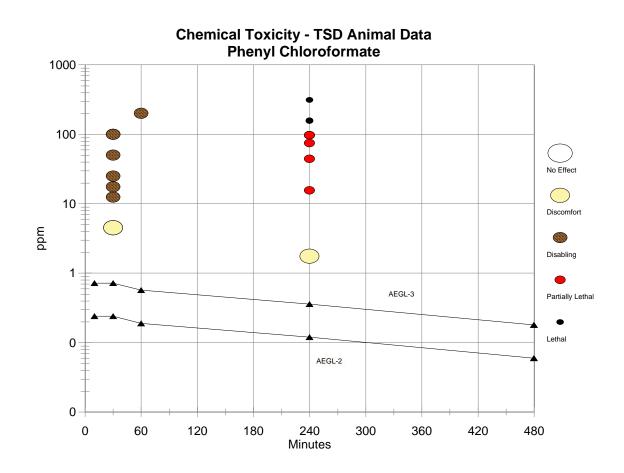
Data quality and research needs: See AEGL-3 Derivation summary table.

10-Min	30-Min	1-Hr	4-Hr	8-Hr
0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm
Key References: BASF. 1990. Study or exposure. Project No. 1 Toxicology and Ecolog	3I0675/887076. Unj	published report, BA	ASF Aktiengesellscha	
	₀ . Hofmann, T. Ho			and female SPF Wistar rats y. Report No. 89.0761.
Test Species/Strain/Se	x/Number: Sprague	Dawley rats/ 5/sex/g	group	
Exposure Route/Conc	entrations/Duration	s: Rats/Inhalation/4	hours	
(BMCL ₀₅ , 3.6 ppm, v	vas the point-of-depa	rture for AEGL-3)		
Endpoint/Concentrati	on/Rationale: BMC	L ₀₅ /3.6 ppm/Estimat	ed threshold for death	for 4 hour exposure in rate
Effects: <u>Concentration</u>	n <u>Mortality</u>			
the tissues; this typ Furthermore, inter were calculated for (Section V.5.3), ar	ate is highly reactive be of effect is not exp - and intraspecies un r the structural analo id n-butyl chloroform	bected to vary greatly certainty factors of 3 gs, methyl chlorofor hate (Section VII.5.3	y between species or a each were also applie mate (Section II.5.3),), and these resulting	ed when AEGL-3 values isopropyl chloroformate
Modifying Factor: NA				
Animal to Human Dos	simetric Adjustmen	t: Insufficient data		
				utes and 1-hour) and $n = 1$ as adopted as the 10-minute
Data Quality and Rese	arch Noods, Sparse	data set		



4

APPENDIX IX-C: CATEGORY PLOT FOR PHENYL CHLOROFORMATE



APPENDIX IX-D: BENCHMARK CONCENTRATION CALCULATION FOR PHENYL CHLOROFORMATE

BMDS MODEL RUN

The form of the probability function is:

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

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

Total number of observations = 8 Total number of records with missing values = 0 Maximum number of iterations = 250 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values

background = 0intercept = -2.32244slope = 0.759796

Asymptotic Correlation Matrix of Parameter Estimates

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

intercept slope	Intercep 1 -0.98	t slope -0.98 1	
Paran Variable		er Estimates Estimate	Std. Err.
Backgro	ound	0	NA
Intercep	t	-4.60327	1.20324
Slope		1.35407	0.307109

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

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-17.6143			
Fitted model	-18.0291	0.829451	6	0.9913
Reduced model	-47.9918	60.755	7	<.0001
AIC: 40.0581				

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

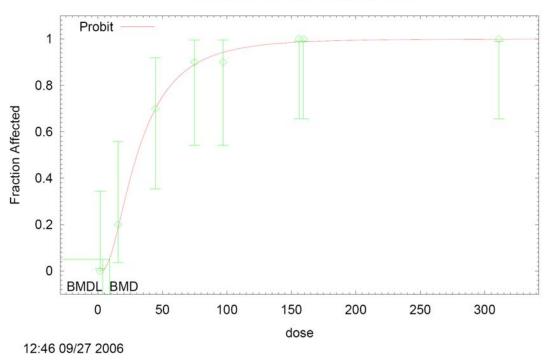
Dose	Est. Prob.	Expected	Observed	Size	Residual
Dose	Lst1100.	Expected	Observed	Size	Residual
1.7600	0.0001	0.001	0	10	-0.0249
15.6000	0.1885	1.885	2	10	0.09264
44.5000	0.7040	7.040	7	10	-0.0280
74.9000	0.8927	8.927	9	10	0.07446
97.0000	0.9442	9.442	9	10	-0.6092
156.0000	0.9873	9.873	10	10	0.359
159.3000	0.9882	9.882	10	10	0.3459
311.0000	0.9992	9.992	10	10	0.08752

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

Benchmark Dose Computation

10	
19	Specified effect $= 0.05$
20	Risk Type = Extra risk
21	Confidence level $= 0.95$
22	BMD = 8.88924
23	BMDL = 3.57025

Probit Model with 0.95 Confidence Level



CHAPTER X: 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 Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate TABLE OF CONTENTS: CHAPTER IX: 2-ETHYLHEXYL CHLOROFORMATE 1 2 LIST OF TABLES: 2-ETHYLHEXYL CHLOROFORMATE......X-4 3 EXECUTIVE SUMMARY:2-ETHYLHEXYL CHLOROFORMATEX-5 HUMAN TOXICITY DATA.....X-6 4 X.1. 5 X.1.1. Acute Lethality.....X-6 6 X.1.2. Non-lethal ToxicityX-6 7 X.1.3. Developmental/Reproductive ToxicityX-6 8 X.1.4. Genotoxicity.....X-6 9 X.1.5. CarcinogenicityX-6 X.1.6. SummaryX-6 10 11 X.2. ANIMAL TOXICITY DATA.....X-6 12 Acute Lethality.....X-6 X.2.1. 13 X.2.1.1. Rats X-6 14 X.2.2. Non-lethal ToxicityX-7 15 X.2.3. Developmental/Reproductive ToxicityX-7 16 X.2.4. Genotoxicity.....X-7 X.2.5. CarcinogenicityX-8 17 18 X.2.6. SummaryX-8 19 DATA ANALYSIS AND AEGL-1X-8 X 3 20 X.3.1. Human Data Relevant to AEGL-1X-8 21 X.3.2. 22 X.3.3. Derivation of AEGL-1.....X-8 DATA ANALYSIS AND AEGL-2 23 X.4. 24 X.4.1. Human Data Relevant to AEGL-2X-8 25 X.4.2. Animal Data Relevant to AEGL-2X-8 26 X.4.3. Derivation of AEGL-2X-9 27 DATA ANALYSIS AND AEGL-3X-9 X.5. 28 X.5.1. Human Data Relevant to AEGL-3X-9 29 X.5.2. Animal Data Relevant to AEGL-3X-9

30

X.5.3.

Derivation of AEGL-3X-9

	Butyl Chloro	<u>05/2008</u> oformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl (formate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Ber te, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate	
1	X.6. SU	MMARY OF AEGLS	X-10
2	X.6.1.	AEGL Values and Toxicity Endpoin	X-10
3	X.6.2.	Comparison with Other Standards and Guidelines	X-10
4	X.6.3.	Data Quality and Research Needs	X-10
5	X.7. RE	FERENCES	11
6 7 8	CHLOROF	X X-A: DERIVATION OF AEGL VALUES FOR 2-ETHYLHEXYL ORMATEDERIVATION OF AEGL-1 VALUES FOR 2-ETHYLHEXYL ORMATE	X-12
9 10	APPENDIX	X X-B: DERIVATION SUMMARY FOR 2-ETHYLHEXYL CHLOROFORM AEGLS	
11	APPENDIX	X X-C: CATEGORY PLOT FOR 2-ETHYLHEXYL CHLOROFORMATE	X-18
12 13 14		X X-D: BENCHMARK CONCENTRATION CALCULATION FOR 2-ETHY ORMATE	

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		LIST OF TABLES: 2-ETHYLHEXYL CHLOROFORMATE	
3	TABLE X-S 1.	Summary of AEGL Values For 2-Ethylhexyl Chloroformate	X-5
4	TABLE X-1.	Mortality in Rats Exposed to 2-Ethylhexyl Chloroformate for 4 hours	X-7
5	TABLE X-2.	AEGL-1 Values for 2-Ethylhexyl Chloroformate	X-8
6	TABLE X-3.	AEGL-2 Values for 2-Ethylhexyl Chloroformate	X-9
7	TABLE X-4.	AEGL-3 Values for 2-Ethylhexyl Chloroformate	X-10
8	TABLE X-5.	Summary of AEGL Values for 2-Ethylhexyl Chloroformate	X-10
0			

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

EXECUTIVE 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 2ethylhexyl 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).

13

14 The 4-hour male rat BMCL₀₅ of 18.1 ppm from the BASF (1985) study was used as the 15 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 16 17 and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is 18 not expected to vary greatly between species or among individuals. Furthermore, inter- and 19 intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were 20 calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl 21 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-22 23 exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-24 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). 25 26 To obtain conservative and protective AEGL values in the absence of an empirically derived 27 chemical-specific scaling exponent, temporal scaling was performed using n=3 when 28 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to 29 longer time points (8-hours The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3

30 31 value.

TABLE X-S 1. Summary of AEGL Values For 2-Ethylhexyl Chloroformate							
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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)	1/3 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)	

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

X.1. HUMAN TOXICITY DATA

X.1.1. Acute Lethality

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

X.1.2. Non-lethal Toxicity

9 Information concerning non-lethal toxicity in humans following inhalation exposure to 2-10 ethylhexyl chloroformate is not available.

12 X.1.3. Developmental/Reproductive Toxicity

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

17 X.1.4. Genotoxicity

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

22 X.1.5. Carcinogenicity

Carcinogenicity studies regarding human exposure to 2-ethylhexyl chloroformate werenot available.

27 X.1.6. Summary

28
 29 No reports regarding lethal toxicity, non-lethal toxicity, developmental/reproductive
 30 toxicity, genotoxicity, or carcinogenicity were available.

31

32 X.2. ANIMAL TOXICITY DATA

33 X.2.1. Acute Lethality

34 X.2.1.1. Rats

35

36 Groups of ten male and ten female SPF Wistar rats were exposed to 22.8, 26.6, 34.3, or 37 46.9 ppm (analytical concentrations) 2-ethylhexyl chloroformate for 4-hours followed by a 14-38 day observation period (BASF, 1985). The whole body exposures were performed in a 200 L 39 glass-steel inhalation chamber, and 2-ethylhexyl chloroformate concentrations were measured 40 hourly during exposure using gas chromatography. Clinical signs noted during exposure included closed palpebral fissure, red ocular and nasal discharge, and irregular respiration, 41 42 restlessness, squatting posture, and ruffled fur in the 26.6, 34.3, and 46.9 ppm groups. Clinical 43 signs during the post-exposure observation period included irregular respiration, respiratory 44 sounds, reddish nasal discharge and staggering in the 46.9 ppm group. In addition, slight apathy

45 was noted in the 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 groups. No clinical signs were noted during or after exposure in the

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 22.8 ppm group. There were no gross treatment-related effects noted at necropsy in animals

2 surviving to study termination. Gross examination of animals that died during the study showed

3 venous congestion and lung emphysema with pneumonia. A 4-hour LC₅₀ value of 33.9 ppm

4 was reported for male and female rats combined. Male rats appear to be more sensitive to 2-

5 ethylhexyl chloroformate than female rats, both with regard to lethality incidence and time of

6 death. BMCL₀₅ and BMC₀₁ values were calculated and are presented in Table X-1, and \overline{C}

7 mortality data are also summarized in Table X-1.

8

TABLE X-1. Mortality in Rats Exposed to 2-Ethylhexyl Chloroformate for 4 hours*								
	Males	Time to death	Females	Time to death	Combined Males and Females			
22.8 ppm	0/10	-	0/10	-	0/20			
26.6 ppm	4/10	2 dead: Day of exposure 2 dead: Day 1 post-exposure	1/10	1 dead: Day 14 post-exposure	5/20			
34.3 ppm	7/10	2 dead: Day of exposure 5 dead: Day 1 post-exposure	2/10	2 dead: Day 1 post-exposure	9/20			
46.9 ppm	10/10	8 dead: Day of exposure 2 dead: Day 1 post-exposure	10/10	3 dead: Day of exposure 7 dead: Day 1 post-exposure	20/20			
LC ₅₀		29.9 ppm		36.3 ppm	33.9 ppm			
BMCL ₀₅		18.1 ppm		26.0 ppm	20.1 ppm			
BMC ₀₁		19.7 ppm		31.9 ppm	21.1 ppm			

*BASF, 1985

9

10

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 20°C 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.

17

18 X.2.2. Non-lethal Toxicity19

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

23 X.2.3. Developmental/Reproductive Toxicity24

No information concerning the developmental/reproductive toxicity of 2-ethylhexyl chloroformate was located in the available literature.

28 X.2.4. Genotoxicity

29

25

26

27

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

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

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.

4 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).

26 27

25

TABLE X-2. AEGL-1 Values for 2-Ethylhexyl Chloroformate							
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr						
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.

28 29

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34

30 X.4. DATA ANALYSIS AND AEGL-2

31 X.4.1. Human Data Relevant to AEGL-2

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

35 X.4.2. Animal Data Relevant to AEGL-2

36
37 No animal data consistent with the definition of AEGL-2 were available.
38

1 2

3 4

X.4.3. Derivation of AEGL-2

3 No acute inhalation data consistent with the definition of AEGL-2 were available. 4 Therefore, the AEGL-2 values for 2-ethylhexyl chloroformate will be based upon a 3-fold 5 reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible 6 effects (NRC, 2001). This approach is justified based on the steep concentration curve with 7 regard to lethality (4-hour rat mortality incidence: 0/20 at 22.8 ppm; 5/20 at 26.6 ppm; 9/20 at 8 34.3 ppm; 20/20 at 46.9 ppm; BASF, 1985). The AEGL-2 values for 2-ethylhexyl chloroformate 9 are presented in Table X-3, and the calculations for these AEGL-2 values are presented in 10 Appendix X-A.

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TABLE X-3. AEGL-2 Values for 2-Ethylhexyl Chloroformate							
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr						
AEGL-2	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)		

12 13

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X.5. DATA ANALYSIS AND AEGL-3

15 X.5.1. Human Data Relevant to AEGL-316

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

X.5.2. Animal Data Relevant to AEGL-3

Four-hour LC₅₀ 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).

26 X.5.3. Derivation of AEGL-3

27 28 The 4-hour male rat BMCL₀₅ of 18.1 ppm from the BASF (1985) study will be used as 29 the point-of-departure for 2-ethylhexyl chloroformate AEGL-3 values. Interspecies and 30 intraspecies uncertainty factors of 3 each will be applied because 2-ethylhexyl chloroformate is 31 highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this 32 type of effect is not expected to vary greatly between species or among individuals. 33 Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-34 3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), 35 isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these 36 resulting AEGL values were considered protective when compared with chemical-specific, 37 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 38 39 gases may be described by $c^n x t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et 40 al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically 41 derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when

- 1 extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to
- 2 longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-
- 3 3 value. The AEGL-3 values for 2-ethylhexyl chloroformate are presented in Table X-4, and
- 4 the calculations for these AEGL-3 values are presented in Appendix X-A.
- 5

TABLE X-4. AEGL-3 Values for 2-Ethylhexyl Chloroformate							
Classification	Classification10-Min30-Min1-Hr4-Hr8-Hr						
AEGL-3	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)		

6 7

8 X.6. **SUMMARY OF AEGLS**

9 X.6.1. AEGL Values and Toxicity Endpoints 10

Data were insufficient for derivation of AEGL-1 values for 2-ethylhexyl chloroformate;

12 therefore, AEGL-1 values are not recommended. AEGL-2 values for 2-ethylhexyl

13 chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for 2-14 ethylhexyl chloroformate were based on a 4-hour rat BMCL₀₅ value.

15

11

TABLE X-5. Summary of AEGL Values for 2-Ethylhexyl Chloroformate						
Classification	10-Min	30-Minute	1-Hr	4-Hr	8-Hr	
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/m ³)	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.

19 20

X.6.2. Comparison with Other Standards and Guidelines

No extant values were located for 2-ethylhexyl chloroformate.

21 22

24

23 X.6.3. Data Quality and Research Needs

25 No human toxicity were available. The only animal toxicity data available were from acute lethality studies in rats.

¹⁶ 17 18

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

X.7. REFERENCES

- BASF. 1968. Study of the acute inhalation hazard (rats). Inhalation hazard test. 2-Ethylhexyl chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. December 9, 1968.
- 23456789 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. 10
- 11 NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure 12 Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC. 13
- 14 ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship 15 of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.
- 16

1

2

3

4 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

APPENDIX X-A: DERIVATION OF AEGL VALUES FOR 2-ETHYLHEXYL CHLOROFORMATEDERIVATION OF AEGL-1 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

AEGL-1 values for 2-ethylhexyl chloroformate are not recommended.

1	DERIVATION OF A	AEGL-2 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE
2		
3	Key studies: BASF, 1985	5
4		
5	Toxicity Endpoint: 1/3 of	f the AEGL-3 values
6		
7		
8	10-min AEGL-2:	$3.6 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
9		
10	30-min AEGL-2:	$3.6 \text{ ppm} \div 3 = 1.2 \text{ ppm}$
11		
12	<u>1-hr AEGL-2</u> :	$2.9 \text{ ppm} \div 3 = 0.97 \text{ ppm}$
13		
14	<u>4-hr AEGL-2</u> :	$1.8 \text{ ppm} \div 3 = 0.60 \text{ ppm}$
15		
16	8-hr AEGL-2:	$0.91 \text{ ppm} \div 3 = 0.30 \text{ ppm}$

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 **DERIVATION OF AEGL-3 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE** 2 3 Key studies: BASF, 1985 4 5 Toxicity Endpoint: 4-hour rat BMCL₀₅ (18.1 ppm) 6 7 8 Scaling: 9 10 30-minutes and 1-hr $C^3 \ge t = k$ 11 $(18.1 \text{ ppm})^3 \text{ x 4 hr} = 23,719 \text{ ppm} \cdot \text{hr}$ 12 13 14 8-hours $C^1 \ge t = k$ 15 $(18.1 \text{ ppm})^1 \text{ x 4 hr} = 72.4 \text{ ppm} \cdot \text{hr}$ 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 $C^3 \ge 0.5 hr = 23,719 ppm hr$ 26 $C^3 = 47438 \text{ ppm}$ 27 28 C = 36.2 ppm29 30-min AEGL-3 = 36.2/10 = 3.6 ppm30 31 1-hr AEGL-3 $C^{3} \ge 1$ hr = 23,719 ppm·hr $C^{3} = 23,719$ ppm 32 33 34 C = 28.7 ppm35 1-hr AEGL-3 = 28.7/10 = 2.9 ppm36 37 4-hr AEGL-3 38 4-hr AEGL-3 = 18.6/10 = 1.8 ppm 39 40 8-hr AEGL-3 $C^1 \ge 8 hr = 72.4 ppm hr$ 41 $C^1 = 9.1 \text{ ppm}$ 42 C = 9.1 ppm43 8-hr AEGL-3 = 9.1/10 = 0.91 ppm 44

APPENDIX X-B: DERIVATION SUMMARY FOR 2-ETHYLHEXYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR 2-ETHYLHEXYL CHLOROFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE								
10 Min	10 Min 30 Min 1 Hr 4 Hr 8 Hr							
NR	NR	NR	NR	NR				
Key Reference: Cher	nical-specific data wer	e insufficient for derivin	ng AEGL-1 values.					
Test Species/Strain/N	Number:							
Exposure Route/Con	centrations/Duration	s:						
Effects:								
Endpoint/Concentra	tion/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.								

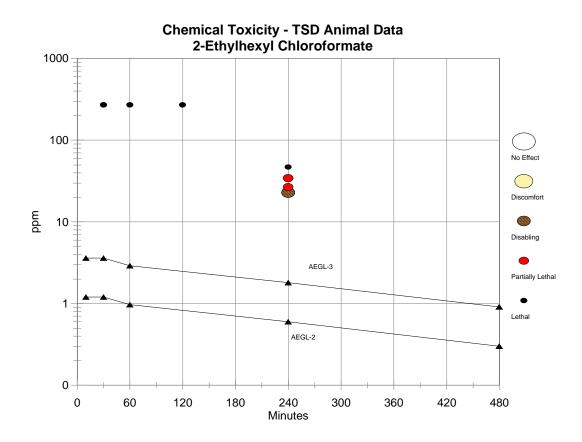
AEGL-2 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE						
10-Min	10-Min 30-Min 1-Hr 4-Hr 8-Hr					
1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm		
Key Reference : BASF. 1985. Acute inhalation toxicity LC ₅₀ for a 4-hour exposure (rats), vapor test of 2-ethylhexyl chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 8, 1985.						
Test Species/Strain/N	umber: See AEGL-3	Derivation summary ta	ble			
Exposure Route/Conc	entrations/Durations	: See AEGL-3 Derivat	tion 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.						
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 research needs: See AEGL-3 Derivation summary table.						

1

	AEGL-3 VALUES H	FOR 2-ETHYLHE	XYL CHLOROFOR	MATE
10-Min	30-Min	1-Hr	4-Hr	8-Hr
3.6 ppm	3.6 ppm	2.9 ppm	1.8 ppm	0.91 ppm
Key Reference:				
chloroformate. Un	ute inhalation toxicity LC npublished report, BASI ermany. February 8, 198	Aktiengesellschaf		
Test Species/Stra	in/Sex/Number: Wistar	rats/ 10/sex/group		
	Concentrations/Duratio 8.1 ppm, was the point-or			
Endpoint/Concer	tration/Rationale: BM	CL ₀₅ /3.6 ppm/Estim	ated threshold for death	h for 4 hour exposure in rats
Effects:				
Concentration	Male Mortality Fe	male Mortality C	ombined 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 Fact Interspecies				
Intraspecies				
-		reactive and clinica	signs are likely caused	d by a direct chemical effect
	; this type of effect is no			
				ied when AEGL-3 values
				isopropyl chloroformate
(Section V.5.	3), and n-butyl chlorofor	mate (Section VII.5	.3), and these resulting	g AEGL values were
considered pr	otective when compared	with chemical-spec	ific, repeated-exposure	e data for these analogs.
Modifying Factor	r: NA			
Animal to Huma	n Dosimetric Adjustme	nt: Insufficient dat	a	
Time Scaling: c ⁿ when extrapt AEGL-3 valu	plating to longer time point	extrapolating to sho nts (8-hours). 30-m	rter time points (30-min inute AEGL-3 value w	nutes and 1-hour) and $n = 1$ as adopted as the 10-minute
Data Quality and	Research Needs: Spars	e data set.		
	r ····			

1 2

APPENDIX X-C: CATEGORY PLOT FOR 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

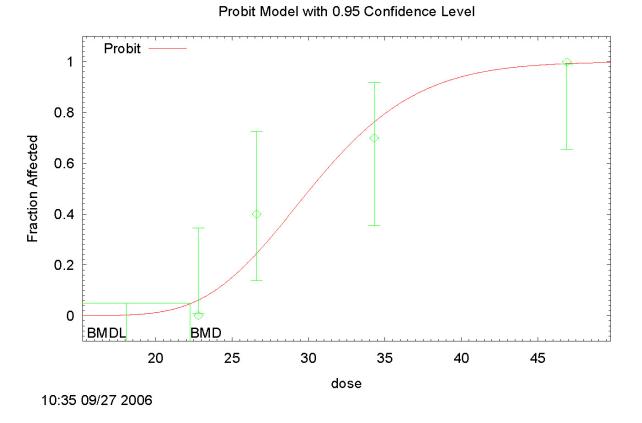
AP	PEND	X X-D: BEN	CHMARK CO	NCENTR	ATION CALCULAT	FION FOR
		2-E T	THYLHEXYL	CHLORO	FORMATE	
Dependent						
Independen						
Slope para	meter is r	not restricted				
Total nu	mber of o	bservations = 4				
		ecords with missi	ng values = 0			
		r of iterations = 2				
			s been set to: 1e-00	08		
		gence has been s				
		log transformed				
background		Specified) Param	eter Values			
intercept =						
slope = 4.3		,				
stop e	, 0, 0					
					del parameter(s) -backgro	
estimated a	it a bound	lary point, or hav	e been specified by	y the user, and	do not appear in the corre	elation matrix)
	•					
	intercept	slope				
intercept	1	-1				
slope	-1	1				
	-	-				
	Ра	arameter Estimate	es			
¥7 · 11						
Variable Backgro		Estimate 0	Std. Err. NA			
Intercept		-18.7737	5.12639			
Slope	•	5.52218	1.51755			
Stope		0.02210	1.01,00			
NA - Indic	ates that	this parameter ha	s hit a bound impli	ed by some in	nequality constraint and the	us has no stan
error.						
			·			
		Analysis of De	eviance l'able			
Model		Log(likelihood)	Deviance	Test DF	P-value	
Full mo	del	-12.8388	Deviance	1050 D1	1 Vulue	
Fitted n		-14.2231	2.76871	2	0.2505	
	d model	-27.6759	29.6742	3	<.0001	
AIC: 32.	4462					
Goodness	of Fit					
Dose	Est. 1	Prob. Expect	Scaled ed Observ	red Siz	ze Residual	

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	22.8000	0.0659	0.659	0	10	-0.8398
2	26.6000	0.2559	2.559	4	10	1.044
3	34.3000	0.7728	7.728	7	10	-0.5491
4	46.9000	0.9934	9.934	10	10	0.2587

P-value = $0.33\overline{90}$ Chi-square = 2.16DF = 2

- Benchmark Dose Computation
- 5 6 7 8 9 10 Specified effect = 0.05
- Risk Type = Extra risk
- 12 13 Confidence level = 0.95
- BMD = 22.2386
- 14 BMDL = 8.0971
- 15



CHAPTER XI: ETHYL CHLOROTHIOFORMATE

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 TABLE OF CONTENTS: CHAPTER XI: ETHYL CHLOROTHIOFORMATE 1 2 LIST OF TABLES: ETHYL CHLOROTHIOFORMATEXI-4 3 EXECUTIVE SUMMARY: ETHYL CHLOROTHIOFORMATE......XI-5 HUMAN TOXICITY DATA......XI-6 4 XI.1. 5 XI.1.1. Acute Lethality......XI-6 6 XI.1.2. 7 XI.1.3. Developmental/Reproductive Toxicity XI-6 8 XI.1.4. Genotoxicity......XI-6 9 XI.1.5. CarcinogenicityXI-6 10 XI.1.6. SummaryXI-6 11 XI.2. ANIMAL TOXICITY DATA......XI-7 12 XI 2 1 Acute Lethality......XI-7 13 XI.2.2. 14 XI.2.3. Developmental/Reproductive ToxicityXI-8 Genotoxicity......XI-8 15 XI.2.4. 16 XI.2.5. Carcinogenicity XI-8 17 XI.2.6. SummaryXI-9 18 XI.3. DATA ANALYSIS AND AEGL-1XI-9 19 XI.3.1. Human Data Relevant to AEGL-1 XI-9 Animal Data Relevant to AEGL-1 XI-9 20 XI.3.2. 21 Derivation of AEGL-1 XI-9 XI.3.3. 22 XI.4. DATA ANALYSIS AND AEGL-2 XI-9 23 Human Data Relevant to AEGL-2 XI-9 XI.4.1. 24 XI.4.2. Animal Data Relevant to AEGL-2 XI-9 25 Derivation of AEGL-2 XI-9 XI.4.3. 26 XI.5. DATA ANALYSIS AND AEGL-3XI-10 27 Human Data Relevant to AEGL-3 XI-10 XI.5.1. 28 XI.5.2. Animal Data Relevant to AEGL-3XI-10 29 Derivation of AEGL-3 XI-10 XI.5.3.

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

1	XI.6. SU	MMARY OF AEGLS	XI-11
2	XI.6.1.	AEGL Values and Toxicity Endpoints	XI-11
3	XI.6.2.	Comparison with Other Standards and Guidelines	XI-11
4	XI.6.3.	Data Quality and Research Needs	XI-11
5	XI.7. RE	FERENCES	XI-11
6 7	APPENDIX	X XI-A: DERIVATION OF AEGL VALUES FOR ETHYL CHLOROTHIOFORMATE	XI-13
8 9	APPENDIX	X XI-B: DERIVATION SUMMARY FOR ETHYL CHLOROTHIOFORMATE AEGLS	XI-16
10 11	APPENDIX	X XI-C: CATEGORY PLOT FOR ETHYL CHLOROTHIOFORMATE	XI-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

1		LIST OF TABLES: ETHYL CHLOROTHIOFORMATE	
2	TABLE XI-S 1.	Summary of AEGL Values For Ethyl Chlorothioformate	XI-5
3	TABLE XI-1.	Mortality of Rats Exposed to Ethyl Chlorothioformate for4-hours	XI-8
4	TABLE XI-2.	AEGL-1 Values for Ethyl Chlorothioformate	XI-9
5	TABLE XI-3.	AEGL-2 Values for Ethyl Chlorothioformate	XI-10
6	TABLE XI-4.	AEGL-3 Values for Ethyl Chlorothioformate	XI-10
7	TABLE XI-5.	Summary of AEGL Values for Ethyl Chlorothioformate	XI-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

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EXECUTIVE SUMMARY: ETHYL CHLOROTHIOFORMATE

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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)).

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13 An estimated 4-hour rat lethality threshold of 15 ppm (1/3 the 4-hr LC₅₀: $1/3 \times 45$ ppm = 14 15 ppm) (Stauffer, 1983) was used for deriving AEGL-3 values for ethyl chlorothioformate. An 15 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 16 17 effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 18 was applied to protect against potential delayed systemic effects that may occur due to the thio-19 moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship 20 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 21 22 protective AEGL values in the absence of an empirically derived chemical-specific scaling 23 exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points 24 (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-25 minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in 26 extrapolating from a 4-hour point-of-departure.

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The calculated values are listed in the table below.

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TABLE XI-S 1. Summary of AEGL Values For Ethyl Chlorothioformate									
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	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)	· · · ·	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.

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

References:

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- 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.
- 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.

XI.1. HUMAN TOXICITY DATA

14 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.

24 XI.1.3. Developmental/Reproductive Toxicity

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

29 XI.1.4. Genotoxicity

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

34 XI.1.5. Carcinogenicity

36 Carcinogenicity studies regarding human exposure to ethyl chlorothioformate were not37 available.

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39 XI.1.6. Summary

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

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

XI.2. ANIMAL TOXICITY DATA

2 XI.2.1. Acute Lethality 3

4 Groups of ten male and ten female Sprague-Dawley rats were exposed to 263 ppm ethyl 5 chlorothioformate for 1 hour (Stauffer, 1982). Animals were exposed in stainless steel and glass 6 chambers with a volume of 447 liters. The ethyl chlorothioformate was aerosolized using a 7 fritted bubbler and was delivered through a 1 inch diameter flexible stainless steel tubing to the 8 chamber inlet. Actual chamber concentrations were measured coulimetrically at 15, 30, and 45 9 minutes after exposure initiation. During exposure, all rats showed lacrimation, salivation, and 10 closed eves 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 11 12 exposure: effects at necropsy included respiratory tract findings (Red mottling of lungs in 20/20) 13 rats; frothiness of the trachea in 17/20 rats; moist, spongy lungs in 8/20; wetness around the 14 nares in 20/20 rats).

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In another study (Stauffer, 1983), groups of ten male and ten female Sprague-Dawley rats 16 17 were exposed to 0, 33, 59, 65, 69, or 124 ppm ethyl chlorothioformate for 4 hours, followed by a 18 14-day observation period. The exposure protocol was similar to that described above (Stauffer, 19 1982) except that chamber concentrations were measured hourly during the 4 hour exposure 20 period. During exposure, animals in all treatment groups showed lethargy, lacrimation, 21 excessive salivation, and breathing difficulty. Clinical signs after exposure included rough coats, rhinorrhea, chromorhinorrhea, salivation, dyspnea, rales, dacryrrhea, chromodachrrhea, and 22 23 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. 24 25 respiratory tract necrosis, basal cell hyperplasia, vascular congestion, and alveolar emphysema. 26 Myocardial degeneration, nephrosis, hepatic necrosis, adrenal necrosis, spleen and lymph node 27 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 28 29 were attributed to a combination of local corrosive and systemic effects. LC_{50} values of 51 ppm 30 and 41 ppm were calculated for male and female rats, respectively. A combined male and 31 female LC₅₀ value of 45 ppm was also calculated. Data are summarized in Table XI-1. 32

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

TABI	TABLE XI-1. Mortality of Rats Exposed to Ethyl Chlorothioformate for4-hours*								
			Male	S					
Concentration (ppm)	Incidence	Incidence Time of Death (Days Post-Exposure)							
		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		-	-	-	-		-	-
			Fema	es					
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 a	and Female LC ₅₀				45	ppm			

*Stauffer, 1983

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XI.2.2. Non-lethal Toxicity

No data on non-lethal effects were available for ethyl chlorothioformate.

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).

17 18

XI.2.5. Carcinogenicity

No information concerning the carcinogenicity of ethyl chlorothioformate was located in
the available literature.

Ethyl Chlorothioformate

XI.2.6. Summary

2 3 Four-hour LC₅₀ values of 51 ppm and 41 ppm were calculated for male and female rats, 4 respectively. A combined male and female LC₅₀ value of 45 ppm was also calculated (Stauffer, 5 1983). Signs of toxicity were consistent with severe respiratory tract irritation/corrosion, and 6 necropsy findings suggest that ethyl chlorothioformate may cause both portal of entry and 7 systemic effects. These systemic effects are likely due to the ability of the thio moiety to interact 8 with other biomolecules. Ethyl chlorothioformate was negative in an Ames assay, and no animal 9 data regarding non-lethal toxicity, developmental/reproductive toxicity, or carcinogenicity were 10 available.

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12 XI.3. DATA ANALYSIS AND AEGL-1 13 XI.3.1. Human Data Relevant to AEGL-1

13 **XI.3.1. H** 14

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).

25

TABLE XI-2. AEGL-1 Values for Ethyl Chlorothioformate							
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr		
AEGL-1	NR	NR	NR	NR	NR		

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

26 XI.4. DATA ANALYSIS AND AEGL-2

27 XI.4.1. Human Data Relevant to AEGL-2

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

3031 XI.4.2. Animal Data Relevant to AEGL-2

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

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XI.4.3. Derivation of AEGL-2

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

38 Therefore, the AEGL-2 values for ethyl chlorothioformate will be based upon a 3-fold reduction

39 in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC,

1 2001). This approach is justified based on the steep concentration curve with regard to lethality

2 (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; Stauffer,

3 1983). The AEGL-2 values for ethyl chlorothioformate are presented in Table XI-3, and the

⁵

TABLE XI-3. AEGL-2 Values for Ethyl Chlorothioformate							
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr		
AEGL-2	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)		

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8 XI.5. DATA ANALYSIS AND AEGL-3

9 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 LC_{50} values of 51 ppm and 41 ppm were calculated for male and female rats, respectively, and the combined sexes LC_{50} was 45 ppm (Stauffer, 1983).

- 18 XI.5.3. Derivation of AEGL-3
- 19 20 An estimated 4-hour rat lethality threshold of 15 ppm (1/3 the 4-hr LC₅₀: 1/3 x 45 ppm = 15 ppm) (Stauffer, 1983) will be used for deriving AEGL-3 values for ethyl chlorothioformate. 21 22 An interspecies uncertainty factor of 3 will be applied because ethyl chlorothioformate is highly 23 reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of 24 effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 25 will be applied to protect against potential delayed systemic effects that may occur due to the 26 thio-moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time 27 relationship for many irritant and systemically-acting vapors and gases may be described by 28 $c^n x = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain 29 conservative and protective AEGL values in the absence of an empirically derived chemical-30 specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to 31 shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points 32 (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the 33 uncertainty in extrapolating from a 4-hour point-of-departure. The AEGL-3 values for ethyl 34 chlorothioformate are presented in Table XI-4, and the calculations for these AEGL-3 values are 35 presented in Appendix XI-A.
- 36

TABLE XI-4. AEGL-3 Values for Ethyl Chlorothioformate							
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr		
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)		

⁴ calculations for these AEGL-2 values are presented in Appendix XI-A.

XI.6. SUMMARY OF AEGLS XI.6.1. AEGL Values and Toxicity Endpoints

XI.6.2. Comparison with Other Standards and Guidelines

XI.6.3. Data Quality and Research Needs

No extant values were located for ethyl chlorothioformate.

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.

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TABLE XI-5. Summary of AEGL Values for Ethyl Chlorothioformate								
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr			
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 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

11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

10

No human toxicity data were available. Animal toxicity data available were limited to rat lethality studies.

XI.7. REFERENCES

- NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.
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 Health Center Inhalation Facility. Stauffer Chemical Company. 400 Farmington Avenue.
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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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APPENDIX XI-A: DERIVATION OF AEGL VALUES FOR ETHYL CHLOROTHIOFORMATE

DERIVATION OF AEGL-1 VALUES FOR ETHYL CHLOROTHIOFORMATE

AEGL-1 values are not recommended for ethyl chlorothioformate due to insufficient data.

1 **DERIVATION OF AEGL-2 VALUES FOR ETHYL CHLOROTHIOFORMATE** 2 3 Key study: Stauffer, 1983 4 5 Toxicity Endpoint: 1/3 the AEGL-3 values 6 7 $1.0 \text{ ppm} \div 3 = 0.33 \text{ ppm}$ <u>10-min AEGL-2</u>: 8 9 <u>30-min AEGL-2</u>: $1.0 \text{ ppm} \div 3 = 0.33 \text{ ppm}$ 10 11 <u>1-hr AEGL-2</u>: 0.79 ppm \div 3 = 0.26 ppm 12 <u>4-hr AEGL-2</u>: 0.5 ppm \div 3 = 0.17 ppm 13 14

15 <u>8-hr AEGL-2:</u> 0.25 ppm ÷ 3 = 0.083 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 2	DERIVATION OF	FAEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE
2 3 4	Key study: Stauffer,	1983
5 6	Toxicity Endpoint: Estin	mated 4-hr rat lethality threshold of 15 ppm (1/3 the LC_{50} of 45 ppm)
7 8	Scaling:	
9	30-minutes and 1-hour	
10		$C^3 \ge t = k$
11		$(15 \text{ ppm})^3 \text{ x 4 hr} = 13,500 \text{ ppm} \cdot \text{hr}$
12	<u>8-hours</u>	
13 14		$C^{1} \mathbf{x} t = k$
14		$(15 \text{ ppm})^1 \text{ x 4 hr} = 60 \text{ ppm} \cdot \text{hr}$
16	Uncertainty Factors:	
17		3 for interspecies variability
18		10 for intraspecies variability
19		
20	<u>10-min AEGL-3</u> :	
21		
22 23		30-minute value adopted as 10-minute value because POD was 4-hours = 1.0 ppm
23 24		4-nouis – 1.0 ppm
25	30-min AEGL-3	
26		$C^3 \ge 0.5 hr = 13,500 ppm hr$
27		$C^3 = 27,000 \text{ ppm}$
28		C = 30 ppm
29		30-min AEGL-3 = 30/30 = 1.0 ppm
30		
31 32	<u>1-hr AEGL-3</u>	$C^3 \ge 1 hr = 13,500 ppm hr$
32 33		$C^{3} = 13,500 \text{ ppm}$
34		C = 23.8 ppm
35		1 - hr AEGL-3 = 23.8/30 = 0.79 ppm
36		
37	<u>4-hr AEGL-3</u>	
38		$15 \text{ ppm} \div 30 = 0.50$
39		
40	<u>8-hr AEGL-3</u>	$C^{1} = 0$ hr = (0 mm) hr
41 42		$C^{1} \ge 8 hr = 60 ppm hr$ $C^{1} = 7.5 ppm$
42 43		C = 7.5 ppm C = 7.5 ppm
44		8-hr AEGL-3 = $7.5/30 = 0.25$ ppm
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APPENDIX XI-B: DERIVATION SUMMARY FOR ETHYL CHLOROTHIOFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR ETHYL CHLOROTHIOFORMATE DERIVATION SUMMARY

AEGL-1 VALUES FOR ETHYL CHLOROTHIOFORMATE									
10 Min	10 Min 30 Min 1 Hr 4 Hr 8 Hr								
NR	NR	NR	NR	NR					
Key Reference: Cher	Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.								
Test Species/Strain/N	Number:								
Exposure Route/Con	Exposure Route/Concentrations/Durations:								
Effects:									
Endpoint/Concentra	tion/Rationale:								
Uncertainty Factors /	Rationale:								
Modifying Factor:									
Animal to Human D	osimetric Adjustment	•							
Time Scaling:									
Data Quality and Research Needs: No chemical-specific data were available for derivation of AEGL-1 values									
for ethyl chloroth	nioformate.								

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-2 VALUES FOR ETHYL CHLOROTHIOFORMATE						
10-Min	30-Min	1-Hr	4-Hr	8-Hr		
0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm		
Key Reference: Stauffer. 1983. Acute i Center Inhalation Facil OTS0538464.	-		· · · · · ·			
Test Species/Strain/N	umber: See AEGL-3 I	Derivation summary tal	ble			
Exposure Route/Cond	centrations/Durations	: See AEGL-3 Derivat	ion summary table			
Effects: See AEGL-3	Derivation summary tal	ble				
	This approach is justi		concentration curv	ve with regard to lethality		
Uncertainty Factors/I	Rationale: See AEGL-	3 Derivation summary	table			
Modifying Factor: Se	e AEGL-3 Derivation s	summary table				
Animal to Human Do	simetric Adjustment:	NA				
Time Scaling: See AE	GL-3 Derivation sumn	nary table				
Data quality and rese	arch needs: See AEG	L-3 Derivation summar	ry table.			

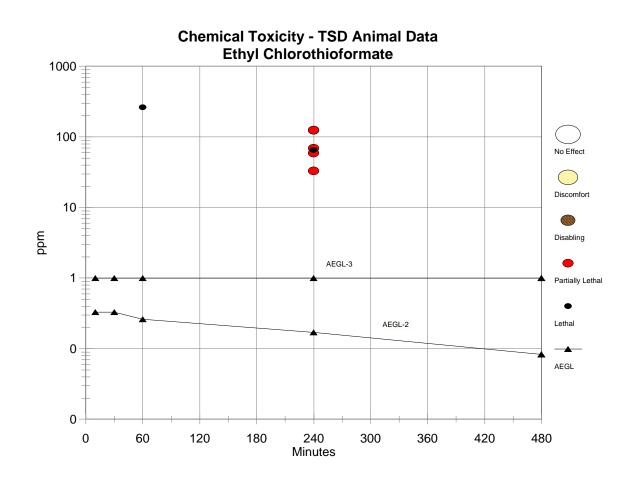
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Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate,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

10-Min	30-Min	1-Hr	4-Hr	8-Hr
1.0 ppm	1.0 ppm	0.79 ppm	0.50 ppm	0.25 ppm
Key Reference:	•		· · ·	
Stauffer. 1983. Acute in Center Inhalation Facilit OTS0538464.				
Test Species/Strain/Sex	x/Number: Sprague D	Dawley rats/ 10/sex/	group	
Exposure Route/Conce (Estimated lethality departure for A	threshold of 1/3 the 4			5 ppm) is the point-of-
Endpoint/Concentration ppm/Estimated three	on/Rationale: 1/3 the shold for death for 4 l			15 ppm)/ 15
Effects: LC ₅₀ =51 ppm (male); 41 ppm (femal	le); 45 ppm (combin	ned male and female)	
	nate is highly reactive		re likely caused by a contract of the second species or among the species or among species or among species or a species of the second species of the seco	lirect chemical effect on ong individuals.
Intraspecies = 10:				
	tial delayed systemic	effects from the thi	o- moiety	
Modifying Factor:				
Animal to Human Dosi	metric Adjustment:	Insufficient data		
		(8-hours). The 30-	r time points (30-minu minute value was adop	
=				





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