INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROFORMATES

Methyl Chloroformate
$C_2H_3ClO_2$ (CAS Reg. No. 79-22-1)

Ethyl Chloroformate
$C_3H_5ClO_2$ (CAS Reg. No. 541-41-3)

Propyl Chloroformate
$C_4H_7ClO_2$ (CAS Reg. No. 109-61-5)

Isopropyl Chloroformate
$C_4H_7ClO_2$ (CAS Reg. No. 108-23-6)

Allyl Chloroformate
$C_4H_5ClO_2$ (CAS Reg. No. 2937-50-0)

n-Butyl Chloroformate
$C_5H_9ClO_2$ (CAS Reg. No. 592-34-7)

Isobutyl Chloroformate
$C_5H_{10}ClO_2$ (CAS Reg. No. 543-27-1)

sec-Butyl Chloroformate
$C_5H_9ClO_2$ (CAS Reg. No. 17462-58-7)

Benzyl Chloroformate
$C_8H_7ClO_2$ (CAS Reg. No. 501-53-1)

Phenyl Chloroformate
$C_7H_5ClO_2$ (CAS Reg. No. 1885-14-9)

2-Ethylhexyl Chloroformate
$C_9H_{17}ClO_2$ (CAS Reg. No. 24468-13-1)

Ethyl Chlorothioformate
C_3H_5ClO-S (CAS Reg. No. 2941-64-2)

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/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, 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/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

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

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

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I.1 General Chemical and Physical Properties

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

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

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

TABLE I-1. Chemical and Physical Data for Methyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	Methyl Chloroformate	HSDB, 2005a
Synonyms	Carbonochloridic acid, methylethyl ester; Chlorocarbonic acid, methylethyl ester; Chloroformic acid methyl ester; Formic acid, chloro-, methyl ester; Methyl chlorocarbonate; K-stoff; Methoxycarbonyl chloride; TL 438	HSDB, 2005a
CAS Registry No.	79-22-1	HSDB, 2005a
Chemical Formula	$C_2H_3ClO_2$	HSDB, 2005a
Molecular Weight	94.5	HSDB, 2005a
Physical State	Colorless liquid	HSDB, 2005a
Vapor Pressure	108.5 mm Hg at 25EC	HSDB, 2005a
Vapor Density	3.26 g/L (air = 1)	HSDB, 2005a
Density/Specific Gravity	1.223 g/cm^3	HSDB, 2005a
Melting/Boiling/Flash Point	-61EC/71.0EC/12.2EC	HSDB, 2005a
Solubility	slightly soluble (hydrolyzes) in water; Soluble in chloroform, benzene, alcohol, ether	HSDB, 2005a
Conversion factors in air	1 mg/m^3 = 0.26 ppm 1 ppm = 3.9 mg/m^3	

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	$C_3H_5ClO_2$	HSDB, 2005b
Molecular Weight	108.53	HSDB, 2005b
Physical State	Water-white liquid	HSDB, 2005b
Vapor Pressure	22.4 mm Hg at 25EC	HSDB, 2005b
Vapor Density	3.7 g/L (air = 1)	HSDB, 2005b
Density/Specific Gravity	1.403 g/cm^3	HSDB, 2005b
Melting/Boiling/Flash Point	-80.6EC/95EC/27.8EC	HSDB, 2005b
Solubility	Gradually decomposes in water	HSDB, 2005b
Conversion factors in air	1 mg/m^3 = 0.23 ppm 1 ppm = 4.4 mg/m^3	

TABLE I-3. Chemical and Physical Data for Propyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	Propyl Chloroformate	HSDB, 2005c
Synonyms	Carbonochloridic acid, propyl ester; Formic acid, chloro-, propyl ester; Propyl chlorocarbonate; N-Propyl chloroformate	HSDB, 2005c
CAS Registry No.	109-61-5	HSDB, 2005c
Chemical Formula	$C_4H_7ClO_2$	HSDB, 2005c
Molecular Weight	122.55	HSDB, 2005c
Physical State	Colorless liquid	HSDB, 2005c
Vapor Pressure	20 mm Hg at 25EC	HSDB, 2005c
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005c
Density/Specific Gravity	1.09 g/cm^3	HSDB, 2005c
Boiling/Flash Point	112.4EC/34.4EC	HSDB, 2005c
Solubility	Miscible in chloroform, benzene, ether	HSDB, 2005c
Conversion factors in air	1 mg/m^3 = 0.20 ppm 1 ppm = 5.0 mg/m^3	

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	$C_4H_7ClO_2$	HSDB, 2005d
Molecular Weight	122.55	HSDB, 2005d
Physical State	Colorless liquid	HSDB, 2005d
Vapor Pressure	100 mm Hg at 47EC	HSDB, 2005d
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005d
Density/Specific Gravity	1.08 g/cm^3	HSDB, 2005d
Boiling/Flash Point	104.6EC/27.8EC	HSDB, 2005d
Solubility	Soluble in ether; hydrolyzes in water	HSDB, 2005d
Conversion factors in air	1 mg/m^3 = 0.20 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	$C_4H_5ClO_2$	HSDB, 2005e
Molecular Weight	120.54	HSDB, 2005e
Physical State	Colorless liquid	HSDB, 2005e
Vapor Pressure	20 mm Hg at 25EC	HSDB, 2005e
Vapor Density	4.2 g/L (air = 1)	HSDB, 2005e
Density/Specific Gravity	1.14 g/cm^3	HSDB, 2005e
Boiling/Flash Point	110EC/31.1EC	HSDB, 2005e
Solubility	Hydrolyzes in water	HSDB, 2005e
Conversion factors in air	1 mg/m^3 = 0.20 ppm 1 ppm = 4.9 mg/m^3	

TABLE I-6. Chemical and Physical Data for n-Butyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	n-butyl Chloroformate	Kreutzberger, 2003
Synonyms	Butyl chlorocarbonate; Butoxycarbonyl chloride; Chloroformic acid, butyl ester	BG Chemie, 2005

CAS Registry No.	592-34-7	Kreutzberger, 2003
Chemical Formula	$C_5H_9ClO_2$	Kreutzberger, 2003
Molecular Weight	136.58	Kreutzberger, 2003
Physical State	liquid	BG Chemie, 2005
Vapor Pressure	7 hPa at 20EC	BG Chemie, 2005
Vapor Density	-	-
Density/Specific Gravity	1.06 g/cm^3	Kreutzberger, 2003
Solubility	Poorly soluble (hydrolyzes) in water; Miscible in ether; soluble in acetone and ethanol	BG Chemie, 2005
Boiling/Flash Point	77.6EC/46.0EC	Kreutzberger, 2003
Conversion factors in air	1 mg/m^3 = 0.18 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	130EC/39.4EC	O'Neil et al., 2001
Solubility	Miscible in chloroform, benzene, ether; Gradually decomposes in water	O'Neil et al., 2001
Conversion factors in air	1 mg/m^3 = 0.18 ppm 1 ppm = 5.6 mg/m^3	

TABLE I-8. Chemical and Physical Data for sec-Butyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	sec-Butyl Chloroformate	Kreutzberger, 2003
Synonyms	Carbonochloridic acid, 1-methylpropyl ester	NLM, 2005
CAS Registry No.	17462-58-7	NLM, 2005
Chemical Formula	$C_5H_9ClO_2$	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/35.6EC	Kreutzberger, 2003
Solubility	-	-
Conversion factors in air	1 mg/m^3 = 0.18 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	$C_8H_7ClO_2$	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 85-87EC	IPCS, 1999
Vapor Density	1 g/L (air = 1)	IPCS, 1999
Density/Specific Gravity	1.22 g/cm^3	Kreutzberger, 2003
Boiling/Flash Point	103EC/80EC	O'Neil et al., 2001
Solubility	Decomposes in water	O'Neil et al., 2001
Conversion factors in air	1 mg/m^3 = 0.14 ppm 1 ppm = 7.0 mg/m^3	

TABLE I-10. Chemical and Physical Data for Phenyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	Phenyl Chloroformate	Kreutzberger, 2003
Synonyms	Carbonochloridic acid phenyl ester; Phenyl chlorocarbonate; Phenoxycarbonyl chloride; Formic acid, chloro-, phenyl ester	IPCS, 2005
CAS Registry No.	1885-14-9	IPCS, 2005
Chemical Formula	$C_7H_5ClO_2$	IPCS, 2005
Molecular Weight	156.6	IPCS, 2005
Physical State	Colorless liquid	IPCS, 2005

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

TABLE I-11. Chemical and Physical Data for 2-Ethylhexyl Chloroformate

Characteristic/Property	Data	Reference
Common Name	2-Ethylhexyl Chloroformate	Kreutzberger, 2003
Synonyms	Chloroformic acid 2-ethylhexyl ester; Carbonochloridic acid, 2-ethylhexyl ester; 2-Ethylhexyl chlorocarbonate; Formic acid, chloro-, 2-ethylhexyl ester	RTECS, 2005
CAS Registry No.	24468-13-1	RTECS, 2005
Chemical Formula	$C_9H_{17}ClO_2$	RTECS, 2005
Molecular Weight	192.71	RTECS, 2005
Physical State	Clear, colorless liquid	RTECS, 2005
Vapor Pressure	1 mm Hg at 45EC	RTECS, 2005
Vapor Density	>1 g/L (air = 1)	RTECS, 2005
Density/Specific Gravity	0.9914 g/cm^3	Kreutzberger, 2003
Boiling/Flash Point	208EC/NA	Kreutzberger, 2003
Solubility	Decomposes in water	RTECS, 2005
Conversion factors in air	1 mg/m^3 = 0.13 ppm 1 ppm = 7.9 mg/m^3	

TABLE I-12. Chemical and Physical Data for Ethyl Chlorothioformate

Characteristic/Property	Data	Reference
Common Name	Ethyl Chlorothioformate	HSDB, 2005f
Synonyms	Ethylthiol chloroformate; Ethylthiocarbonyl chloride; Formin acid, chlorothio-, S-ethyl ester	HSDB, 2005f
CAS Registry No.	2941-64-2	HSDB, 2005f
Chemical Formula	C_3H_5ClO-S	HSDB, 2005f
Molecular Weight	124.59	HSDB, 2005f
Physical State	Amber liquid	Stauffer Chemical Company, 1983
Vapor Pressure	8.3 mm Hg at 21EC	Stauffer Chemical Company, 1983

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

I.2 Production and Use

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

Chloroformates are used as intermediates in the synthesis of pesticides, herbicides, perfumes, pharmaceuticals, foods, polymers, and dyes. Chloroformates are also used for conversion to peroxydicarbonates, which then serve as free radical initiators for polymerization of vinyl chloride, ethylene, and other unsaturated monomers (Kreutzberger, 2003).

I.3 Absorption, Metabolism, Disposition and Excretion

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

I.4 Mechanism of Toxicity

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

I.5 Concurrent Exposure Issues

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

I.6 Species Sensitivity

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

I.7 Temporal Extrapolation

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

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

I. 8 References

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CHAPTER II. METHYL CHLOROFORMATE

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SUMMARY: Methyl Chloroformate

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

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

The calculated 4-hr $BMCL_{05}$ value in rats (42.4 ppm) (Hoechst, 1986) was used as the point-of-departure for methyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 each were applied because methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-min, 30-min and 1-hr) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC_{50} study (Bio-Test, 1975); utilizing the $BMCL_{05}$ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986).

The AEGL values are listed in the table below.

Summary of AEGL Values For Methyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data
AEGL-2 (Disabling)	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)	⅓ 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.

References:

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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.

II.1.2 Non-lethal Toxicity

II.1.2.1 Case Reports

A healthy 41-year-old chemical production worker inhaled 2-3 breaths of an atmosphere containing methyl chloroformate in the vicinity of leaking equipment (Schuckmann, 1972). The concentration of methyl chloroformate in the discharge was not reported. The worker left the contaminated area immediately because of a penetrating odor and coworkers' warnings. About an hour after exposure, he experienced slight eye irritation and an irritating cough and reported to the medical facility at the factory. Auscultation of lungs was largely unremarkable; isolated respiratory sounds were found in the upper lobes. The next day (about 24 hours later), a follow-up examination was performed. The worker reported increasing cough since early morning and presented with abnormal respiratory sounds in the upper lung lobes during auscultation. A codeine preparation (Codipront) was prescribed and a follow-up examination was scheduled for the next day. However, the worker returned in the afternoon of the same day because of increasingly severe signs and symptoms as the day progressed, as evidenced by extensive abnormal sounds in the upper lung lobes, moderate dyspnea, and a temperature of 37.2EC. The worker was kept for observation over night, with an oxygen supply, a bronchodilator (Brondilat) and 40 mg Urbason i.v. During the night the symptoms receded and the worker slept well to the early morning hours. At that time, the cough resumed and auscultation showed slight dry rales in the right lower lung lobe. The worker was sent home following administration of Omnicillin and Codipront. Examination on the next day revealed no notable complaints. The following day, however, the worker complained of a severely irritating cough and dyspnea; slight cyanosis of the lips was also observed. Auscultation of the lungs, revealing rales in all lung areas, confirmed the subjective findings. The worker was then admitted to the factory's medical facility and stayed there for about three days. Urbason, Brondilat, and Hostacyclin were administered during this time period. The symptoms started to recede with a morning cough still present, and drug treatment was discontinued.

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

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

II.1.3 Developmental/Reproductive Toxicity

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

II.1.4 Genotoxicity

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

II.1.5 Carcinogenicity

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

II.1.6 Summary

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

II.2 ANIMAL TOXICITY DATA

II.2.1 Lethality

II.2.1.1 Rats

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

TABLE II-1*. Mortality of Rats Exposed to Methyl Chloroformate for1-hour

Concentration (ppm)	Male	Female
0	0/5	0/5
145	4/5	0/5
173	5/5	2/5
233	5/5	4/5
274	5/5	1/5
$BMCL_{05}$	74 ppm	
LC_{50}	163 ppm	

*Bio Test Laboratories, Inc. (1975)

In another study, groups of ten male Sprague Dawley rats were exposed to 735, 2947, 9610, or 66,235 ppm (nominal concentrations) methyl chloroformate for 1 hour (WARF Institute, Inc., 1972). A "semi-portable" exposure chamber containing an exhaust fan for adjustable air flow was utilized. Methyl chloroformate was administered into the incoming air stream just before it entered the chamber port, and exposure concentrations were calculated by dividing the total amount sprayed into the chamber by the total cubic feet of air circulated through the chamber. All animals died within 18 hours of exposure. Data are summarized in Table II-2.

TABLE II-2*. Mortality of Rats Exposed to Methyl Chloroformate for1-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)

Groups of five male and five female Fischer 344 rats (main group) were exposed to 0, 26, 110, 133, 159, or 192 ppm methyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber (Fisher et al., 1981). Methyl chloroformate chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. In addition 10, 10, and 20 rats/sex (satellite rats) were concurrently exposed to 26, 110, or 133 ppm methyl chloroformate, respectively. One satellite rat/sex/concentration and 2 rats/sex at the lower three concentrations of the main group were sacrificed at 4 and 24 hours and 9 or 10 days post-exposure. All other surviving animals were sacrificed 14 days post-exposure. The LC_{50} values were 100 ppm for female rats, and between 92 and 123 ppm for male rats at 14 days post-exposure. Respiratory distress occurred in all main group rats at 110, 133, 159, and 192 ppm during the first 24 hours following exposure. The respiratory distress resolved within 24 hours in the 110 ppm group;

however, the effect persisted through day 14 in the other exposure groups and was accompanied by lethargy, weakness, and inactivity. Concentration-related red or clear ocular and nasal discharge and gross lung lesions were observed in rats at 110, 133, 159, and 192 ppm. Controls and rats in the 26 ppm group were clinically normal. Rats in the satellite group responded similarly to corresponding rats in the main group. In the main study group, decreased mean body weight and body weight gain were observed in the 110, 133, 159, and 192 ppm rats and correlated with poor clinical status prior to death or study termination. No effect on body weight was observed in rats exposed to 26 ppm. Lesions in satellite rats exposed to 110 and 133 ppm were comparable at all three sacrifice times and included severe degeneration, necrosis, erosion, and ulceration of the nasal turbinates and tracheal mucosal epithelia; alveolar hemorrhage; and erosion of bronchial and bronchiolar epithelia. By day 9 or 10, the nasal turbinate effects had resolved, but regeneration was incomplete and purulent rhinitis persisted. Other respiratory tract and lung lesions seen at 4 and 24 hours had resolved after 9 or 10 days. Pulmonary edema was observed in some rats in the 110, 133, 159, and 192 ppm groups. No pulmonary edema was observed in controls or in the group receiving 26 ppm.

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

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

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

Groups of ten male and ten female Sprague-Dawley rats were exposed to 16, 65, 96, or 127 ppm (nominal concentrations) methyl chloroformate for 4-hours, followed by a 14-day observation period (BASF, 1980). Analytical concentrations are reported as 1.5, 13.7, 33.6, and 31.0 ppm for the 16, 65, 96, and 127 ppm groups, respectively. Whole body exposures were conducted in a glass-steel inhalation chamber with a volume of 200 L. Analytical concentrations were measured via gas chromatography. Clinical signs in the 65, 96, and 127 ppm groups included dyspnea, gasping, blistering in front of noses, red ocular and nasal discharge and encrustations, ruffled and sticky fur, staggering, distended abdomen, poor general state, attempts to escape, impaired coordination, salivation, and squatting posture. Animals in the 16 ppm group exhibited jerky respiration and eyelid closure. Body weight gain was initially decreased in the three highest concentration groups; this effect had resolved in surviving animals by day 14 post-exposure. Four hour LC_{50} values of 13 ppm and 18 ppm were calculated for males and females, respectively. A combined male and female LC_{05} value of 15 ppm was also calculated. It should be noted that the LC_{50} values calculated from this study appear to be inconsistent with the other available data (see Table II-6). Data are summarized in Table II-4.

TABLE II-4*. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours

Nominal Concentration (ppm)	Analytical Concentration (ppm)	Male	Female
16	1.5	0/10	0/10
65	13.7	5/10	3/10
96	33.6	10/10	7/10
127	31.0	10/10	10/10
LC_{50}		13 ppm	18 ppm
		15 ppm	

*BASF, 1980

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

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

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

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

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

A 4-week repeated exposure study (BASF, 1993) described both lethal and nonlethal effects in rats; this study is described in Section II.2.2.

II.2.1.2 Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 16.5, 25, 35, 50, 75, or 125 ppm methyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted methyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9 L stainless steel chamber which was continuously evacuated at 20 L/min. An RD_{50} of 52.4 ppm was calculated. Results are summarized in Table II-5.

TABLE II-5. Exposure of Male Swiss-Webster Mice to Methyl Chloroformate for 30 minutes*

Concentration (ppm)	Respiratory rates(control/exposed)	% Decrease in respiratory rate	Mortality
16.5	265/230	13.2	-
25	250/180	26	-
35	285/190	33.3	-
50	270/140	46.3	1/4 (<6 hr.)
75	275/100	63.6	1/4 (<6 hr.)
125	250/50	80	4/4 (<5 hr.)
125	280/50	82.1	3/4 (<20 hr.)

.*Carpenter, 1982

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

II.2.2. Repeated-Exposure

In an inhalation range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to 0, 1.9, 6.2, or 19.5 ppm methyl chloroformate 6 hours/day for 5 days (HRC, 1992). No treatment-related effects were noted in the 1.9 ppm group. Clinical signs in the 6.2 and 19.5 ppm groups included blinking, licking the inside of the mouth, ruffled fur, and sneezing. In the 19.5 ppm group, males sneezed and had noisy nasal breathing in between exposures. Decreased body weight was accompanied by decreased food and water consumption in rats exposed to 19.5 ppm. Animals were necropsied three days post-exposure. Lungs failed to collapse in 1/5 males and 3/5 females in the 6.2 ppm group and 5/5 females in the 19.5 ppm group. Petechial bleeding was noted in the lungs of 1/5 males in the 6.2 ppm group and 5/5 males and 1/5 females in the 19.5 ppm group. Lung weight was increased in all high-concentration females; organ weights were not examined in males due to experimental error during necropsy. Inflammatory and erosive mucous membrane lesions were noted in the nose, larynx, and trachea, and bronchiolitis and pneumonia were noted in high-concentration rats. Focal epithelial hyperplasia of the nasal mucosa was noted in the 6.2 and 19.5 ppm groups. Comparison of histological findings in a satellite group examined immediately after three days of exposure suggested that regeneration and repair of epithelial lesions had occurred in animals examined three days post-exposure.

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

Groups of ten male and ten female Wistar rats were exposed to 0, 0.40, 2.15, 3.98, or 7.83 ppm methyl chloroformate 6 hours/day, 5 days/week for 3, 10, 20, or 65 exposures (90-day study with interim necropsies after 3, 14, and 28 study days; satellite groups also contained 10 rats/sex/concentration) (BASF, 1999). In addition to observation for clinical signs and complete necropsy, cell proliferation measurements were performed in four female rats per group. 5-Bromo-2'-deoxyuridine (BrdU) was administered to these females via subcutaneously implanted minipumps. Pumps remained in the animals for 8 hours or 3 days for evaluation of cell proliferation in nasal cavity and laryngeal epithelia. Four male rats in the 7.83 ppm group died; deaths occurred after 24, 32, 36, and 41 exposures. Clinical signs were noted only in high-

concentration animals and included rubbing of snout, sneezing, nasal crusts in the animals that subsequently died, as well as abnormal respiration, and general morbidity. Decreased body weight and body weight gain were noted in males in the 3.98 and 7.83 ppm groups sacrificed after three exposures and at study termination. At necropsy, gross effects were observed only in the 7.83 ppm group and included red foci in the lungs. Animals in the high concentration group, except for those sacrificed after three exposures, exhibited increased lung weight. Concentration and duration-related histological effects were limited to the respiratory tract and occurred in 2.15, 3.98, and 7.83 ppm animals at all sacrifice times. Nasal and laryngeal squamous cell metaplasia were noted at 2.15, 3.98, and 7.83 ppm. Focal epithelial hyperplasia and squamous cell metaplasia and hyperplasia of the trachea and lungs were noted at 3.98 and 7.83 ppm. No histopathology was noted in the 0.40 ppm group. Cell proliferation was increased at 2.15 ppm after 20 and 65 days, and at 3.98 and 7.83 ppm after 10, 20, and 65 days. The significant increases involved respiratory and transitional cell epithelium of the nose and in the ciliated and squamous epithelium of the larynx. No cell proliferation was noted at 0.40 ppm.

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

II.2.3. Developmental/Reproductive Toxicity

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

II.2.4. Genotoxicity

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

II.2.5 Carcinogenicity

Animal carcinogenicity data were not located**.**

II.2.6 Summary

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

Charles River rats (Bio-Test Laboratories, Inc., 1975), 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), and 88 ppm and 103 ppm for male and female Sprague Dawley rats, respectively (Vernot et al., 1977). Rat 4-hr LC_{50} values were reported to be 51-53 ppm (Hoechst, 1986) and 15 ppm (BASF, 1980); however, the 15 ppm value is an outlier when compared to other available data. Signs of toxicity included body weight loss, weakness and lethargy, respiratory distress, hematological effects consistent with decreased oxygen availability (assumed secondary to pulmonary congestion and edema), and bronchiolitis, fibrosis, and pulmonary edema. A 30-min RD_{50} of 47.2 ppm (nominal concentration) methyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). Methyl chloroformate did not induce mutations in an Ames bacterial reverse mutation assay ((BASF, 1988; Miltenburger, 1985; Hoechst, 1977) but did induce chromosomal aberrations in Chinese hamster V79 cells in the presence of S9 (Miltenburger, 1986). No data concerning developmental/reproductive toxicity or carcinogenicity of methyl chloroformate were located in the available literature. Animal data are summarized in Table II-6.

Table II-6. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Acute Exposure				
Rat	37,500	3 minutes	12/12 dead	BASF, 1978
Rat	735 (nominal)	20 minutes	10/10 dead	WARF Institute, Inc., 1972
Rat	26	1 hour	No effects	Fisher et al., 1981
Rat	74 (nominal)	1 hour	$BMCL_{05}$	Bio-Test Labs, Inc., 1975
Rat-male	88	1 hour	LC_{50}	Vernot et al., 1977
Rat-male	92-123	1 hour	LC_{50}	Fisher et al., 1981
Rat-female	100	1 hour	LC_{50}	Fisher et al., 1981
Rat-female	103	1 hour	LC_{50}	Vernot et al., 1977
Rat	163 (nominal)	1 hour	LC_{50}	Bio-Test Labs Inc., 1975
Rat	2974 (nominal)	1 hour	10/10 dead	WARF Institute, Inc., 1972
Rat	15	4 hours	LC_{50}	BASF, 1980
Rat	42.4 ppm	4 hours	$BMCL_{05}$	Hoechst, 1986
Rat-male	51	4 hours	LC_{50}	Hoechst, 1986
Rat-female	53	4 hours	LC_{50}	Hoechst, 1986
Mouse	52.4	30 minutes	RD_{50}	Carpenter, 1982
Repeated Exposure				
Rat	0.40	6 hr/day, 3 days	No effects	BASF, 1999
Rat	2.15	6 hr/day, 3 days	Histopathology	BASF, 1999

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

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

II.3. DATA ANALYSIS AND AEGL-1

II.3.1 Human Data Relevant to AEGL-1

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

II.3.2 Animal Data Relevant to AEGL-1

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

II.3.3 Derivation of AEGL-1

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

TABLE II-7. AEGL-1 Values for Methyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

II.4. DATA ANALYSIS AND AEGL-2

II.4.1 Human Data Relevant to AEGL-2

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

II.4.2 Animal Data Relevant to AEGL-2

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

II.4.3 Derivation of AEGL-2

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for methyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat LC_{50}: 51-53 ppm, 0% mortality in rats exposed to 45 ppm and 80% mortality in rats exposed to 57 ppm for 4 hours (Hoechst, 1986); 1-hour rat LC_{50}: 100 ppm; rats exposed to 26 ppm for 1-hr were clinically normal and had no mortality (Fisher et al., 1981). The AEGL-2 values for methyl chloroformate are presented in Table II-8, and the calculations for these AEGL-2 values are presented in Appendix II-A.

TABLE II-8. AEGL-2 Values for Methyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)

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

II.5. DATA ANALYSIS AND AEGL-3

II.5.1 Human Data Relevant to AEGL-3

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

II.5.2 Animal Data Relevant to AEGL-3

Rat 1-hr LC_{50} values were as follows: 163 ppm for male and female Charles River rats (Bio-Test Laboratories, In., 1975), 92-123 ppm and 100 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), and 88 ppm and 103 ppm for male and female Sprague Dawley rats, respectively (Vernot et al., 1977). Exposure of male and female Fischer 344 rats to 26 ppm methyl chloroformate for 1 hour resulted in no deaths (Fisher et al., 1981). Four hour LC_{50} values of 51 ppm and 53 ppm were calculated for male and female Wistar rats, respectively; a combined

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

II.5.3 Derivation of AEGL-3

The calculated 4-hr $BMCL_{05}$ value in rats (42.4 ppm) (Hoechst, 1986) will be used as the point-of-departure for methyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 45 ppm for 4 hours (Hoechst, 1986). Interspecies and intraspecies uncertainty factors of 3 each will be applied because methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-min, 30-min and 1-hr) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC_{50} study (Bio-Test, 1975); utilizing the $BMCL_{05}$ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986). The AEGL-3 values for methyl chloroformate are presented in Table II-9, and the calculations for these AEGL-3 values are presented in Appendix II-A.

TABLE II-9. AEGL-3 Values for Methyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	12 ppm (47 mg/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)

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).

II.6. SUMMARY OF AEGLS

II.6.1 AEGL Values and Toxicity Endpoints

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.

TABLE II-10. Summary of AEGL Values For Methyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.0 ppm (16 mg/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.

II.6.2 Other Exposure Criteria

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

II.6.3 Data Adequacy and Research Needs

Human data are limited to anecdotal reports. Animal data include acute and repeated-exposure rat inhalation studies and a mouse RD_{50} study. Support provided by the repeated-exposure studies adds to confidence in the derived AEGL values.

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APPENDIX II-A: Time Scaling Calculations for Methyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR METHYL CHLOROFORMATE

Data are insufficient for derivation of AEGL-1 values; therefore, AEGL-1 values are Not Recommended.

DERIVATION OF AEGL-2 VALUES FOR METHYL CHLOROFORMATE

Key study: Hoechst, 1986

Toxicity Endpoint: ⅓ of the AEGL-3 values

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

DERIVATION OF AEGL-3 VALUES FOR METHYL CHLOROFORMATE

Key study: Hoechst, 1986

Toxicity Endpoint: Calculated $BMCL_{05}$ (42.4 ppm) from a 4-hour exposure in rats.

Scaling:	10-min, 30-min, and 1-hour
	$C^3 \times t = k$
	$(42.4\ ppm)^3 \times 4\ hr = 304900\ ppm"hr$
	8-hours
	$C^1 \times t = k$
	$(42.4\ ppm)^1 \times 4\ hr = 170\ ppm"hr$
Uncertainty Factors:	
	3 for interspecies variability
	3 for intraspecies variability
10-min AEGL-3	$C^3 \times 0.167\ hr = 304900\ ppm"hr$
	$C^3 = 1825748\ ppm$
	$C = 122\ ppm$
	10-min AEGL-3 = 122/10 = 12 ppm
30-min AEGL-3	
	$C^3 \times 0.5\ hr = 304900\ ppm"hr$
	$C^3 = 609800\ ppm$
	$C = 84.8\ ppm$
	30-min AEGL-3 = 84.8/10 = 8.5 ppm
1-hr AEGL-3	$C^3 \times 1\ hr = 304900\ ppm"hr$
	$C^3 = 304900\ ppm$
	$C = 67.3\ ppm$
	1-hr AEGL-3 = 67.3/10 = 6.7 ppm
4-hr AEGL-3	4-hr AEGL-3 = 42.4/10 = 4.2 ppm
8-hr AEGL-3	$C^1 \times 8\ hr = 170\ ppm"hr$
	$C^1 = 21.2\ ppm$
	$C = 21.2\ ppm$
	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-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
NR	NR	NR	NR	NR

Reference: NA

Test Species/Strain/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

Data quality and research needs: Data were insufficient for derivation of AEGL-1 values. AEGL-1 values are not recommended.

AEGL-2 VALUES FOR METHYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
4.0 ppm	**2.8 ppm**	**2.2 ppm**	**1.4 ppm**	**0.70 ppm**

Key Reference: Hoechst. 1986. Chloroformic acid methyl ester. Inhalation toxicity in the flow through system in male and female SPF Wistar rats. 4-hour LC_{50}. Hollander, H., Weigland, W, Mayer, D., and Langer, K.H. Hoechst Pharmaceutical Research Toxicology. Report No. 86.0432. April 11, 1986.

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

AEGL-3 VALUES FOR METHYL CHLOROFORMATE

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
12 ppm	8.5 ppm	6.7 ppm	4.2 ppm	2.1 ppm

Key Reference: Hoechst. 1986. Chloroformic acid methyl ester. Inhalation toxicity in the flow through system in male and female SPF Wistar rats. 4-hour LC_{50}. Hollander, H., Weigland, W, Mayer, D., and Langer, K.H. Hoechst Pharmaceutical Research Toxicology. Report No. 86.0432. April 11, 1986.

Test Species/Strain/Sex/Number: Rats/Wistar/5/sex/group

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

Endpoint/Concentration/Rationale: Calculated $BMCL_{05}$ in rats after a 4 hr-exposure/ 42.4 ppm/Estimated threshold for death for 1 hour exposure in rats

Effects:
Male rat LC_{50} = 51 ppm; female rat LC_{50} = 53 ppm
Male and Female $BMCL_{05}$ = 42.4
Male and Female BMC_{01} = 47.8

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

Uncertainty Factors/Rationale:
Interspecies = 3:
Intraspecies = 3:
Methyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals.

Total UF = 10.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $c^n \times t = k$, where n=3 when extrapolating to shorter time points (10-min, 30-min and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). Time scaling from 4-hours to 10-minutes is justified based on a 1-hr LC_{50} study (Bio-Test, 1975); utilizing the $BMCL_{05}$ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986).

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

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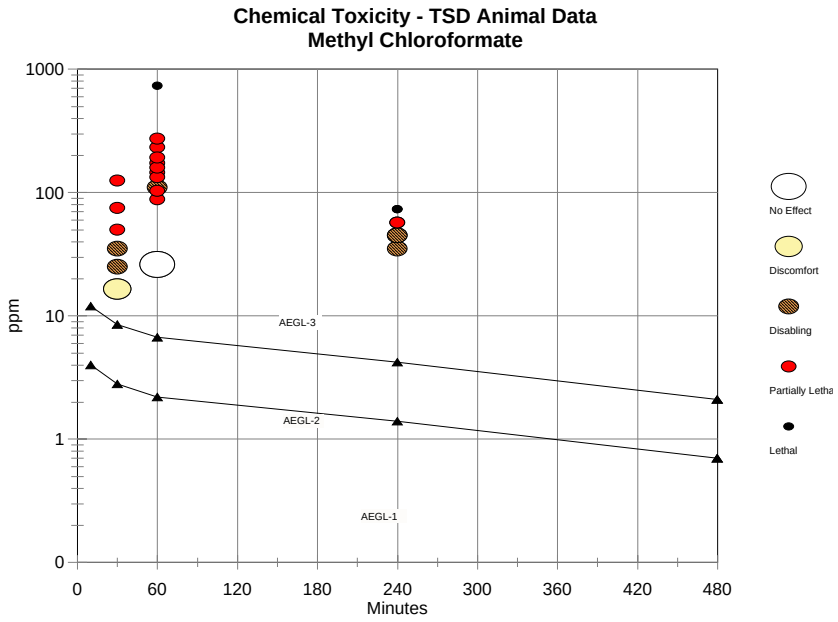
APPENDIX II-C:

Category Plot for Methyl Chloroformate


Chemical Toxicity - TSD Animal Data
Methyl Chloroformate
1000
100
10
1
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Letha
Lethal

APPENDIX II-D:

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

  User has chosen the log transformed model

              Default Initial (and Specified) Parameter Values
                background =           0
                 intercept =     -20.4973
                     slope =      5.16963

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

            intercept
intercept           1

                    Parameter Estimates

      Variable         Estimate          Std. Err.
    background                0              NA
     intercept          -71.9357          0.449759
         slope               18              NA

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

                  Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -5.00402
    Fitted model       -5.00722    0.00639048      3         0.9999
   Reduced model        -27.5256      45.0431      3         <.0001

          AIC:         12.0144
```

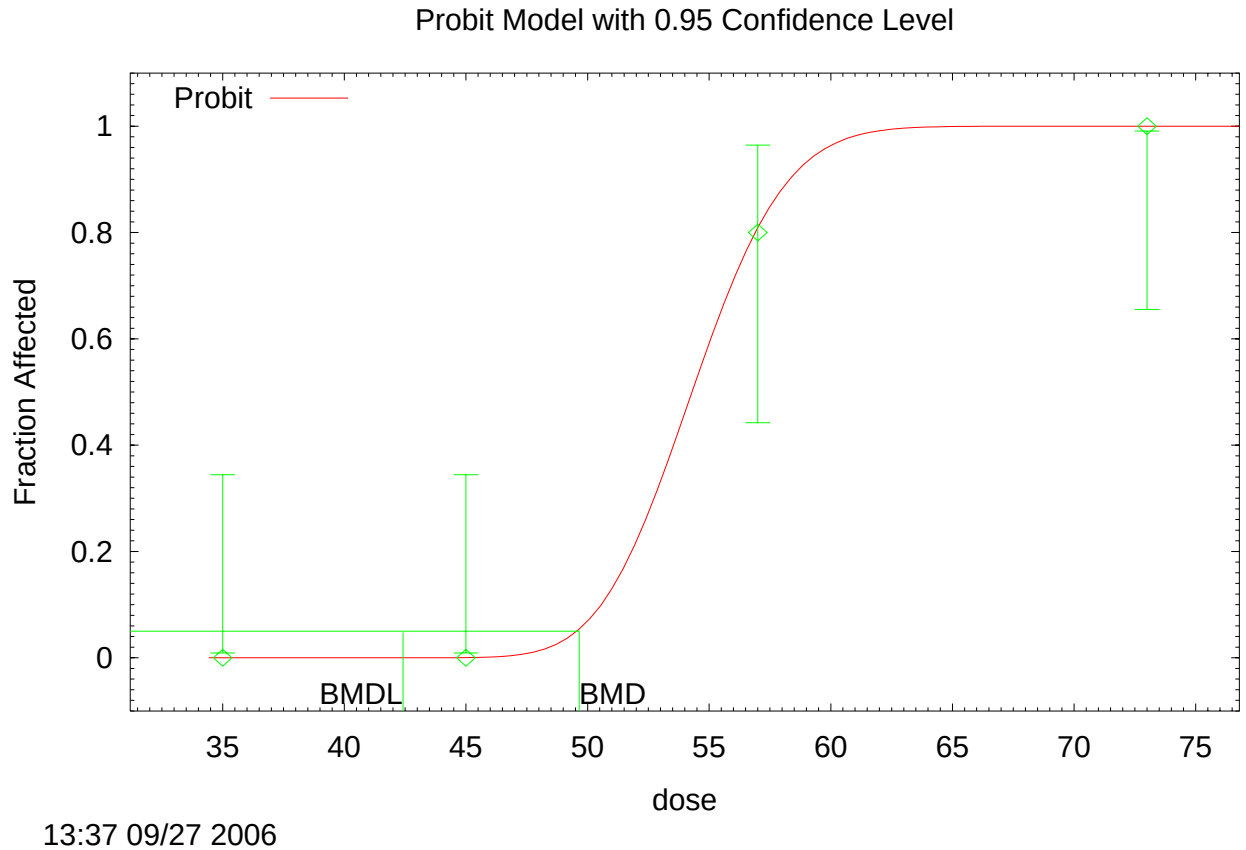
Goodness of Fit

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

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

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 49.6524
BMDL = 42.4113



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CHAPTER III. ETHYL CHLOROFORMATE

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SUMMARY: ETHYL CHLOROFORMATE

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

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

One-third of the most conservative 1-hr LC_{50} value in rats (145 ppm x ⅓ =48 ppm) (Vernot et al., 1977) was used as the point-of-departure for ethyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and intraspecies uncertainty factors of 3 each were applied because ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

The calculated values are listed in the table below.

Summary of AEGL Values For Ethyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (8.8 mg/m^3)	1.6 ppm (7.0 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.88 mg/m^3)	⅓ 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.

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.

III.1. HUMAN TOXICITY DATA

III.1.1 Acute Lethality

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

III.1.2 Non-lethal Toxicity

III.1.2.1 Case Report

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

III.1.3 Developmental/Reproductive Toxicity

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

III.1.4 Genotoxicity

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

III.1.5 Carcinogenicity

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

III.1.6 Summary

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

III.2. ANIMAL TOXICITY DATA

III.2.1 Acute Lethality

III.2.1.1 Rats

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

Groups of five male and five female Fischer 344 rats were exposed to 0, 47, 153, 180, 245, or 270 ppm ethyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber, followed by a 14-day observation period (Fisher et al., 1981). Ethyl chloroformate chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. The LC_{50} values were 189 (164-216) ppm for male rats, and 200 (173-232) ppm for female rats at 14 days post-exposure. Controls and rats in the 47 ppm group were clinically normal and showed no treatment-related effects at necropsy. Body weight gain was decreased for surviving males and females in the 153 and 180 ppm groups at day 7 and at termination. All rats in the 245 and 270 ppm groups died prior to scheduled sacrifice. Average relative lung weight of animals in the 245 and 270 ppm groups was approximately three-times greater than that of controls, and corroborating lesions indicative of acute alveolar hemorrhage were noted. Relative lung weight was also increased (magnitude not specified) in the 153 and 180 ppm groups. Red lung coloration was noted in one male and one female in the 153 ppm group, and two females and one male in the 180 ppm group.

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

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

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

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

in isopropanol (Gage, 1970). The vapor concentrations were produced by injecting liquid at a known rate into a metered stream of air with a controlled fluid-feed atomizer. No effects were observed at 1 ppm, decreased weight gain was observed at 5 ppm, and nasal irritation, respiratory difficulty, weight loss, and poor condition were observed at 20 ppm. Distended lungs and lung hemorrhage were noted at autopsy in the 20 ppm group. No further details were provided.

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

III.2.1.2 Mice

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

TABLE III-1. Exposure of Male Swiss-Webster Mice to Ethyl Chloroformate for 30 minutes*

Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs
25	285/255	11	0/4
50	280/235	52	0/4
100	260/120	54	3/4
200	215/55	74	4/4

*Carpenter, 1982

III.2.2 Developmental/Reproductive Toxicity

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

III.2.3 Genotoxicity

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

III.2.4 Carcinogenicity

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

Van Duuren et al. (1987) investigated the carcinogenicity of ethyl chloroformate in female ICR/Ha Swiss mice by dermal and subcutaneous administration. Groups of 30 to 50 mice received dermal applications of 3.0, 4.3, or 5.5 mg ethyl chloroformate in acetone three times/week for 18-22 months. Tumor incidence was 0/50, 1/30, and 0/50, for the 3.0, 4.3, and 5.5 mg dose groups, respectively. In a dermal initiation-promotion assay, mice were administered a single 5.5 mg dose of ethyl chloroformate, followed 2 weeks later by thrice weekly applications of phorbol mysterate acetate (as a promoter) for 18-22 months. Tumors were noted in 6/50 animals (4 papillomas, 2 squamous cell carcinomas), suggesting that ethyl chloroformate may be active as a tumor promoter. In a subcutaneous injection study, mice were injected in the left flank once weekly with 0.3 or 1.1 mg ethyl chloroformate in 0.1 mL tricaprylin for 18-22 months. Tumor incidence was 1/50 for the 0.3 mg group (squamous cell carcinoma) and 0/50 in the 1.1 mg group.

III.2.5 Summary

Animal toxicity data for ethyl chloroformate are limited. Rat 1-hr LC_{50} values were relatively consistent between studies as follows: 189 ppm and 200 ppm for male and female Fischer 344 rats, respectively (Fisher et al., 1981), and 145 ppm and 170 ppm for male and female sprague Dawley rats, respectively (Vernot et al., 1977). Signs of toxicity included decreased body weight gain, respiratory distress, increased lung weight and pulmonary edema. A 30-min RD_{50} of 77.5 ppm (nominal concentration) ethyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). No data concerning developmental/reproductive toxicity were located in the available literature. Ethyl chloroformate was negative in the Ames assay. Carcinogenicity data (Van Duuren et al., 1987) suggest that ethyl chloroformate may be a tumor promoter by the dermal route. Animal data are summarized in Table III-2.

Table III-2. Summary of Acute Inhalation Data of Animals Exposed to Ethyl Chloroformate

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	47	1 hour	No effects	Fisher et al., 1981
Rat-male	145	1 hour	LC_{50}	Vernot et al., 1977
Rat-female	170	1 hour	LC_{50}	Vernot et al., 1977
Rat-male	189	1 hour	LC_{50}	Fisher et al., 1981
Rat-female	200	1 hour	LC_{50}	Fisher et al., 1981
Rat	245	1 hour	10/10 dead	Fisher et al., 1981
Rat	270	1 hour	10/10 dead	Fisher et al., 1981

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

III.3. DATA ANALYSIS AND AEGL-1

III.3.1 Human Data Relevant to AEGL-1

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

III.3.2 Animal Data Relevant to AEGL-1

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

III.3.3 Derivation of AEGL-1

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

TABLE III-3. AEGL-1 Values for Ethyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

III.4. DATA ANALYSIS AND AEGL-2

III.4.1 Human Data Relevant to AEGL-2

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

III.4.2 Animal Data Relevant to AEGL-2

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

III.4.3 Derivation of AEGL-2

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

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

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

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

III.5. DATA ANALYSIS AND AEGL-3

III.5.1 Human Data Relevant to AEGL-3

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

III.5.2 Animal Data Relevant to AEGL-3

Rat 1-hr LC_{50} 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).

III.5.3 Derivation of AEGL-3

One-third of the most conservative 1-hr LC_{50} value in rats (145 ppm x ⅓ =48 ppm) (Vernot et al., 1977) will be used as the point-of-departure for ethyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and intraspecies uncertainty factors of 3 each will be applied because ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for ethyl chloroformate are presented in Table III-5, and the calculations for these AEGL-3 values are presented in Appendix III-A.

TABLE III-5. AEGL-3 Values for Ethyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	8.8 ppm (39 mg/m^3)	6.1 ppm (27 mg/m^3)	4.8 ppm (21 mg/m^3)	1.2 ppm (5.3 mg/m^3)	0.60 ppm (2.6 mg/m^3)

III.6. SUMMARY OF AEGLS

III.6.1 AEGL Values and Toxicity Endpoints

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

TABLE III-6. Summary of AEGL Values for Ethyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (8.8 mg/m^3)	1.6 ppm (7.0 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.88 mg/m^3)
AEGL-3 (Lethal)	8.8 ppm (39 mg/m^3)	6.1 ppm (27 mg/m^3)	4.8 ppm (21 mg/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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APPENDIX III-A:

Derivation of AEGL Values for Ethyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR ETHYL CHLOROFORMATE

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

Derivation of AEGL-2 Values for Ethyl Chloroformate

Key study: Vernot et al., 1977

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2: 8.8 ppm ÷ 3 = 2.9 ppm

30-min AEGL-2: 6.1 ppm ÷3 = 2.0 ppm

1-hr AEGL-2: 4.8 ppm ÷ 3 = 1.6 ppm

4-hr AEGL-2: 1.2 ppm ÷ 3 = 0.40 ppm

8-hr AEGL-2: 0.60 ppm ÷ 3 = 0.20 ppm

DERIVATION OF AEGL-3 VALUES FOR ETHYL CHLOROFORMATE

Key study: Vernot et al., 1977

Toxicity Endpoint: Estimated LC_{01} (⅓ the LC_{50}) from a 1-hour exposure in male rats.

LC50 = 145 ppm; ⅓ x 145 ppm = 48.3 ppm (point of departure)

Scaling: 10-minutes and 30-minutes

$C^3 \times t = k$

$(48.3 \text{ ppm})^3 \times 1 \text{ hr} = 112769 \text{ ppm"hr}$

4-hours and 8-hours

$C^1 \times t = k$

$(48.3 \text{ ppm})^1 \times 1 \text{ hr} = 48.3 \text{ ppm"hr}$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3 :

$C^3 \times 0.167 \text{ hr} = 112769 \text{ ppm"hr}$

$C^3 = 675263 \text{ ppm}$

$C = 87.7 \text{ ppm}$

10-min AEGL-3 = 87.7/10 = 8.8 ppm

30-min AEGL-3

$C^3 \times 0.5 \text{ hr} = 112769 \text{ ppm"hr}$

$C^3 = 225538 \text{ ppm}$

$C = 60.9 \text{ ppm}$

30-min AEGL-3 = 60.9/10 = 6.1 ppm

1-hr AEGL-3

1-hr AEGL-3 = 48.3/10 = 4.8 ppm

4-hr AEGL-3

$C^1 \times 4 \text{ hr} = 48.3 \text{ ppm"hr}$

$C^1 = 12 \text{ ppm}$

$C = 12 \text{ ppm}$

4-hr AEGL-3 = 12/10 = 1.2 ppm

8-hr AEGL-3

$C^1 \times 8 \text{ hr} = 48.3 \text{ ppm"hr}$

$C^1 = 6.0 \text{ ppm}$

C = 6.0 ppm

8-hr AEGL-3 = 6.0/10 = 0.60 ppm

APPENDIX III- B:

Derivation Summary for Ethyl Chloroformate

AEGL-1 VALUES FOR ETHYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Strain/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				
Data quality and research needs: Data were insufficient for derivation of AEGL-1 values. AEGL-1 values are not recommended.				

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

AEGL-3 VALUES FOR ETHYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
8.8 ppm	**6.1 ppm**	**4.8 ppm**	**1.2 ppm**	**0.60 ppm**

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

Test Species/Strain/Sex/Number: Sprague-Dawley rats/ males

Exposure Route/Concentrations/Durations: Rats/Inhalation/ 1 hour
(⅓ the 1-hour male rat LC_{50} was the point-of-departure for AEGL-3) (⅓ x 145 ppm = 48.3 ppm)

Endpoint/Concentration/Rationale: Estimated LC_{01} in rats after a 1 hr-exposure/ 48.3 ppm/Estimated threshold for death for 1 hour exposure in rats

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

Uncertainty Factors/Rationale:
Interspecies = 3:
Intraspecies = 3:
Ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the 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

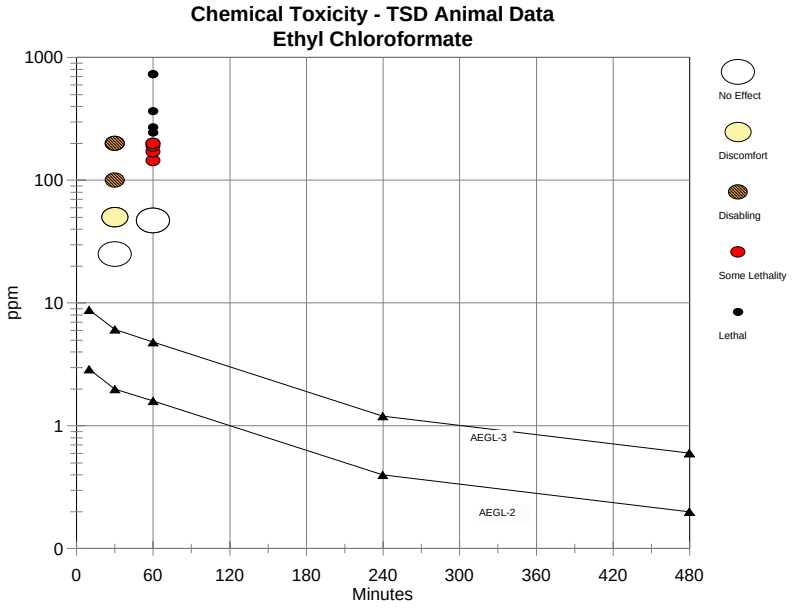
Animal to Human Dosimetric Adjustment: Insufficient data

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

Data Quality and Research Needs: Two rat acute lethality studies with consistent results. Appropriate endpoint for AEGL-3.

APPENDIX III-C:

CATEGORY PLOT FOR ETHYL CHLOROFORMATE


Chemical Toxicity - TSD Animal Data
Ethyl Chloroformate
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Some Lethality
Lethal

1 # CHAPTER IV: PROPYL CHLOROFORMATE

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SUMMARY: PROPYL CHLOROFORMATE

Data were insufficient for derivation of AEGL-1 values for propyl 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 propyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 333 ppm; 10/10 at 1000 ppm; Bio-Test, 1970).

The calculated 1-hour rat $BMCL_{05}$ of 216 ppm (Bio-Test Laboratories, Inc., 1970) was used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each were applied because propyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. A modifying factor of 2 was also applied because the key study reported nominal, not analytical, concentrations and there are no confirmatory studies. Thus, the total uncertainty/modifying factor is 20. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

The calculated values are listed in the table below.

Summary of AEGL Values For Propyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data
AEGL-2 (Disabling)	6.7 ppm (34 mg/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)	⅓ 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

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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.

IV.1.4 Genotoxicity

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

IV.1.5 Carcinogenicity

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

IV.1.6 Summary

Data concerning human exposure to propyl chloroformate are not available.

IV.2. ANIMAL TOXICITY DATA

IV.2.1 Acute Lethality

IV.2.1.1 Rats

Groups of five male and five female young adult Charles River albino rats (avg. wt. 320 g) were exposed to nominal concentrations of 249, 333, 1000, 3077, or 21,538 ppm propyl chloroformate vapor for one hour (Bio-Test Laboratories, Inc., 1970). Vapor was generated by bubbling clean, dry air through undiluted propyl chloroformate. The resulting vapor was mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was then introduced into the top of a 70 L Plexiglass inhalation chamber, dispersed by a baffle plate, and exhausted at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the propyl chloroformate vaporized by the total volume of air used during each inhalation exposure. No adverse effects were observed in the 249 ppm group during exposure. Bloody nasal discharge and dyspnea were observed in the 333 ppm group toward the end of the exposure period, while hyperactivity, clear nasal discharge, dyspnea, and salivation were observed in the 1000, 3077, and 21,538 ppm groups. No adverse effects on body weight were observed in any animals that survived the 14-day observation

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

TABLE IV-1. Exposure of Albino Rats to Propyl Chloroformate 1 hour*

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

*Bio-Test Laboratories, Inc., 1970

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

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

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

IV.2.1.2. Mice

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

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

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

IV.2.2. Nonlethal Toxicity

IV.2.2.1. Rabbits

Corneal opacity and iridal and conjunctival irritation were observed within one minute after installation of 0.1 ml undiluted propyl chloroformate into the eyes of albino rabbits (Bio-Test Laboratories, Inc., 1970). The irritation became progressively worse and within three to seven days, maximum damage was present in all ocular tissues. No improvement was observed after 14 days, and the chemical is considered extremely irritating to the eyes of albino rabbits.

Propyl chloroformate is also considered extremely irritating to the skin of albino rabbits (Bio-Test Laboratories, Inc., 1970). Severe erythema, edema, and burns were observed after dermal exposure of rabbits to 0.5 ml undiluted propyl chloroformate for 24 hours. Effects persisted through the 72-hr observation period.

IV.2.3. Developmental/Reproductive Toxicity

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

IV.2.4. Genotoxicity

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

IV.2.5. Carcinogenicity

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

IV.2.6 Summary

Animal toxicity data are limited. A 30-min RD_{50} of 83.5 ppm (nominal concentration) propyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982). A 1-hr LC_{50} of 410 ppm, $BMCL_{05}$ of 216 ppm, and BMC_{01} of 229 ppm were calculated for Charles River albino rats (Bio-Test Laboratories, Inc., 1970).

Propyl chloroformate is severely irritating to the skin and eyes of albino rabbits (Bio-Test Laboratories, Inc., 1970). The compound was negative in a *Salmonella* mutagenicity reversion assay. No data concerning developmental/reproductive toxicity or carcinogenicity for exposure to propyl chloroformate were located in the available literature.

IV.3. DATA ANALYSIS AND AEGL-1

IV.3.1 Human Data Relevant to AEGL-1

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

IV.3.2 Animal Data Relevant to AEGL-1

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

IV.3.3 Derivation of AEGL-1

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

TABLE IV-3. AEGL-1 Values for Propyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

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

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

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

TABLE IV-4. AEGL-2 Values for Propyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	6.7 ppm (34 mg/m^3)	4.7 ppm (24 mg/m^3)	3.7 ppm (19 mg/m^3)	0.90 ppm (4.5 mg/m^3)	0.47 ppm (2.4 mg/m^3)

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.

IV.5.2 Animal Data Relevant to AEGL-3

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

IV.5.3 Derivation of AEGL-3

The calculated 1-hour rat $BMCL_{05}$ of 216 ppm (Bio-Test Laboratories, Inc., 1970) will be used for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because propyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. A modifying factor of 2 will be applied because the key study reported nominal, not analytical, concentrations and there are no other confirmatory studies. Thus, the total uncertainty/modifying factor is 20. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for propyl chloroformate are presented in Table IV-5, and the calculations for these AEGL-3 values are presented in Appendix IV-A.

TABLE IV-5. AEGL-3 Values for Propyl Chloroformate

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

IV.6. SUMMARY OF AEGLS

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

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

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
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.

IV.6.2. Comparison with Other Standards and Guidelines

No extant values were located for propyl chloroformate.

IV.6.3 Data Quality and Research Needs

Data are extremely limited. Human data do not exist and animal data are limited to rat acute lethality studies and one mouse RD_{50} study. The limited data set necessitated the application of a modifying factor for AEGL value derivation.

IV.7. REFERENCES

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

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

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

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

Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG Industries, Inc. IBT No. A8345. OTS0570701.

Carpenter, C.P. 1982. Ethyl chloroformate, n-propyl chloroformate, Isobutyl chloroformate, Sec-butyl chloroformate. Sensory Irritation. Report by Mellon Institute. Report to PPG Industries, Inc., Chemicals Division. Report No. 82-49S.

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.

APPENDIX IV-A:

Derivation of AEGL Values for Propyl Chloroformate

DERIVATION OF AEGL-1 VALUES FOR PROPYL CHLOROFORMATE

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: ⅓ of the AEGL-3 values

10-min AEGL-2: 20 ppm ÷ 3 = 6.7 ppm

30-min AEGL-2: 14 ppm ÷3 = 4.7 ppm

1-hr AEGL-2: 11 ppm ÷ 3 = 3.7 ppm

4-hr AEGL-2: 2.7 ppm ÷ 3 = 0.90 ppm

8-hr AEGL-2: 1.4 ppm ÷ 3 = 0.47 ppm

DERIVATION OF AEGL-3 VALUES FOR PROPYL CHLOROFORMATE

Key study: Bio-Test Laboratories, Inc., 1970
Toxicity Endpoint: Calculated $BMCL_{05}$ (216 ppm) from a 1-hour exposure in rats.

Scaling: 10-minutes and 30-minutes
$C^3 \times t = k$
$(216\ ppm)^3 \times 1\ hr = 10077696\ ppm"hr$

4-hours and 8-hours
$C^1 \times t = k$
$(216\ ppm)^1 \times 1\ hr = 216\ ppm"hr$

Uncertainty Factors:
3 for interspecies variability
3 for intraspecies variability
Modifying Factor:
2 for sparse data base and use of key study with nominal concentrations

10-min AEGL-3:
$C^3 \times 0.167\ hr = 10,077,696\ ppm"hr$
$C^3 = 60345485\ ppm$
$C = 392\ ppm$
10-min AEGL-3 =392/20 = 20 ppm

30-min AEGL-3
$C^3 \times 0.5\ hr = 10,077,696\ ppm"hr$
$C^3 = 20155392\ ppm$
$C = 272\ ppm$
30-min AEGL-3 = 272/20 = 14 ppm

1-hr AEGL-3
1-hr AEGL-3 = 216/20 = 11 ppm

4-hr AEGL-3
$C^1 \times 4\ hr = 216\ ppm"hr$
$C^1 = 54\ ppm$
$C = 54\ ppm$
4-hr AEGL-3 = 54/20 = 2.7 ppm

8-hr AEGL-3
$C^1 \times 8\ hr = 216\ ppm"hr$
$C^1 = 27\ ppm$
$C = 27\ ppm$
8-hr AEGL-3 = 27/20 = 1.4 ppm

APPENDIX IV-B:

Derivation Summary for Propyl Chloroformate AEGLS

AEGL-1 VALUES FOR PROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: NA				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data quality and research needs: AEGL-1 values are not recommended for propyl chloroformate. Data are insufficient to derive values				

AEGL-2 VALUES FOR PROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
6.7 ppm	**4.7 ppm**	**3.7 ppm**	**0.90 ppm**	**0.47 ppm**
Key Reference: Bio-Test Laboratories, Inc. 1970. Acute toxicity studies on n-propyl chloroformate. Report to PPG Industries, Inc. IBT No. A8345.				
Test Species/Strain/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 Derivation summary table				
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 249 ppm; 2/10 at 333 ppm; 10/10 at 1000 ppm; Bio-Test Laboratories, Inc., 1970).				
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: See AEGL-3 Derivation summary table				
Data quality and research needs: See AEGL-3 Derivation summary table.				

AEGL-3 VALUES FOR PROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
20 ppm	**14 ppm**	**11 ppm**	**2.7 ppm**	**1.4 ppm**

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

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

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

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

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

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

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

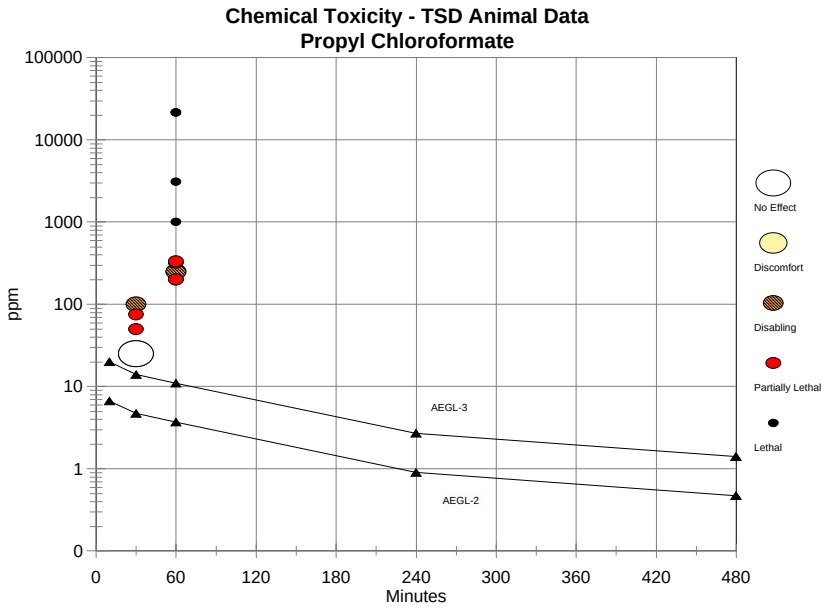
Animal to Human Dosimetric Adjustment: Insufficient data

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

Data Quality and Research Needs: Sparse data set.

APPENDIX IV-C:

Category Plot for Propyl Chloroformate


Chemical Toxicity - TSD Animal Data
Propyl Chloroformate
ppm
100000
10000
1000
100
10
1
0
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

APPENDIX IV-D:

Benchmark Concentration Calculation for Propyl 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 = 3
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model
            Default Initial (and Specified) Parameter Values
              background =           0
               intercept =     -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            NA
  slope        NA            NA

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

                    Parameter Estimates

     Variable         Estimate          Std. Err.
   background               0             NA
    intercept         -99.4462          20016.9
      slope            16.977          3446.36

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

      Model      Log(likelihood)  Deviance  Test DF     P-value
    Full model        -5.00402
   Fitted model       -5.00402  7.62052e-008     1        0.9998
  Reduced model        -20.1904      30.3727     2        <.0001

          AIC:          14.008
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
249.0000	0.0000	0.000	0	10	-0.0001952
333.0000	0.2000	2.000	2	10	4.115e-007
1000.0000	1.0000	10.000	10	10	0

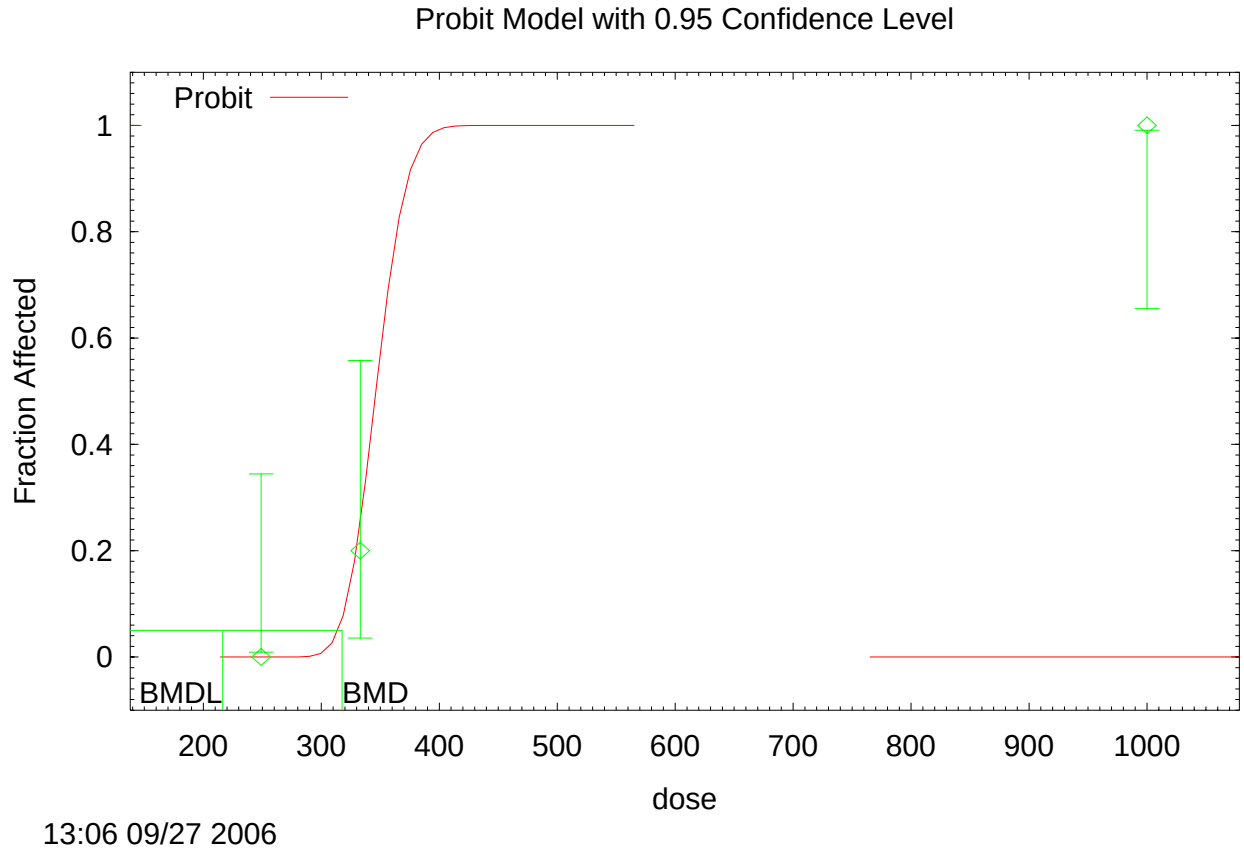
Chi-square = 0.00 DF = 1 P-value = 0.9998

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95
BMD = 317.612
BMDL = 216.399



CHAPTER V: Isopropyl Chloroformate

TABLE OF CONTENTS: CHAPTER V: ISOPROPYL CHLOROFORMATE

LIST OF TABLES

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).

One-third of the 1-hr LC_{50} value in rats (300 ppm x ⅓ = 100 ppm) (Bio Test Laboratories, Inc., 1970) was used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

Summary of AEGL Values For Isopropyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient Data
AEGL-2 (Disabling)	6.0 ppm (30 mg/m^3)	4.3 ppm (22 mg/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)	⅓ 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-hour exposure (Bio Test Laboratories, Inc., 1970)

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

References

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

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

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.

V.1. HUMAN TOXICITY DATA

V.1.1 Acute Lethality

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

V.1.2 Non-lethal Toxicity

Short-term task-specific industrial hygiene monitoring for isopropyl chloroformate was conducted at a resins plant (Martin, 1994). The monitoring was conducted to evaluate potential employee exposure during tank truck unloading operations. Exposures were considered potential because, due to the acute toxicity of isopropyl chloroformate, employees wore full-face supplied-air respirators, neoprene gloves, rubber boots, and neoprene clothing. Four personal monitoring results ranged from 0.2 ppm to 5.6 ppm for the sampled activity (20-40 minutes). Two area sample results were 0.06 ppm and 1.7 ppm.

V.1.3 Developmental/Reproductive Toxicity

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

V.1.4 Genotoxicity

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

V.1.5 Carcinogenicity

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

V.1.6 Summary

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

V23. ANIMAL TOXICITY DATA

V.2.1 Acute Lethality

V.2.1.1. Rats

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

isopropyl chloroformate (8-10 ºC) in a water bath. The resulting vapor was mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was then introduced into the top of a 70 L Plexiglass inhalation chamber, dispersed by a baffle plate, and exhausted at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the isopropyl chloroformate vaporized by the total volume of air used during each inhalation exposure. Animals in the mid- and high-exposure groups started gasping for breath within 15 minutes after the initiation of exposure and exhibited convulsions and salivation. Low-concentration animals exhibited gasping and slight salivation. Necropsy of animals that died revealed moderate to severe lung hyperemia. Rats that survived the 14-day observation period exhibited no gross abnormalities at necropsy. The 1-hour LC_{50} was determined to be 300 ppm. Data are summarized in Table V-1

TABLE V-1. Exposure of Albino Rats to Isopropyl Chloroformate for up to 1 hour*

Nominal Concentration (ppm)	Exposure Duration (min)	Mortality	Time of Death After Initiation of Exposure
300	60	5/10	3 at 2 hr; 1 each at 2 and 10 days
1640	60	10/10	40, 48, 48, 52, 57, 60, 65, 67, 70, and 70 min
15,600	41	10/10	17, 17, 24, 24, 35, 37, 37, 37, 37, and 41 min

Bio-Test Laboratories, Inc., 1970

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

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

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

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

In an acute oral toxicity study (Bio-Test Laboratories, Inc., 1971), Charles River albino rats (2/sex/dose) were administered 118.5, 177.8, 266.7, or 400 mg/kg isopropyl chloroformate by gavage and observed up to 14 days. There were no deaths at the low dose, 2/4 animals died at 177.8 mg/kg, and all animals died at the two highest doses. Deaths occurred between one hour and 5 days post-exposure. Hypoactivity, muscular weakness, ptosis, hyperpnea, and ruffed fur were observed following dosing. Hemorrhages were observed in the stomachs of animals that died during the study. An LD_{50} of 177.8 mg/kg was calculated. An approximate oral LD_{50} of 800 mm^3 was reported in rats (BASF, 1968c).

V.2.1.2. Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 50, 75, 100, 200, or 500 ppm isopropyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted isopropyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9 L stainless steel chamber which was continuously evacuated at 20 L/min. An RD_{50} of 104 ppm was calculated. Data are summarized in Table V-2.

TABLE V-2. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 30 minutes*

Concentration (ppm)	Respiratory rates(control/exposed)	% Decrease in respiratory rate	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

In another study (Anderson, 1984), groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 177, 306, 443, or 883 ppm isopropyl chloroformate vapor for 15 minutes. The vapor was introduced through a Harvard apparatus syringe drive into a Pitt #1 generator. The glass exposure chamber and had a capacity of 2.2 L, and air flow was 8.8 L/min. Baseline respiratory rates of each mouse were recorded for 10 minutes before exposure. Respiratory rates were recorded at 5 and 10 minutes into the 15 minute exposure period, and percent respiratory depression was calculated from these values. Lung weights were obtained at necropsy following death from exposure or scheduled sacrifice. In this study, the RD_{50} is calculated to be 375 ppm, and a 15-min. LC_{50} is estimated to be between 283 and 345 ppm. Concentration-related increases in lung weight, indicative of pulmonary edema, were observed in treated animals compared to controls. Data are summarized in Table V-3.

TABLE V-3. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 15 minutes*

Concentration (ppm)		% Decrease in respiratory rate			Mean lung weight (g)	Lung/Body wt. Ratio (x100)	Mortality within 24 hr.
Nominal	Analytical	5 min.	10 min.	Average			
0	0	-	-	-	0.17	0.62	0/4
177	141	20	16	18	0.26	0.9	0/4
306	283	35	40	38	0.35	1.29	2/4
443	345	45	41	43	0.39	1.23	2/4
883	730	70	85	76	0.45	1.45	4/4

Anderson, 1984

V.2.2 Nonlethal Toxicity

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

V.2.3 Developmental/Reproductive Toxicity

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

V.2.4 Genotoxicity

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

V.2.5 Carcinogenicity

Animal carcinogenicity data for isopropyl chloroformate were not available.

V.2.6 Summary

Animal toxicity data are limited. A 30-min RD_{50} of 104 ppm (nominal concentration) isopropyl chloroformate was reported for male Swiss-Webster mice (Carpenter, 1982), while a 15-minute RD_{50} of 375 ppm (analytical concentration) and estimated 15-min LC_{50} of 283 to 345 ppm were determined for male Swiss-Webster mice (Anderson, 1984). A 1-hr LC_{50} of 300 ppm was calculated for Charles River albino rats (Bio-Test Laboratories, Inc., 1970). Repeated exposure to 100 ppm isopropyl chloroformate resulted in death in Sprague-Dawley rats, while lower concentrations resulted in body weight loss, increased lung weight, and bronchiolitis. Increased lung weight and edema were consistently observed in decedents in most studies. Isopropyl chloroformate was negative in the Ames assay. No data concerning developmental/reproductive toxicity or carcinogenicity from exposure to isopropyl chloroformate were located in the available literature. Animal inhalation data are summarized in Table V-4.

Table V-4. Summary of Inhalation Data of Animals Exposed to Isopropyl Chloroformate

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Acute Exposure				
Rat	15,600 (nominal)	17-41 minutes	10/10 dead	Bio Test Labs, Inc., 1970
Rat	1640 (nominal)	40-60 minutes	10/10 dead	Bio Test Labs, Inc., 1970
Rat	200 (approximate)	1 hour	0/12 dead	BASF, 1968a
Rat	300 (nominal)	1 hour	LC_{50}	Bio Test Labs, Inc., 1970
Rat	200	5 hours	2/8 dead	Gage, 1970
Mouse	283-345	15 minutes	LC_{50}	Anderson, 1984
Mouse	375	15 minutes	RD_{50}	Anderson, 1984

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

V.3. DATA ANALYSIS AND AEGL-1

V.3.1 Human Data Relevant to AEGL-1

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

V.3.2 Animal Data Relevant to AEGL-1

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

V.3.3 Derivation of AEGL-1

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

TABLE V-5. AEGL-1 Values for Isopropyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

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.

TABLE V-6. AEGL-2 Values for Isopropyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	6.0 ppm (30 mg/m^3)	4.3 ppm (22 mg/m^3)	3.3 ppm (17 mg/m^3)	0.83 ppm (4.2 mg/m^3)	0.43 ppm (2.2 mg/m^3)

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)

V.5. DATA ANALYSIS AND AEGL-3

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 LC_{50} value of 300 ppm was calculated (Bio Test, 1970). A 15-minute mouse LC_{50} of 283-345 was estimated (Anderson, 1984).

V.5.3 Derivation of AEGL-3

One-third of the 1-hr LC_{50} value in rats (300 ppm x ⅓ = 100 ppm) (Bio-Test Laboratories, Inc., 1970) will be used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality and is supported by the fact that 0/12 rats died when exposed to approximately 200 ppm for 1 hour (BASF, 1968a). Interspecies and intraspecies uncertainty factors of 3 each will be applied because isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of

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

TABLE V-7. AEGL-3 Values for Isopropyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	18 ppm (90 mg/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)

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

V.6. SUMMARY OF AEGLS

V.6.1 AEGL Values and Toxicity Endpoints

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

TABLE V-8. Summary of AEGL Values for Isopropyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	6.0 ppm (30 mg/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

Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 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

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2005)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. No ERPG-1 for isopropyl chloroformate is derived because of insufficient data.

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

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

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

V.6.3 Data Quality and Research Needs

Animal data are limited to acute and repeated-exposure rat inhalation studies and a two mouse 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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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.

Derivation of AEGL-2 Values for Isopropyl Chloroformate

Key study: Bio-Test Laboratories, Inc., 1970

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2:	18 ppm ÷ 3 = 6.0 ppm
30-min AEGL-2:	13 ppm ÷3 = 4.3 ppm
1-hr AEGL-2:	10 ppm ÷ 3 = 3.3 ppm
4-hr AEGL-2:	2.5 ppm ÷ 3 = 0.83 ppm
8-hr AEGL-2:	1.3 ppm ÷ 3 = 0.43 ppm

DERIVATION OF AEGL-3 VALUES FOR ISOPROPYL CHLOROFORMATE

Key study: Bio-Test Laboratories, Inc., 1970

Toxicity Endpoint: Estimated LC_{01} (⅓ the LC_{50}) from a 1-hour exposure in male rats.

LC50 = 300 ppm; ⅓ x 300 ppm = 100 ppm (point of departure)

Scaling: 10-minutes and 30-minutes

$C^3 \times t = k$

$(100\ ppm)^3 \times 1\ hr = 1{,}000{,}000\ ppm^3hr$

4-hours and 8-hours

$C^1 \times t = k$

$(100\ ppm)^1 \times 1\ hr = 100\ ppm^3hr$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3:

$C^3 \times 0.167\ hr = 1{,}000{,}000\ ppm^3hr$

$C^3 = 5988024\ ppm$

$C = 182\ ppm$

10-min AEGL-3 = 182/10 = 18 ppm

30-min AEGL-3

$C^3 \times 0.5\ hr = 1{,}000{,}000\ ppm^3hr$

$C^3 = 2{,}000{,}000\ ppm$

$C = 126\ ppm$

30-min AEGL-3 = 126/10 = 13 ppm

1-hr AEGL-3

1-hr AEGL-3 = 100/10 = 10 ppm

4-hr AEGL-3

$C^1 \times 4\ hr = 100\ ppm^3hr$

$C^1 = 25\ ppm$

$C = 25\ ppm$

4-hr AEGL-3 = 25/10 = 2.5 ppm

8-hr AEGL-3

$C^1 \times 8\ hr = 100\ ppm^3hr$

$C^1 = 12.5\ ppm$

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

APPENDIX V-B:

Derivation Summary for Isopropyl Chloroformate AEGLS

AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
NR	**NR**	**NR**	**NR**	**NR**
Reference: NA				
Test Species/Strain/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				
Data quality and research needs: AEGL-1 values are not recommended for isopropyl chloroformate. Data were insufficient for deriving values.				

AEGL-2 VALUES FOR ISOPROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
6.0 ppm	**4.3 ppm**	**3.3 ppm**	**0.83 ppm**	**0.43 ppm**
Key Reference: Bio-Test Laboratories, Inc. 1970. Acute vapor inhalation toxicity study with IPCF in albino rats. Report to PPG Industries, Inc. IBT No. N9129.				
Test Species/Strain/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 Derivation summary table				
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape.				
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
Modifying Factor: NA				
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. Values are considered protective because rats showed only nasal irritation when exposed to 20 ppm, 6 hours/day for 20 days (Gage, 1970).				

AEGL-3 VALUES FOR ISOPROPYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
18 ppm	**13 ppm**	**10 ppm**	**2.5 ppm**	**1.3 ppm**

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

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

Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour
(⅓ the 1-hour rat LC_{50} was the point-of-departure for AEGL-3) (⅓ x 300 ppm = 100 ppm)

Endpoint/Concentration/Rationale: ⅓ the 1-hour rat LC_{50} / 100 ppm/Estimated threshold for death for 1 hour exposure in rats

Effects: LC_{50} =300 ppm

Uncertainty Factors/Rationale:
Interspecies = 3:
Intraspecies = 3:
Isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

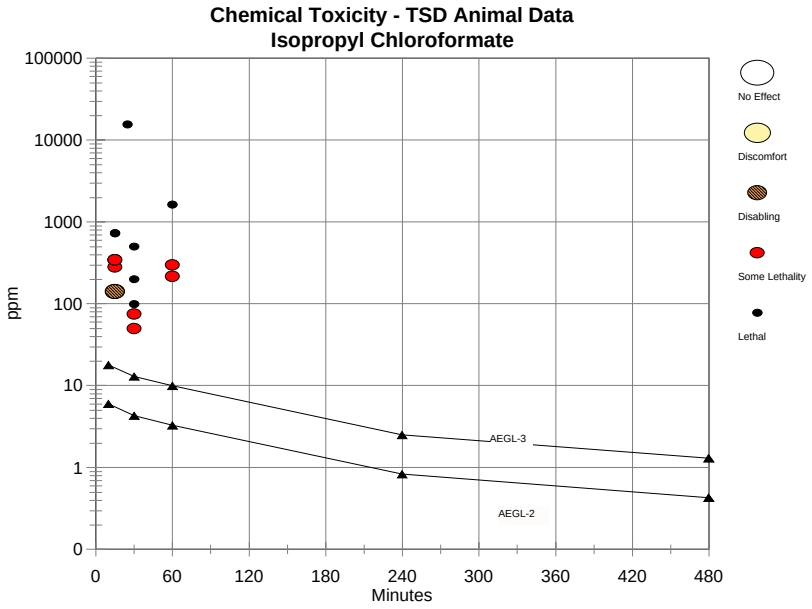
Time Scaling: $c^n \times t = k$, where n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

Data Quality and Research Needs: Sparse acute toxicity data set, with repeated-exposure studies available for support. Values are considered protective because no deaths were noted in rats exposed to 42 ppm, 6 hours/day for 5 days (Collins and Proctor, 1984).

APPENDIX V-C:

CATEGORY PLOT FOR ISOPROPYL CHLOROFORMATE

1
2
3


Chemical Toxicity - TSD Animal Data
Isopropyl Chloroformate
100000
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Some Lethality
Lethal

1 # CHAPTER VI: ALLYL CHLOROFORMATE

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LIST OF TABLES

SUMMARY: ALLYL CHLOROFORMATE

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

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

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

Summary of AEGL Values For Allyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	1.3 ppm (6.4 mg/m^3)	0.87 ppm (4.3 mg/m^3)	0.70 ppm (3.4 mg/m^3)	0.18 ppm (0.88 mg/m^3)	0.090 ppm (0.44 mg/m^3)	⅓ the AEGL-3 values (Stillmeadow Inc., 1987)
AEGL-3 (Lethality)	3.8 ppm (19 mg/m^3)	2.6 ppm (13 mg/m^3)	2.1 ppm (10 mg/m^3)	0.53 ppm (2.6 mg/m^3)	0.26 ppm (1.3 mg/m^3)	1-hour rat $BMCL_{05}$ (Stillmeadow Inc., 1987)

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

References

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

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

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.

V.1.2 Non-lethal Toxicity

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

V.1.3 Developmental/Reproductive Toxicity

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

V.1.4 Genotoxicity

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

V.1.5 Carcinogenicity

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

V.1.6 Summary

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

VI.2. ANIMAL TOXICITY DATA

VI.2.1 Acute Lethality

VI.2.1.1. Rats

Groups of five male and five female Sprague Dawley rats were exposed to 33.7, 65.0, 77.7, 134.5, 175.7, or 233.3 ppm allyl chloroformate for 1 hour, followed by a 14-day observation period (Stillmeadow Inc., 1987). Animals were exposed in a 200 liter stainless steel dymanic flow inhalation chamber. The aerosol was generated by aspirating the allyl chloroformate through a pressure operated spray nozzle. The concentrated aerosol was then diluted with dried, filtered air and drawn into the exposure chamber. Air flow was maintained through the use of a calibrated critical orifice, and air flow was recorded at 30 minute intervals during the exposure period. The concentration of allyl chloroformate in the exposure atmosphere was determined analytically at 30 and 60 minutes via gas chromatography. Clinical signs were noted in all exposure groups and included decreased activity, body tremors, constricted pupils, diarrhea, emaciation, epistaxis, gasping, lacrimation, nasal discharge,

piloerection, polyuria, ptosis, respiratory gurgle, and salivation. Nine of the ten rats exposed to 33.7 ppm gained weight over the 14 day observation period, and the tenth animal retained a constant weight. All eight of the rats exposed to higher concentrations and surviving the 14-day observation period lost weight. Gross necropsy findings included discoloration of the lungs, pulmonary edema, clear fluid in the thoracic cavity, gas distended gastrointestinal tract, and discoloration of gastrointestinal tract contents. An LC_{50} of 65.1 ppm, a $BMCL_{05}$ of 21 ppm, and a BMC_{01} of 25.7 ppm were calculated. Data are summarized in Table VI-1.

TABLE V1-1. Exposure of Sprague Dawley Rats to Allyl Chloroformate 1 hour*

Concentration (ppm)	Mortality- Males	Mortality- Females	Mortality- Combined Males & Females
33.7	0/5	0/5	0/10
65.0	3/5	3/5	6/10
77.7	3/5	4/5	7/10
134.5	5/5	4/5	9/10
175.7	5/5	5/5	10/10
233.3	5/5	5/5	10/10
LC_{50}			65.1 ppm
$BMCL_{05}$			21 ppm
BMC_{01}			25.7 ppm

*Stillmeadow Inc., 1987

VI.2.2 Developmental/Reproductive Toxicity

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

VI.2.3 Genotoxicity

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

VI.2.4 Carcinogenicity

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

VI.2.5 Summary

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

VI.3. DATA ANALYSIS AND AEGL-1

VI.3.1 Human Data Relevant to AEGL-1

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

VI.3.2 Animal Data Relevant to AEGL-1

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

VI.3.3 Derivation of AEGL-1

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

TABLE VI-2. AEGL-1 Values for Allyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

VI.4. DATA ANALYSIS AND AEGL-2

VI.4.1 Human Data Relevant to AEGL-2

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

VI.4.2 Animal Data Relevant to AEGL-2

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

VI.4.3 Derivation of AEGL-2

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

TABLE VI-3. AEGL-2 Values for Allyl Chloroformate					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-2	1.3 ppm (6.4 mg/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)

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 $BMCL_{05}$ of 21 ppm were calculated (Stillmeadow Inc., 1987).

VI.5.3 Derivation of AEGL-3

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

TABLE VI-4. AEGL-3 Values for Allyl Chloroformate					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-3	3.8 ppm (19 mg/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)

VI.6. SUMMARY OF AEGLS

VI.6.1 AEGL Values and Toxicity Endpoints

Chemical-specific data were insufficient for derivation of AEGL-1 values for allyl chloroformate. AEGL-1 values are not recommended, and AEGL-2 values were based on a three-fold reduction of AEGL-3 values. AEGL-3 values were based on the $BMCL_{05}$ from a 1-hour rat study.

TABLE VI-5. Summary of AEGL Values for Allyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	1.3 ppm (6.4 mg/m^3)	0.87 ppm (4.3 mg/m^3)	0.70 ppm (3.4 mg/m^3)	0.18 ppm (0.88 mg/m^3)	0.090 ppm (0.44 mg/m^3)
AEGL-3 (Lethal)	3.8 ppm (19 mg/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.

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 $BMCL_{05}$ from a well-conducted rat study.

VI.7. REFERENCES

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

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

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.

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.

Derivation of AEGL-2 Values for Allyl Chloroformate

Key study: Stillmeadow Inc., 1987

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2: 3.8 ppm ÷ 3 = 1.3 ppm

30-min AEGL-2: 2.6 ppm ÷3 = 0.87 ppm

1-hr AEGL-2: 2.1 ppm ÷ 3 = 0.70 ppm

4-hr AEGL-2: 0.53 ppm ÷ 3 = 0.18 ppm

8-hr AEGL-2: 0.26 ppm ÷ 3 = 0.090 ppm

DERIVATION OF AEGL-3 VALUES FOR ALLYL CHLOROFORMATE

Key study: Stillmeadow Inc., 1987

Toxicity Endpoint: 1-hour rat $BMCL_{05}$ (21 ppm)

Scaling: 10-minutes and 30-minutes

$C^3 \times t = k$

$(21\ ppm)^3 \times 1\ hr = 9261\ ppm^3 hr$

4-hours and 8-hours

$C^1 \times t = k$

$(21\ ppm)^1 \times 1\ hr = 21\ ppm^1 hr$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3:

$C^3 \times 0.167\ hr = 9261\ ppm^3 hr$

$C^3 = 55455\ ppm$

$C = 38\ ppm$

10-min AEGL-3 = 38/10 = 3.8 ppm

30-min AEGL-3

$C^3 \times 0.5\ hr = 9261\ ppm^3 hr$

$C^3 = 18522\ ppm$

$C = 26.4\ ppm$

30-min AEGL-3 = 26.4/10 = 2.6 ppm

1-hr AEGL-3

1-hr AEGL-3 = 21/10 = 2.1 ppm

4-hr AEGL-3

$C^1 \times 4\ hr = 21\ ppm^1 hr$

$C^1 = 5.25\ ppm$

$C = 5.25\ ppm$

4-hr AEGL-3 = 5.25/10 = 0.53 ppm

8-hr AEGL-3

$C^1 \times 8\ hr = 21\ ppm^1 hr$

$C^1 = 2.63\ ppm$

C = 2.63 ppm

8-hr AEGL-3 = 2.63/10 = 0.26 ppm

APPENDIX VI-B:

Derivation Summary for Allyl Chloroformate AEGLS

AEGL-1 VALUES FOR ALLYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/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 allyl chloroformate.				

AEGL-2 VALUES FOR ALLYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
1.3 ppm	**0.87 ppm**	**0.70 ppm**	**0.18 ppm**	**0.090 ppm**
Key Reference: Stillmeadow Inc. 1987. Rat Acute Inhalation Toxicity: Allyl Chloroformate. Stillmeadow, Inc. Biological Testing Laboratory. Houston, TX. Project No. 4438-86. Report Submitted to PPG Industries, Inc., Chicago, IL. February 19, 1987. OTS0536028.				
Test Species/Strain/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 Derivation summary table				
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (1-hour rat mortality incidence: 0/10 at 33.7 ppm; 6/10 at 65 ppm; 10/10 at 175.7 ppm; Stillmeadow Inc., 1970).				
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: See AEGL-3 Derivation summary table				
Data quality and research needs: See AEGL-3 Derivation summary table.				

AEGL-3 VALUES FOR ALLYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
3.8 ppm	**2.6 ppm**	**2.1 ppm**	**0.53 ppm**	**0.26 ppm**

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

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

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

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

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

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

Modifying Factor: NA

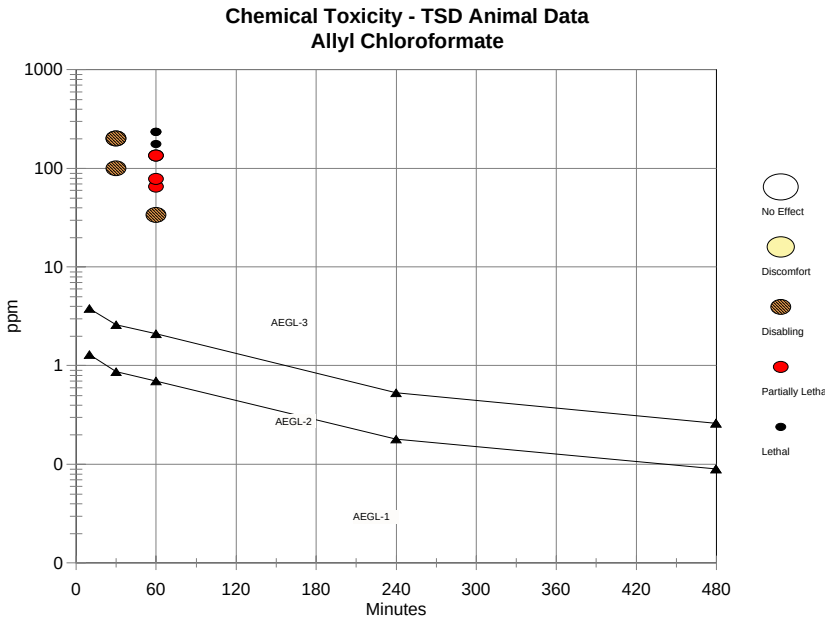
Animal to Human Dosimetric Adjustment: Insufficient data

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

Data Quality and Research Needs: Sparse data set.

APPENDIX VI-C:

Category Plot for Allyl Chloroformate


Chemical Toxicity - TSD Animal Data
Allyl Chloroformate
1000
100
10
1
0
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Letha
Lethal

APPENDIX VI-D:

Benchmark Concentration Calculation for Allyl Chloroformate

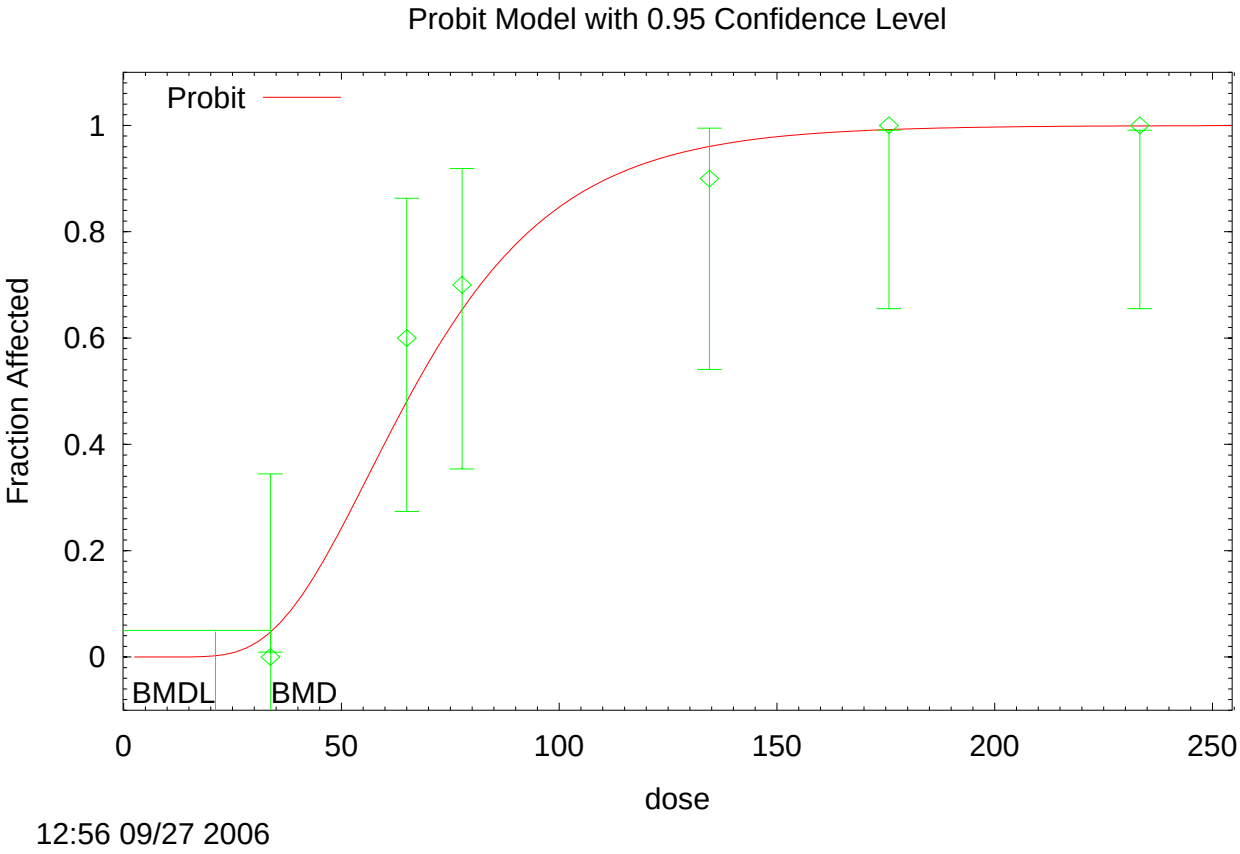
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:
  P[response] = Background
        + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

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

  Total number of observations = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  User has chosen the log transformed model
            Default Initial (and Specified) Parameter Values
              background =          0
               intercept =     -7.2918
                   slope =     1.72308

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background
            have been estimated at a boundary point, or have been specified by the user,
            and do not appear in the correlation matrix )
          intercept       slope
intercept         1          -1
    slope        -1           1

                    Parameter Estimates

     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.

                  Analysis of Deviance Table

      Model      Log(likelihood)  Deviance  Test DF     P-value
   Full model        -16.0896
  Fitted model       -17.3239      2.46858     4         0.6503
 Reduced model       -36.6519      41.1245     5         <.0001

       AIC:         38.6478
             Goodness  of  Fit
                                          Scaled
   Dose     Est._Prob.    Expected    Observed     Size      Residual
  ---------------------------------------------------------------------
  33.7000      0.0495         0.495          0          10      -0.7219
```

1	65.0000	0.4929	4.929	6	10	0.6774
2	77.7000	0.6648	6.648	7	10	0.236
3	134.5000	0.9632	9.632	9	10	-1.06
4	175.7000	0.9929	9.929	10	10	0.2674
5	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



CHAPTER VII:

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

TABLE OF CONTENTS: CHAPTER VII:

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

LIST OF TABLES

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

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

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for n-butyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). The resulting values are considered protective because rats showed no effects when exposed to1.8 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 2.9 ppm 6 hours/day for 5 days (HRC 1990).

One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl chloroformate (200 ppm x ⅓ = 66.7 ppm) (BASF, 1970) was used as the point-of-departure for n-butyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because n-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor was 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The resulting values are considered protective because no rats died when exposed to 5.1 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 28.4 ppm 6 hours.day for 5 days (HRC 1990).

Summary of AEGL Values for n-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)	⅓ AEGL-3 values
AEGL-3 (Lethality)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)	Estimated 1-hr lethality threshold in rats (BASF, 1970)

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

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

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

Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	By analogy to n-butyl chloroformate
AEGL-2 (Disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)	By analogy to n-butyl chloroformate
AEGL-3 (Lethality)	12 ppm (68 mg/m^3)	8.4 ppm (100 mg/m^3)	6.7 ppm (80 mg/m^3)	1.7 ppm (20 mg/m^3)	0.83 ppm (10 mg/m^3)	By analogy to n-butyl chloroformate

VII.1. HUMAN TOXICITY DATA

VII.1.1 Acute Lethality

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

VII.1.2 Non-lethal Toxicity

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

VII.1.3 Developmental/Reproductive Toxicity

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

VII.1.4 Genotoxicity

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

VII.1.5 Carcinogenicity

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

VII.1.6 Summary

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

VII.2. ANIMAL TOXICITY DATA

VII.2.1 Acute Lethality

n-Butyl Chloroformate

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

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

Oral LD_{50} values of 1325 mg/kg (administered in 10% aqueous tragacanth gum emulsion) and

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

VII.2.2 Non-lethal Toxicity

n-Butyl Chloroformate

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

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

Isobutyl Chloroformate

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 25, 50, 100, 150, or 200 ppm isobutyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted isobutyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 6 L stainless steel chamber which was continuously evacuated at 18.3 L/min. An RD_{50} of 97.0± 5.82 ppm was calculated. Results are summarized in Table VII-1.

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

sec-Butyl Chloroformate

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 50, 100, 150, or 200 ppm sec-butyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted sec-butyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 6 L stainless steel chamber which was continuously evacuated at 18.3 L/min. An RD_{50} of 117± 1.64 ppm was calculated. Results are summarized in Table VII-2.

TABLE VII-2. Exposure of Male Swiss-Webster Mice to sec-butyl Chloroformate for 30 minutes*

Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs
50	195/175	10	0/4
100	280/165	41	0/4
150	295/130	55	0/4
200	225/40	82	1/4

*Carpenter, 1982

VII.2.3 Developmental/Reproductive Toxicity

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

VII.2.4 Genotoxicity

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

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.

VII.2.6 Summary

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 RD_{50} 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.

VII.3. DATA ANALYSIS AND AEGL-1

VII.3.1 Human Data Relevant to AEGL-1

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

VII.3.2 Animal Data Relevant to AEGL-1

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

VII.3.3 Derivation of AEGL-1

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

TABLE VII-3. AEGL-1 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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.

VII.4.3 Derivation of AEGL-2

n-Butyl 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 n-butyl chloroformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). The AEGL-2 values for n-butyl chloroformate are presented in Table VII-4, and the calculations for these AEGL-2 values are presented in Appendix VII-A.

TABLE VII-4. AEGL-2 Values for n-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)

These values are considered protective because rats showed no effects when exposed to1.8 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).

Isobutyl Chloroformate and sec-Butyl Chloroformate

Chemical-specific data were insufficient for the derivation of AEGL-2, values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the , AEGL-2 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate. The AEGL-2 values for isobutyl chloroformate and sec-butyl chloroformate are presented in Table VII-5.

TABLE VII-5. AEGL-2 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)

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).

VII.5.3 Derivation of AEGL-3

n-Butyl Chloroformate

One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl chloroformate (200 ppm x ⅓ = 66.7 ppm) (BASF, 1970) will be used as the point-of-departure for n-butyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each will be applied because n-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours). The AEGL-3 values for n-butyl chloroformate are presented in Table VII-6, and the calculations for these AEGL-3 values are presented in Appendix VII-A.

TABLE VII-6. AEGL-3 Values for n-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	12 ppm (68 mg/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)

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

Isobutyl Chloroformate and sec-Butyl Chloroformate

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

TABLE VII-7. AEGL-3 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	12 ppm (68 mg/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)

VII.6. SUMMARY OF AEGLS

VII.6.1 AEGL Values and Toxicity Endpoints

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

TABLE VII-8: Summary of AEGL Values for n-butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/m^3)
AEGL-3 (Lethality)	12 ppm (68 mg/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.

Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity. Thus, the AEGL-1, AEGL-2, and AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate

TABLE VII-9: Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.0 ppm (22 mg/m^3)	2.8 ppm (33 mg/m^3)	2.2 ppm (27 mg/m^3)	0.57 ppm (6.7 mg/m^3)	0.28 ppm (3.3 mg/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.

VII.6.2. Comparison with Other Standards and Guidelines

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

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

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

VII.6.3 Data Quality and Research Needs

No human data are available and animal data are sparse.

VII.7. REFERENCES

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APPENDIX VII-A:

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

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

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

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

n-Butyl Chloroformate

Key study: BASF, 1970

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2: 12 ppm ÷ 3 = 4.0 ppm

30-min AEGL-2: 8.4 ppm ÷3 = 2.8 ppm

1-hr AEGL-2: 6.7 ppm ÷ 3 = 2.2 ppm

4-hr AEGL-2: 1.7 ppm ÷ 3 = 0.57 ppm

8-hr AEGL-2: 0.83 ppm ÷ 3 = 0.28 ppm

Isobutyl Chloroformate and sec-Butyl Chloroformate

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

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

Key study: BASF, 1970
Toxicity Endpoint: 1-hour rat lethality threshold estimate

Scaling: 10-minutes and 30-minutes

$C^3 \times t = k$

$(66.7 \text{ ppm})^3 \times 1 \text{ hr} = 296{,}741 \text{ ppm}^3\text{hr}$

4-hours and 8-hours

$C^1 \times t = k$

$(66.7 \text{ ppm})^1 \times 1 \text{ hr} = 66.7 \text{ ppm}^1\text{hr}$

Uncertainty Factors:
3 for interspecies variability
3 for intraspecies variability

10-min AEGL-3:
$C^3 \times 0.167 \text{ hr} = 296{,}741 \text{ ppm}^3\text{hr}$
$C^3 = 1{,}776{,}892 \text{ ppm}$
C = 121 ppm
10-min AEGL-3 = 121/10 = 12 ppm

30-min AEGL-3
$C^3 \times 0.5 \text{ hr} = 296{,}741 \text{ ppm}^3\text{hr}$
$C^3 = 593482 \text{ ppm}$
C = 84.0 ppm
30-min AEGL-3 = 84.0/10 = 8.4 ppm

1-hr AEGL-3
1-hr AEGL-3 = 66.7/10 = 6.7 ppm

4-hr AEGL-3
$C^1 \times 4 \text{ hr} = 66.7 \text{ ppm}^1\text{hr}$
$C^1 = 16.8 \text{ ppm}$
C = 16.8 ppm
4-hr AEGL-3 = 16.8/10 = 1.7 ppm

8-hr AEGL-3
$C^1 \times 8 \text{ hr} = 66.7 \text{ ppm}^1\text{hr}$
$C^1 = 8.34 \text{ ppm}$
C = 8.34 ppm
8-hr AEGL-3 = 8.34/10 = 0.83 ppm

Isobutyl Chloroformate and sec-Butyl Chloroformate
AEGL-3 values for n-butyl chloroformate adopted as AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate.

APPENDIX VII-B:

Derivation Summary for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate AEGLS

AEGL-1 VALUES FOR n-BUTYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**

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

Test Species/Strain/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 n-butyl chloroformate.

AEGL-1 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**

Key Reference:

Test Species/Strain/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. No data were available to derive values by analogy to n-butyl chloroformate.

AEGL-2 VALUES FOR n-BUTYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
4.0 ppm	**2.8 ppm**	**2.2 ppm**	**0.57 ppm**	**0.28 ppm**
Key Reference: BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. N-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung. Unpublished Report No. XIX 352.				
Test Species/Strain/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 Derivation summary table				
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape.				
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: See AEGL-3 Derivation summary table				
Data quality and research needs: Sparse data set. Values are considered protective because rats showed no effects when exposed to1.8 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).				

AEGL-2 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
4.0 ppm	**2.8 ppm**	**2.2 ppm**	**0.57 ppm**	**0.28 ppm**
Key Reference: Derived by analogy to n-butyl chloroformate. n-Butyl chloroformate AEGL-2 values adopted as AEGL-2 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-2 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the AEGL-2 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.				

AEGL-3 VALUES FOR n-BUTYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
12 ppm	**8.4 ppm**	**6.7 ppm**	**1.7 ppm**	**0.83 ppm**

Key Reference: BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. N-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung. Unpublished Report No. XIX 352.

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

Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour
(⅓ the concentration causing death in 4/10 rats was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: ⅓ the concentration causing death in 4/10 rats after a 1 hr-exposure; 66.7 ppm; Estimated threshold for death for 1 hour exposure in rats

Effects:

Uncertainty Factors/Rationale:
Interspecies = 3:
Intraspecies = 3:
N-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

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

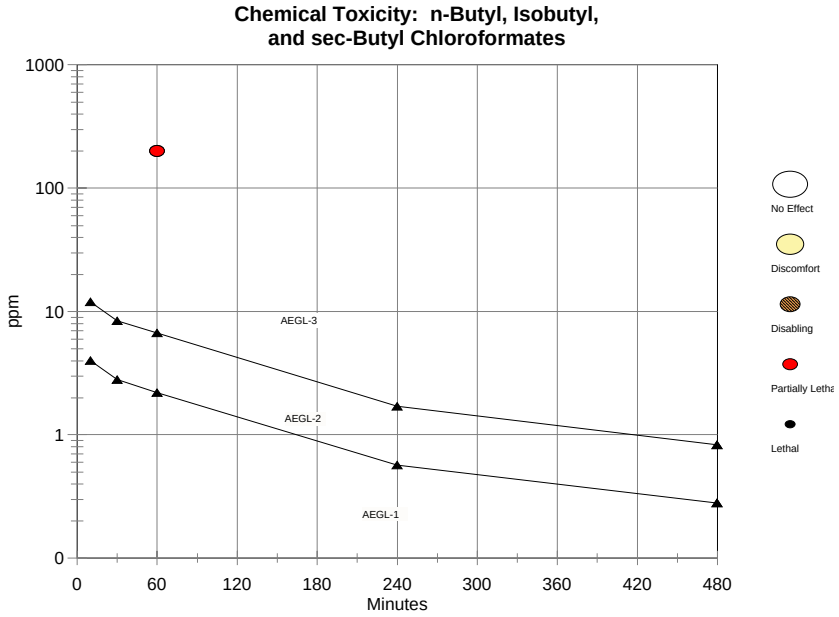
Data Quality and Research Needs: Sparse data set. Values are considered protective because rats showed no deaths when exposed to 5.1 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks, and when exposed to 28.4 ppm 6 hours.day for 5 days (HRC 1990).

AEGL-3 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
12 ppm	**8.4 ppm**	**6.7 ppm**	**1.7 ppm**	**0.83 ppm**
Key Reference: 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 RD_{50} data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD_{50} values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.				

APPENDIX VII-C:

Category Plot for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec-Butyl Chloroformate

1
2
3


Chemical Toxicity: n-Butyl, Isobutyl, and sec-Butyl Chloroformates
1000
100
10
1
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Letha
Lethal

CHAPTER VIII: BENZYL CHLOROFORMATE

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SUMMARY: BENZYL CHLOROFORMATE

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

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

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

Summary of AEGL Values For Benzyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)	⅓ 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.

VIII.1. HUMAN TOXICITY DATA

VIII.1.1 Acute Lethality

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

VIII.1.2 Non-lethal Toxicity

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

VIII.1.3 Developmental/Reproductive Toxicity

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

VIII.1.4 Genotoxicity

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

VIII.1.5 Carcinogenicity

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

VIII.1.6 Summary

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

VIII.2. ANIMAL TOXICITY DATA

VIII.2.1 Acute Lethality

Groups of five male and five female SPF Wistar rats were exposed to 18.6 or 84.6 ppm (analytical concentrations) benzyl chloroformate for 4-hours followed by a 14-day observation period (BASF, 1990). The nose-only exposures were performed in a 55 L glass-steel system; animals were restrained in tubes and noses projected into the chamber. Benzyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs noted during exposure included accelerated respiration and restlessness in the low-concentration group and irregular respiration, reddish nasal discharge, and restlessness in the high-concentration group. Clinical signs during the post-exposure observation period included accelerated respiration and ruffled fur in low-concentration rats and intermittent respiration, respiratory sounds, reddish nasal discharge, aggressiveness (males only), ruffled fur, and deteriorated general state. All clinical signs had resolved by day 2 post-exposure in the 18.6 ppm group and by day 5 post-exposure in survivors in the 84.6 ppm group. Body weight gain was decreased in high-concentration animals of both sexes during the first week after exposure; however animals surviving to study termination adjusted to normal body weight. There were no gross treatment-related effects noted at necropsy in animals surviving

to study termination. Gross examination of animals that died during the study showed lung emphysema with hyperemia and tympanism of the intestinal tract. An approximate LC_{50} of 85 ppm was reported for male and female rats combined. Mortality data are summarized in Table VIII-1.

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

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

*BASF, 1990.

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

VIII.2.2 Non-lethal Toxicity

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

VIII.2.3 Developmental/Reproductive Toxicity

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

VIII.2.4 Genotoxicity

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

VIII.2.5 Carcinogenicity

No information on the carcinogenicity of benzyl chloroformate was located.

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

VIII.3.1 Human Data Relevant to AEGL-1

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

VIII.3.2 Animal Data Relevant to AEGL-1

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

V.III.3.3 Derivation of AEGL-1

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

TABLE VIII-2. AEGL-1 Values for Benzyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

VIII.4. DATA ANALYSIS AND AEGL-2

VIII.4.1 Human Data Relevant to AEGL-2

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

VIII.4.2 Animal Data Relevant to AEGL-2

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

VIII.4.3 Derivation of AEGL-2

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

TABLE VIII-3. AEGL-2 Values for Benzyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	1.2 ppm (8.7 mg/m^3)	1.2 ppm (8.7 mg/m^3)	0.97 ppm (6.7 mg/m^3)	0.63 ppm (4.3 mg/m^3)	0.31 ppm (2.2 mg/m^3)

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).

VIII.5.3 Derivation of AEGL-3

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

TABLE VIII-4. AEGL-3 Values for Benzyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	3.7 ppm (26 mg/m^3)	3.7 ppm (26 mg/m^3)	2.9 ppm (20 mg/m^3)	1.9 ppm (13 mg/m^3)	0.93 ppm (6.5 mg/m^3)

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-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	1.2 ppm (8.7 mg/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)

VIII.6.2. Comparison with Other Standards and Guidelines

No extant values were located for benzyl chloroformate.

VIII.6.3 Data Quality and Research Needs

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

VIII.7. REFERENCES

Allen, J. S. and Panfili, J. 1986. Ames Salmonella/mammalian-microsome testing of peptides and peptide synthesis reagents. Mutation Research. 170: 23-29.

BASF. 1973. Study of the acute inhalation hazard (rats). Inhalation hazard test. Benzyl chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. December 9, 1973.

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.

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.

APPENDIX VIII-A:

DERIVATION OF AEGL VALUES FOR BENZYL CHLOROFORMATE

DERIVATION OF AEGL-1 VALUES FOR BENZYL CHLOROFORMATE

AEGL-1 values for benzyl chloroformate are not recommended.

Derivation of AEGL-2 Values for Benzyl Chloroformate

Key study: BASF, 1990

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2:	3.7 ppm ÷ 3 = 1.2 ppm
30-min AEGL-2:	3.7 ppm ÷3 = 1.2 ppm
1-hr AEGL-2:	2.9 ppm ÷ 3 = 0.97 ppm
4-hr AEGL-2:	1.9 ppm ÷ 3 = 0.63 ppm
8-hr AEGL-2:	0.93 ppm ÷ 3 = 0.31 ppm

DERIVATION OF AEGL-3 VALUES FOR BENZYL CHLOROFORMATE

Key study: BASF, 1990

Toxicity Endpoint: Concentration causing no mortality in 4-hour rat study (18.6 ppm)

Scaling: 30-minutes and 1-hr

$C^3 \times t = k$

$(18.6 \text{ ppm})^3 \times 4 \text{ hr} = 25739 \text{ ppm}^3\text{hr}$

8-hours

$C^1 \times t = k$

$(18.6 \text{ ppm})^1 \times 4 \text{ hr} = 74.4 \text{ ppm}^1\text{hr}$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3: 30-minute value adopted as 10-minute value = 3.7 ppm

30-min AEGL-3

$C^3 \times 0.5 \text{ hr} = 25739 \text{ ppm}^3\text{hr}$

$C^3 = 51478 \text{ ppm}$

$C = 37.2 \text{ ppm}$

30-min AEGL-3 = 37.2/10 = 3.7 ppm

1-hr AEGL-3

$C^3 \times 1 \text{ hr} = 25739 \text{ ppm}^3\text{hr}$

$C^3 = 25739 \text{ ppm}$

$C = 29.5 \text{ ppm}$

1-hr AEGL-3 = 29/10 = 2.9 ppm

4-hr AEGL-3

4-hr AEGL-3 = 18.6/10 = 1.9 ppm

8-hr AEGL-3

$C^1 \times 8 \text{ hr} = 74.4 \text{ ppm}^1\text{hr}$

$C^1 = 9.3 \text{ ppm}$

$C = 9.3 \text{ ppm}$

8-hr AEGL-3 = 9.3/10 = 0.93 ppm

APPENDIX VIII-B:

Derivation Summary for Benzyl Chloroformate AEGLS

AEGL-1 VALUES FOR BENZYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/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 chloroformate.				

AEGL-2 VALUES FOR BENZYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
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/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 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 AEGL-3 Derivation summary table				
Data quality and research needs: See AEGL-3 Derivation summary table.				

AEGL-3 VALUES FOR BENZYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
3.7 ppm	**3.7 ppm**	**2.9 ppm**	**1.9 ppm**	**0.93 ppm**

Key Reference: BASF. 1990. Study on the acute inhalation toxicity LC_{50} of benzyl chloroformate as a vapor in rats, 4-hour exposure. Project No. 13I0674/887075. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 15, 1990.

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

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours
(Concentration causing no mortality, 18.6 ppm, was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: Concentration causing no mortality/18.6 ppm/Estimated threshold for death for 4 hour exposure in rats

Effects: No mortality = 18.6 ppm; 5/10 dead = 84.6 ppm

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

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

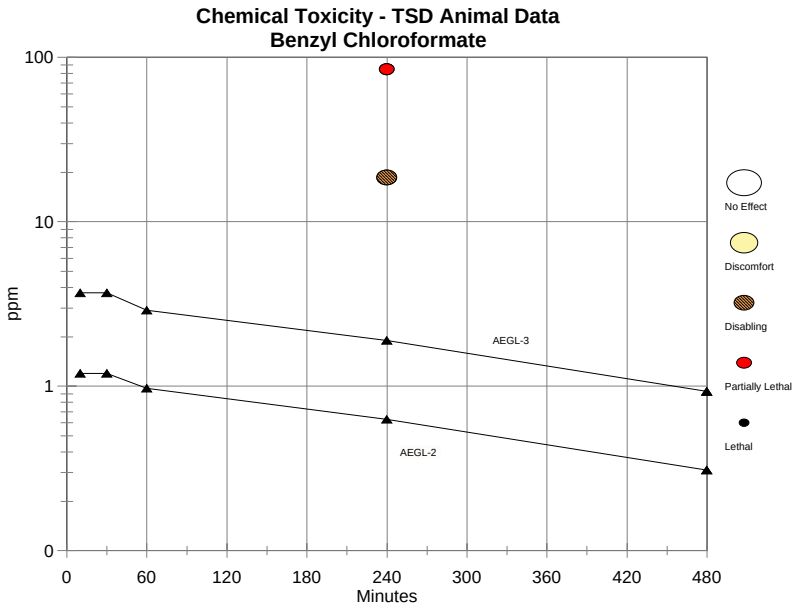
Time Scaling: $c^n \times t = k$, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value.

Data Quality and Research Needs: Sparse data set.

APPENDIX VIII-C:

Category Plot for Benzyl Chloroformate

1


Chemical Toxicity - TSD Animal Data
Benzyl Chloroformate
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

1 # CHAPTER IX: PHENYL CHLOROFORMATE

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SUMMARY: PHENYL CHLOROFORMATE

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

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

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

Summary of AEGL Values For Phenyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.060 ppm (0.38 mg/m^3)	⅓ 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.

IX.1. HUMAN TOXICITY DATA

IX.1.1 Acute Lethality

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

IX.1.2 Non-lethal Toxicity

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

IX.1.3 Developmental/Reproductive Toxicity

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

IX.1.4 Genotoxicity

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

IX.1.5 Carcinogenicity

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

IX.1.6 Summary

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

IX.2. ANIMAL TOXICITY DATA

IX.2.1 Acute Lethality

IX.2.1.1 Rats

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

low-concentration animals had resolved by day 3 post-exposure; clinical signs persisted through observation day 13 in mid- and high-concentration animals. Body weight gain was decreased (compared to historical controls) in low-concentration males and females and in mid-concentration males during the first week after exposure; however animals surviving to study termination adjusted to normal body weight. Body weight gain of mid-concentration females and high-concentration males and females was decreased during week one of the observation period; all animals in these groups died by week 2. There were no gross treatment-related effects noted at necropsy in low-concentration males and females surviving to study termination. One male rat in the mid–concentration group exhibited small atelectatic areas in the lung. Gross examination of animals that died during the study showed lung emphysema with hyperemia and pneumonia and necrotic foci and grey-brown lobular periphery of the liver. Four-hour LC_{50} values of 46.8 ppm, 15.8 ppm and 28 ppm (95% CI: 16-48 ppm) were reported for male rats, female rats, male and female rats combined, respectively. $BMCL_{05}$ and BMC_{01} values were calculated and are presented in Table IX-1; however, the toxicological validity of these values is questionable because of a lack of study concentrations in the lower portion of the concentration-response curve. Mortality data are summarized in Table IX-1.

Table IX-1. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*

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

*BASF, 1990

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

Table IX-2. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*			
	Males	**Females**	**Combined Males and Females**
1.76 ppm	**0/5**	**0/5**	**0/10**
44.5 ppm	**4/5**	**3/5**	**7/10**
97 ppm	**5/5**	**4/5**	**9/10**
156 ppm	**5/5**	**5/5**	**10/10**
311 ppm	**5/5**	**5/5**	**10/10**
LC_{50}	38.9 ppm	43 ppm	39.6 ppm
$BMCL_{05}$	0.68 ppm	1.9 ppm	1.33 ppm
BMC_{01}	27 ppm	31 ppm	5.3 ppm

*Hoechst, 1989

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

Table IX-3. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*				
	Males	**Females**	**Combined Males and Females**	**Reference**
1.76 ppm	**0/5**	**0/5**	**0/10**	Hoechst, 1989
15.6 ppm	**0/5**	**2/5**	**2/10**	BASF, 1990
44.5 ppm	**4/5**	**3/5**	**7/10**	Hoechst, 1989
74.9 ppm	**4/5**	**5/5**	**9/10**	BASF, 1990
97 ppm	**5/5**	**4/5**	**9/10**	Hoechst, 1989
156 ppm	**5/5**	**5/5**	**10/10**	Hoechst, 1989
159.3 ppm	**5/5**	**5/5**	**10/10**	BASF, 1990
311 ppm	**5/5**	**5/5**	**10/10**	Hoechst, 1989
LC_{50}	**37.6 ppm**	**24.2 ppm**	**30.0 ppm**	
$BMCL_{05}$	**6.3 ppm**	**0.82 ppm**	**3.6 ppm**	
BMC_{01}	**12.4 ppm**	**2.6 ppm**	**5.4 ppm**	

*BASF, 1990; Hoechst, 1989 Data Combined

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

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

IX.2.2 Non-lethal Toxicity

IX.2.2.1 Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to concentrations of 0, 4.5, 6.25, 12.5, 17.5, 25, 50, or 100 ppm phenyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted phenyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9 L stainless steel chamber which was continuously evacuated at 20 L/min. An RD_{50} of 19.5 ppm was calculated. Results are summarized in Table IX-4.

TABLE IX-4. Exposure of Male Swiss-Webster Mice to Phenyl Chloroformate for 30 minutes*

Concentration (ppm)	Respiratory rates (control/exposed)	% Decrease in respiratory rate	Mortality Within 24-hrs
4.5	285/240	16.1	0/4
6.25	250/180	26.0	0/4
12.5	265/145	45.3	0/4
17.5	265/140	47.2	0/4
25	250/90	64.0	0/4
50	200/70	65.0	0/4
100	245/50	79.6	0/4

*Carpenter, 1982

IX.2.3 Developmental/Reproductive Toxicity

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

IX.2.4 Genotoxicity

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

IX.2.5 Carcinogenicity

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

IX.2.6 Summary

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

IX.3. DATA ANALYSIS AND AEGL-1

IX.3.1 Human Data Relevant to AEGL-1

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

IX.3.2 Animal Data Relevant to AEGL-1

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

IX.3.3 Derivation of AEGL-1

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

TABLE IX-5. AEGL-1 Values for Phenyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

IX.4. DATA ANALYSIS AND AEGL-2

IX.4.1 Human Data Relevant to AEGL-2

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

IX.4.2 Animal Data Relevant to AEGL-2

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

IX.4.3 Derivation of AEGL-2

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

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

TABLE IX-6. AEGL-2 Values for Phenyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.060 ppm (0.38 mg/m^3)

IX.5. DATA ANALYSIS AND AEGL-3

IX.5.1 Human Data Relevant to AEGL-3

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

IX.5.2 Animal Data Relevant to AEGL-3

Four-hour LC_{50} 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 LC_{50} value of 30.00 ppm and $BMCL_{05}$ value of 3.6 ppm was calculated for male and female rats when the BASF (1990) and Hoechst (1989) studies were combined.

IX.5.3 Derivation of AEGL-3

The 4-hour rat $BMCL_{05}$ of 3.6 ppm from the combined BASF (1990) and Hoechst (1989) studies will be used as the point-of-departure for phenyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because phenyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value. The AEGL-3 values for phenyl chloroformate are presented in Table IX-7, and the calculations for these AEGL-3 values are presented in Appendix IX-A.

TABLE IX-7. AEGL-3 Values for Phenyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	0.72 ppm (4.6 mg/m^3)	0.72 ppm (4.6 mg/m^3)	0.57 ppm (3.6 mg/m^3)	0.36 ppm (2.3 mg/m^3)	0.18 ppm (1.2 mg/m^3)

IX.6. SUMMARY OF AEGLS

IX.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for phenyl chloroformate; therefore, AEGL-1 values are not recommended. AEGL-2 values for phenyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for phenyl chloroformate were based on a 4-hour rat $BMCL_{05}$ value.

TABLE IX-8. Summary of AEGL Values for Phenyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.24 ppm (1.5 mg/m^3)	0.24 ppm (1.5 mg/m^3)	0.19 ppm (1.2 mg/m^3)	0.12 ppm (0.77 mg/m^3)	0.060 ppm (0.38 mg/m^3)
AEGL-3 (Lethal)	0.72 ppm (4.6 mg/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.

IX.6.2. Comparison with Other Standards and Guidelines

No extant values were located for phenyl chloroformate.

IX.6.3 Data Quality and Research Needs

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

IX.7. REFERENCES

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APPENDIX IX-A:

DERIVATION OF AEGL VALUES FOR PHENYL CHLOROFORMATE

DERIVATION OF AEGL-1 VALUES FOR PHENYL CHLOROFORMATE

AEGL-1 values for phenyl chloroformate are not recommended.

Derivation of AEGL-2 Values for Phenyl Chloroformate

Key studies: BASF, 1990; Hoechst, 1989

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2: 0.72 ppm ÷ 3 = 0.24 ppm

30-min AEGL-2: 0.72 ppm ÷3 = 0.24 ppm

1-hr AEGL-2: 0.57 ppm ÷ 3 = 0.19 ppm

4-hr AEGL-2: 0.36 ppm ÷ 3 = 0.12 ppm

8-hr AEGL-2: 0.18 ppm ÷ 3 = 0.060 ppm

DERIVATION OF AEGL-3 VALUES FOR PHENYL CHLOROFORMATE

Key studies: BASF, 1990; Hoechst, 1989

Toxicity Endpoint: 4-hour rat $BMCL_{05}$ (3.6 ppm)

Scaling: 30-minutes and 1-hr

$C^3 \times t = k$

$(3.6\ ppm)^3 \times 4\ hr = 186.7\ ppm^3 hr$

8-hours

$C^1 \times t = k$

$(3.6\ ppm)^1 \times 4\ hr = 14.4\ ppm^3 hr$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3: 30-minute value adopted as 10-minute value = 0.72 ppm

30-min AEGL-3

$C^3 \times 0.5\ hr = 186.7\ ppm^3 hr$

$C^3 = 373.4\ ppm$

$C = 7.2\ ppm$

30-min AEGL-3 = 7.2/10 = 0.72 ppm

1-hr AEGL-3

$C^3 \times 1\ hr = 186.7\ ppm^3 hr$

$C^3 = 186.7\ ppm$

$C = 5.7\ ppm$

1-hr AEGL-3 = 5.7/10 = 0.57 ppm

4-hr AEGL-3

4-hr AEGL-3 = 3.6/10 = 0.36 ppm

8-hr AEGL-3

$C^1 \times 8\ hr = 14.4\ ppm^3 hr$

$C^1 = 1.8\ ppm$

$C = 1.8\ ppm$

8-hr AEGL-3 = 1.8/10 = 0.18 ppm

APPENDIX IX-B:

Derivation Summary for Phenyl Chloroformate AEGLS

AEGL-1 VALUES FOR PHENYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/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 phenyl chloroformate.				

AEGL-2 VALUES FOR PHENYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
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.				

AEGL-3 VALUES FOR PHENYL CHLOROFORMATE

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
0.72 ppm	**0.72 ppm**	**0.57 ppm**	**0.36 ppm**	**0.18 ppm**

Key References: BASF. 1990. Study on the acute inhalation toxicity LC_{50} of phenyl chloroformate as a vapor in rats, 4-hour exposure. Project No. 13I0675/887076. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. January 18, 1990.

Hoechst. 1989. Chloroformic acid phenyl ester. Aerosol inhalation toxicity in male and female SPF Wistar rats. 4-hour LC_{50}. Hofmann, T. Hoechst Pharmaceutical Research Toxicology. Report No. 89.0761. April 26, 1989.

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

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours
($BMCL_{05}$, 3.6 ppm, was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: $BMCL_{05}$/3.6 ppm/Estimated threshold for death for 4 hour exposure in rats

Effects:

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

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

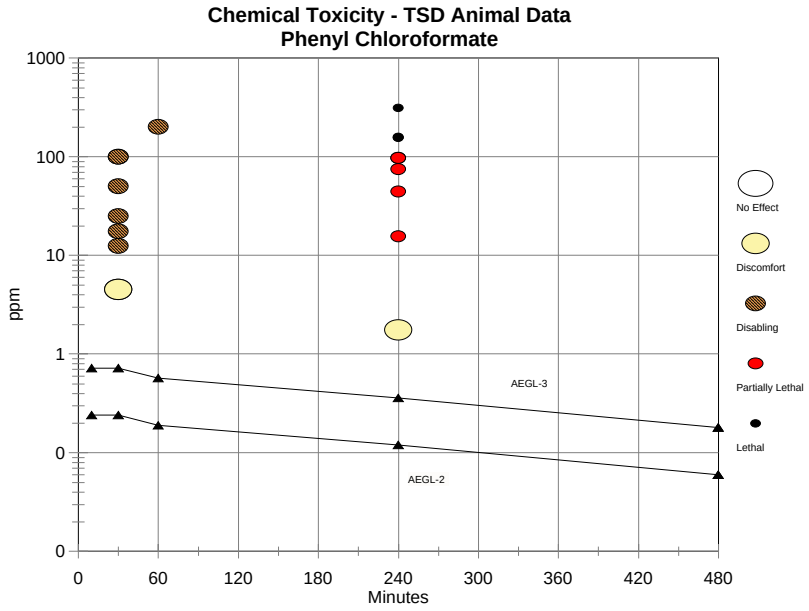
Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

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

Data Quality and Research Needs: Sparse data set.

APPENDIX IX-C: CATEGORY PLOT FOR PHENYL CHLOROFORMATE


Chemical Toxicity - TSD Animal Data
Phenyl Chloroformate
ppm
1000
100
10
1
0
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

APPENDIX IX-D: BENCHMARK CONCENTRATION CALCULATION FOR PHENYL CHLOROFORMATE

```
 1    BMDS MODEL RUN
 2    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 3
 4      The form of the probability function is:
 5      P[response] = Background
 6              + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
 7      where CumNorm(.) is the cumulative normal distribution function
 8
 9      Dependent variable = Mean
10      Independent variable = Dose
11      Slope parameter is not restricted
12
13      Total number of observations = 8
14      Total number of records with missing values = 0
15      Maximum number of iterations = 250
16      Relative Function Convergence has been set to: 1e-008
17      Parameter Convergence has been set to: 1e-008
18
19      User has chosen the log transformed model
20                 Default Initial (and Specified) Parameter Values
21                   background =           0
22                    intercept =     -2.32244
23                        slope =     0.759796
24
25            Asymptotic Correlation Matrix of Parameter Estimates
26            ( *** The model parameter(s)  -background
27                 have been estimated at a boundary point, or have been specified by the user,
28                 and do not appear in the correlation matrix )
29
30                intercept       slope
31     intercept          1       -0.98
32       slope        -0.98           1
33
34                        Parameter Estimates
35
36          Variable         Estimate          Std. Err.
37        background                0               NA
38         intercept          -4.60327          1.20324
39             slope           1.35407         0.307109
40
41     NA - Indicates that this parameter has hit a bound
42         implied by some inequality constraint and thus
43         has no standard error.
44
45                        Analysis of Deviance Table
46
47           Model      Log(likelihood)  Deviance  Test DF     P-value
48        Full model          -17.6143
49       Fitted model         -18.0291     0.829451      6      0.9913
50     Reduced model          -47.9918       60.755      7      <.0001
51
52              AIC:          40.0581
53
54
55
```

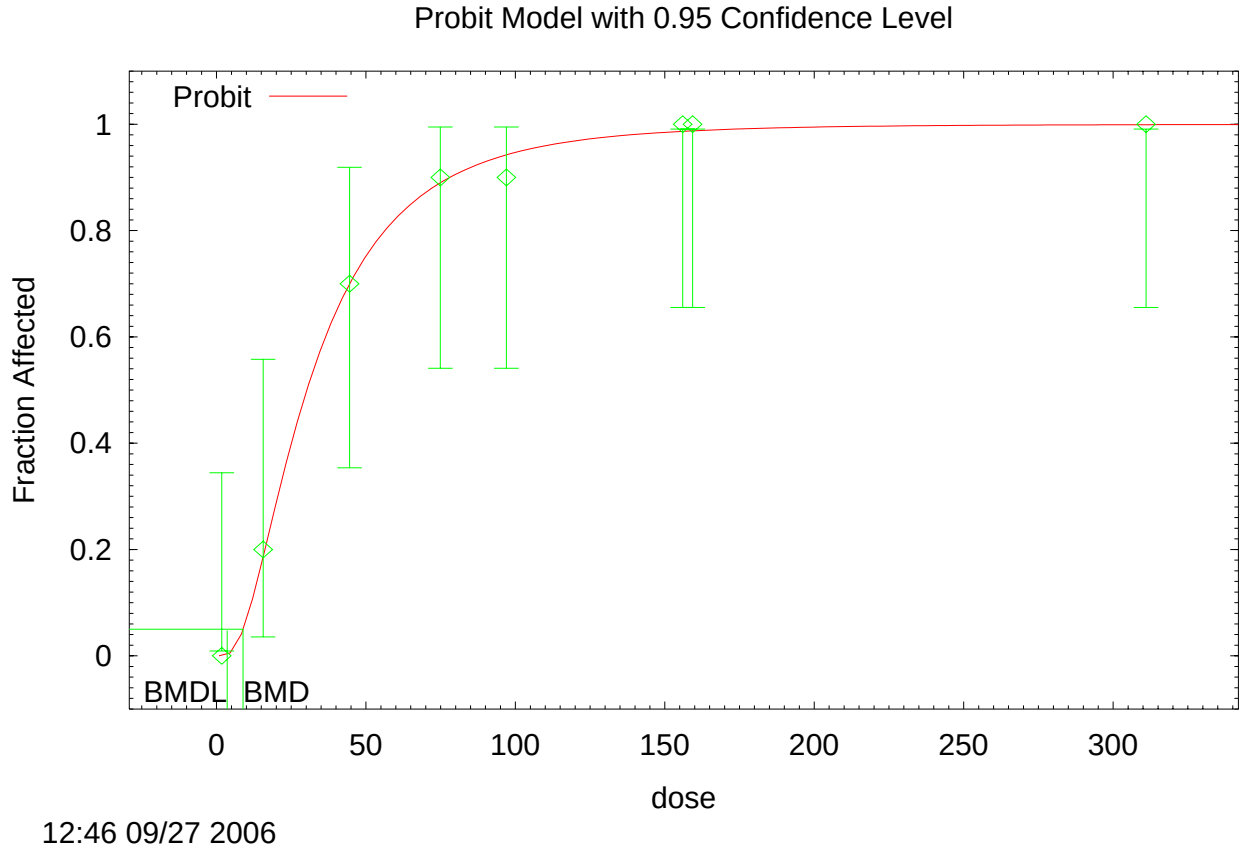
Goodness of Fit

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

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

Benchmark Dose Computation

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



CHAPTER X: 2-ETHYLHEXYL CHLOROFORMATE

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LIST OF TABLES

SUMMARY:2-ETHYLHEXYL CHLOROFORMATE

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

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

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

Summary of AEGL Values For 2-Ethylhexyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)	⅓ the AEGL-3 values (BASF, 1985)
AEGL-3 (Lethality)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/m^3)	1.8 ppm (14 mg/m^3)	0.91 ppm (7.2 mg/m^3)	4-hr rat $BMCL_{05}$ (BASF, 1985)

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

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

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

X.1.3 Developmental/Reproductive Toxicity

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

X.1.4 Genotoxicity

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

X.1.5 Carcinogenicity

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

X.1.6 Summary

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

X.2. ANIMAL TOXICITY DATA

X.2.1 Acute Lethality

X.2.1.1 Rats

Groups of ten male and ten female SPF Wistar rats were exposed to 22.8, 26.6, 34.3, or 46.9 ppm (analytical concentrations) 2-ethylhexyl chloroformate for 4-hours followed by a 14-day observation period (BASF, 1985). The whole body exposures were performed in a 200 L glass-steel inhalation chamber, and 2-ethylhexyl chloroformate concentrations were measured hourly during exposure using gas chromatography. Clinical signs noted during exposure included closed palpebral fissure, red ocular and nasal discharge, and irregular respiration, restlessness, squatting posture, and ruffled fur in the 26.6, 34.3, and 46.9 ppm groups. Clinical signs during the post-exposure observation period included irregular respiration, respiratory sounds, reddish nasal discharge and staggering in the 46.9 ppm group. In addition, slight apathy was 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 22.8 ppm group. There were no gross treatment-related effects noted at necropsy in animals surviving to study termination. Gross examination of

animals that died during the study showed venous congestion and lung emphysema with pneumonia. A 4-hour LC_{50} value of 33.9 ppm was reported for male and female rats combined. Male rats appear to be more sensitive to 2-ethylhexyl chloroformate than female rats, both with regard to lethality incidence and time of death. $BMCL_{05}$ and BMC_{01} values were calculated and are presented in Table X-1, and mortality data are also summarized in Table X-1.

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

	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

Death occurred in 0/12, 3/6, 6/6, 3/3, and 6/6 rats exposed to an "atmosphere enriched or saturated" with 2-ethylhexyl chloroformate vapor at 20EC for 3 minutes, 10 minutes, 30 minutes, 1 hour, and 2 hours, respectively (BASF, 1968). The approximate concentration was reported as 270 ppm 2-ethylhexyl chloroformate and 40 ppm phosgene contaminant. Clinical signs included mucous membrane irritation and difficulty breathing. Lung edema was noted at necropsy.

X.2.2 Non-lethal Toxicity

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

X.2.3 Developmental/Reproductive Toxicity

No information concerning the developmental/reproductive toxicity of 2-ethylhexyl chloroformate was

located in the available literature.

X.2.4 Genotoxicity

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

X.2.5 Carcinogenicity

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

X.2.6 Summary

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

X.3. DATA ANALYSIS AND AEGL-1

X.3.1 Human Data Relevant to AEGL-1

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

X.3.2 Animal Data Relevant to AEGL-1

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

X.3.3 Derivation of AEGL-1

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

TABLE X-2. AEGL-1 Values for 2-Ethylhexyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR

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

X.4. DATA ANALYSIS AND AEGL-2

X.4.1 Human Data Relevant to AEGL-2

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

X.4.2 Animal Data Relevant to AEGL-2

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

X.4.3 Derivation of AEGL-2

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

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

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

X.5. DATA ANALYSIS AND AEGL-3

X.5.1 Human Data Relevant to AEGL-3

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

X.5.2 Animal Data Relevant to AEGL-3

Four-hour LC_{50} values of 29.9 ppm, 36.3 ppm, and 33.9 ppm were calculated for male rats, female rats, and male and female rats combined, respectively (BASF, 1985). Four-hour $BMCL_{05}$ 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).

X.5.3 Derivation of AEGL-3

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

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

TABLE X-4. AEGL-3 Values for 2-Ethylhexyl Chloroformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	3.6 ppm (28 mg/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)

X.6. SUMMARY OF AEGLS

X.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for 2-ethylhexyl chloroformate; therefore, AEGL-1 values are not recommended. AEGL-2 values for 2-ethylhexyl chloroformate were based on a three-fold reduction of AEGL-3 values. AEGL-3 values for 2-ethylhexyl chloroformate were based on a 4-hour rat $BMCL_{05}$ value.

TABLE X-5. Summary of AEGL Values for 2-Ethylhexyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	1.2 ppm (9.5 mg/m^3)	1.2 ppm (9.5 mg/m^3)	0.97 ppm (7.7 mg/m^3)	0.60 ppm (4.7 mg/m^3)	0.30 ppm (2.4 mg/m^3)
AEGL-3 (Lethal)	3.6 ppm (28 mg/m^3)	3.6 ppm (28 mg/m^3)	2.9 ppm (23 mg/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.

X.6.2. Comparison with Other Standards and Guidelines

No extant values were located for 2-ethylhexyl chloroformate.

X.6.3 Data Quality and Research Needs

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

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.

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.

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.

APPENDIX X-A:

DERIVATION OF AEGL VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

DERIVATION OF AEGL-1 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

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

Derivation of AEGL-2 Values for 2-Ethylhexyl Chloroformate

Key studies: BASF, 1985

Toxicity Endpoint: ⅓ of the AEGL-3 values

10-min AEGL-2: 3.6 ppm ÷ 3 = 1.2 ppm

30-min AEGL-2: 3.6 ppm ÷3 = 1.2 ppm

1-hr AEGL-2: 2.9 ppm ÷ 3 = 0.97 ppm

4-hr AEGL-2: 1.8 ppm ÷ 3 = 0.60 ppm

8-hr AEGL-2: 0.91 ppm ÷ 3 = 0.30 ppm

DERIVATION OF AEGL-3 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

Key studies: BASF, 1985

Toxicity Endpoint: 4-hour rat $BMCL_{05}$ (18.1 ppm)

Scaling: 30-minutes and 1-hr

$C^3 \times t = k$

$(18.1 \text{ ppm})^3 \times 4 \text{ hr} = 23{,}719 \text{ ppm"hr}$

8-hours

$C^1 \times t = k$

$(18.1 \text{ ppm})^1 \times 4 \text{ hr} = 72.4 \text{ ppm"hr}$

Uncertainty Factors:

3 for interspecies variability

3 for intraspecies variability

10-min AEGL-3: 30-minute value adopted as 10-minute value = 3.6 ppm

30-min AEGL-3

$C^3 \times 0.5 \text{ hr} = 23{,}719 \text{ ppm"hr}$

$C^3 = 47438 \text{ ppm}$

$C = 36.2 \text{ ppm}$

30-min AEGL-3 = 36.2/10 = 3.6 ppm

1-hr AEGL-3

$C^3 \times 1 \text{ hr} = 23{,}719 \text{ ppm"hr}$

$C^3 = 23{,}719 \text{ ppm}$

$C = 28.7 \text{ ppm}$

1-hr AEGL-3 = 28.7/10 = 2.9 ppm

4-hr AEGL-3

4-hr AEGL-3 = 18.6/10 = 1.8 ppm

8-hr AEGL-3

$C^1 \times 8 \text{ hr} = 72.4 \text{ ppm"hr}$

$C^1 = 9.1 \text{ ppm}$

$C = 9.1 \text{ ppm}$

8-hr AEGL-3 = 9.1/10 = 0.91 ppm

APPENDIX X-B:

Derivation Summary for 2-Ethylhexyl Chloroformate AEGLS

AEGL-1 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/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 2-ethylhexyl chloroformate.				

AEGL-2 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
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/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.				
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.				

AEGL-3 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
3.6 ppm	**3.6 ppm**	**2.9 ppm**	**1.8 ppm**	**0.91 ppm**

Key Reference: BASF. 1985. Acute inhalation toxicity LC_{50} for a 4-hour exposure (rats), vapor test of 2-ethylhexyl chloroformate. Unpublished report, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 8, 1985.

Test Species/Strain/Sex/Number: Wistar rats/ 10/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours
(Male $BMCL_{05}$, 18.1 ppm, was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: $BMCL_{05}$/3.6 ppm/Estimated threshold for death for 4 hour exposure in rats

Effects:

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

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

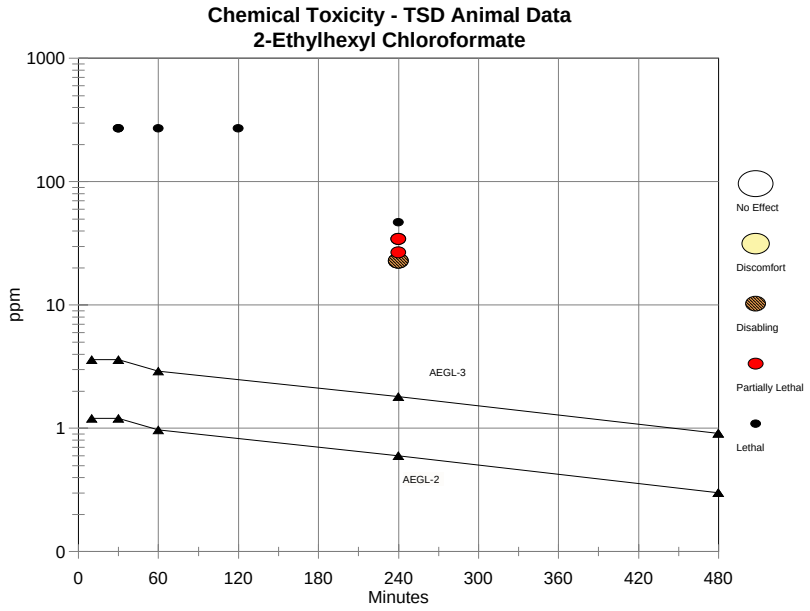
Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

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

Data Quality and Research Needs: Sparse data set.

APPENDIX X-C: CATEGORY PLOT FOR 2-ETHYLHEXYL CHLOROFORMATE


Chemical Toxicity - TSD Animal Data
2-Ethylhexyl Chloroformate
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

APPENDIX X-D: BENCHMARK CONCENTRATION CALCULATION FOR 2-ETHYLHEXYL CHLOROFORMATE

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values

background = 0
intercept = -15.0226
slope = 4.37693

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-18.7737	5.12639
slope	5.52218	1.51755

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-12.8388			
Fitted model	-14.2231	2.76871	2	0.2505
Reduced model	-27.6759	29.6742	3	<.0001

AIC: 32.4462

Goodness of Fit

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

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

Benchmark Dose Computation

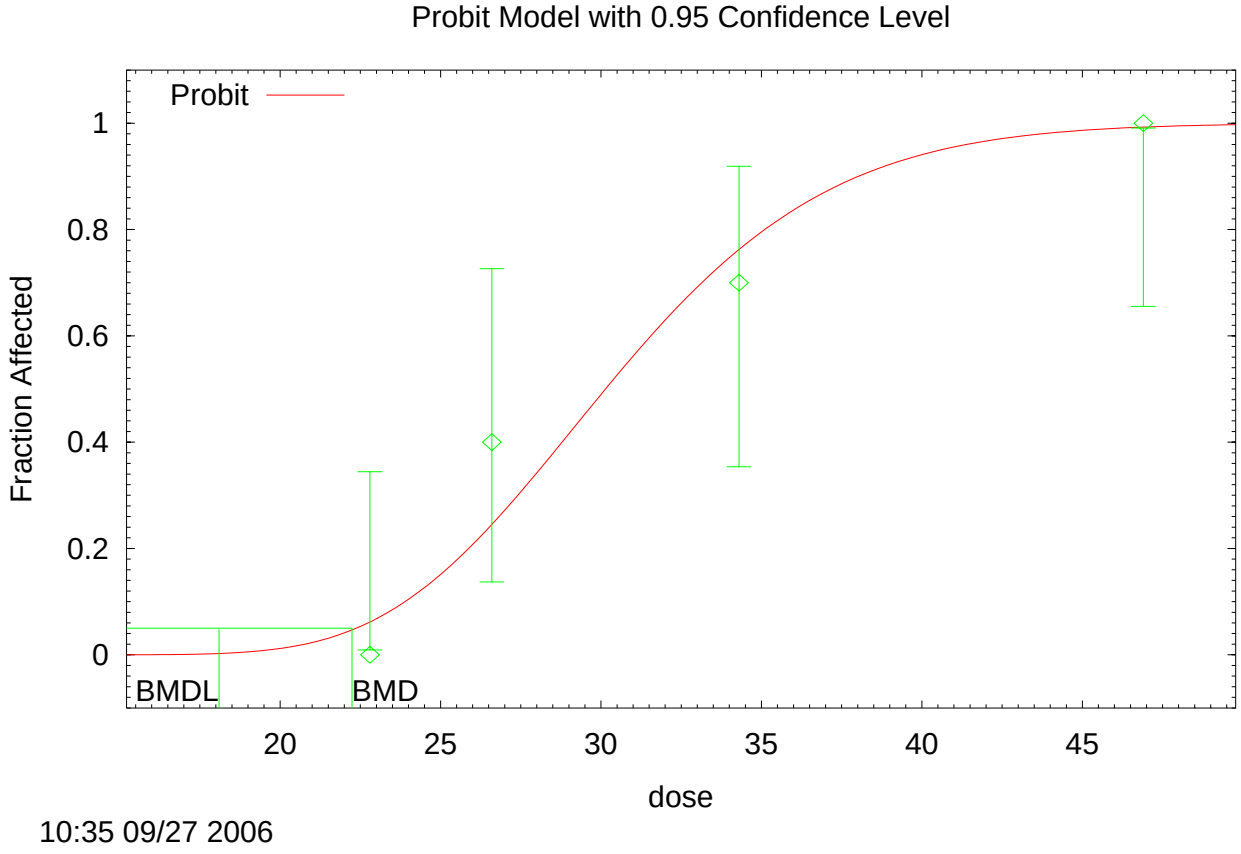
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.2386

BMDL = 18.0971



CHAPTER XI: ETHYL CHLOROTHIOFORMATE

TABLE OF CONTENTS: CHAPTER XI: ETHYL CHLOROTHIOFORMATE

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SUMMARY: ETHYL CHLOROTHIOFORMATE

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

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for ethyl chlorothioformate were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; (Stauffer, 1983)).

An estimated 4-hour rat lethality threshold of 15 ppm (⅓ the 4-hr LC_{50}: ⅓ x 45 ppm = 15 ppm) (Stauffer, 1983) was used for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies uncertainty factor of 3 was applied because ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 was applied to protect against potential delayed systemic effects that may occur due to the thio- moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in extrapolating from a 4-hour point-of-departure.

The calculated values are listed in the table below.

Summary of AEGL Values For Ethyl Chlorothioformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	0.33 ppm (1.7 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.26 ppm (1.3 mg/m^3)	0.17 ppm (0.87 mg/m^3)	0.083 ppm (0.42 mg/m^3)	⅓ the AEGL-3 values (Stauffer, 1983)
AEGL-3 (Lethality)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.79 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)	Estimated 4-hour rat lethality threshold (Stauffer, 1983)

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

References:

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

Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.

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

XI.1.1 Acute Lethality

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

XI.1.2 Non-lethal Toxicity

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

XI.1.3 Developmental/Reproductive Toxicity

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

XI.1.4 Genotoxicity

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

XI.1.5 Carcinogenicity

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

XI.1.6 Summary

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

XI.2. ANIMAL TOXICITY DATA

XI.2.1 Acute Lethality

Groups of ten male and ten female Sprague-Dawley rats were exposed to 263 ppm ethyl chlorothioformate for 1 hour (Stauffer, 1982). Animals were exposed in stainless steel and glass chambers with a volume of 447 liters. The ethyl chlorothioformate was aerosolized using a fritted bubbler and was delivered through a 1 inch diameter flexible stainless steel tubing to the chamber inlet. Actual chamber concentrations were measured coulimetrically at 15, 30, and 45 minutes after exposure initiation. During exposure, all rats showed lacrimation, salivation, and closed eyes within 15 minutes of the start of exposure. Prostration and gasping were noted in a majority of rats within 30 minutes of the start of exposure. All rats died within 24-hours of exposure; effects at necropsy included respiratory tract findings (Red mottling of lungs in 20/20 rats; frothiness of the trachea in 17/20 rats; moist, spongy lungs in 8/20; wetness around the nares in 20/20 rats).

In another study (Stauffer, 1983), groups of ten male and ten female Sprague-Dawley rats were exposed to 0, 33, 59, 65, 69, or 124 ppm ethyl chlorothioformate for 4 hours, followed by a 14-day observation period. The exposure protocol was similar to that described above (Stauffer, 1982) except that chamber concentrations were measured hourly during the 4 hour exposure period. During exposure, animals in all treatment groups showed lethargy, lacrimation, excessive salivation, and breathing difficulty. Clinical signs after exposure included rough coats, rhinorrhea, chromorhinorrhea, salivation, dyspnea, rales, dacryrrhea, chromodachrrhea, and paleness. Rats that survived the exposure became dehydrated and/or emaciated as the 14-day observation period progressed. Treatment-related necropsy findings included discolored lungs, respiratory tract necrosis, basal cell hyperplasia, vascular congestion, and alveolar emphysema. Myocardial degeneration, nephrosis, hepatic necrosis, adrenal necrosis, spleen and lymph node necrosis, and lymphoid cell depletion were also noted. Deaths in rats during or shortly after exposure were attributed to respiratory tract corrosion; whereas, those occurring after exposure were attributed to a combination of local corrosive and systemic effects. LC_{50} values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC_{50} value of 45 ppm was also calculated. Data are summarized in Table XI-1.

TABLE XI-1*. Mortality of Rats Exposed to Ethyl Chlorothioformate for4-hours

Males									
Concentration (ppm)	**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								
Females									
33	2/10	0	1	0	0	0	0	0	1
59	8/10	0	3	3	1	0	0	0	1
65	10/10	0	6	2	2	0	0	0	0
69	10/10	0	6	4	0	0	0	0	0
124	10/10	4	6	0	0	0	0	0	0
LC_{50}	41 ppm								
Combined Male and Female LC_{50}	45 ppm								

*Stauffer, 1983

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).

XI.2.5 Carcinogenicity

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

XI.2.6 Summary

Four-hour LC_{50} values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC_{50} value of 45 ppm was also calculated (Stauffer, 1983). Signs of toxicity were consistent with severe respiratory tract irritation/corrosion, and necropsy findings suggest that ethyl chlorothioformate may cause both portal of entry and systemic effects. These systemic effects are likely due to the ability of the thio moiety to interact with other biomolecules. Ethyl chlorothioformate was negative in an Ames assay, and no animal data regarding non-lethal toxicity, developmental/reproductive toxicity, or carcinogenicity were available.

XI.3. DATA ANALYSIS AND AEGL-1

XI.3.1 Human Data Relevant to AEGL-1

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

XI.3.2 Animal Data Relevant to AEGL-1

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

XI.3.3 Derivation of AEGL-1

AEGL-1 values are not recommended for ethyl chlorothioformate due to insufficient data (Table XI-2).

TABLE XI-2. AEGL-1 Values for Ethyl Chlorothioformate

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

XI.4. DATA ANALYSIS AND AEGL-2

XI.4.1 Human Data Relevant to AEGL-2

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

XI.4.2 Animal Data Relevant to AEGL-2

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

XI.4.3 Derivation of AEGL-2

No acute inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for ethyl chlorothioformate will be based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects (NRC, 2001). This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; Stauffer, 1983). The AEGL-2 values for ethyl chlorothioformate are presented in Table XI-3, and the calculations for these AEGL-2 values are presented in Appendix XI-A.

TABLE XI-3. AEGL-2 Values for Ethyl Chlorothioformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	0.33 ppm (1.7 mg/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)

XI.5. DATA ANALYSIS AND AEGL-3

XI.5.1 Human Data Relevant to AEGL-3

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

XI.5.2 Animal Data Relevant to AEGL-3

Four-hour 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).

XI.5.3 Derivation of AEGL-3

An estimated 4-hour rat lethality threshold of 15 ppm (⅓ the 4-hr LC_{50}: ⅓ x 45 ppm = 15 ppm) (Stauffer, 1983) will be used for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies

uncertainty factor of 3 will be applied because ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 will be applied to protect against potential delayed systemic effects that may occur due to the thio- moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in extrapolating from a 4-hour point-of-departure. The AEGL-3 values for ethyl chlorothioformate are presented in Table XI-4, and the calculations for these AEGL-3 values are presented in Appendix XI-A.

TABLE XI-4. AEGL-3 Values for Ethyl Chlorothioformate

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.79 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)

XI.6. SUMMARY OF AEGLS

XI.6.1 AEGL Values and Toxicity Endpoints

Data were insufficient for derivation of AEGL-1 values for ethyl chlorothioformate. The AEGL-2 values were obtained by a three-fold reduction of AEGL-3 values, and the AEGL-3 values were based on an estimated 4-hour rat lethality threshold.

TABLE XI-5. Summary of AEGL Values for Ethyl Chlorothioformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.33 ppm (1.7 mg/m^3)	0.33 ppm (1.7 mg/m^3)	0.26 ppm (1.3 mg/m^3)	0.17 ppm (0.87 mg/m^3)	0.083 ppm (0.42 mg/m^3)
AEGL-3 (Lethal)	1.0 ppm (5.1 mg/m^3)	1.0 ppm (5.1 mg/m^3)	0.79 ppm (4.0 mg/m^3)	0.50 ppm (2.6 mg/m^3)	0.25 ppm (1.3 mg/m^3)

NR: Not Recommended

XI.6.2. Comparison with Other Standards and Guidelines

No extant values were located for ethyl chlorothioformate.

XI.6.3 Data Quality and Research Needs

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.

Stauffer. 1982. Acute inhalation toxicity of ethyl chlorothioformate (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0545667.

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.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ. Mol. Mutagen. 11: (Suppl 12): 1-158.

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.

Derivation of AEGL-2 Values for Ethyl Chlorothioformate

Key study: Stauffer, 1983

Toxicity Endpoint: ⅓ the AEGL-3 values

10-min AEGL-2: 1.0 ppm ÷ 3 = 0.33 ppm

30-min AEGL-2: 1.0 ppm ÷3 = 0.33 ppm

1-hr AEGL-2: 0.79 ppm ÷ 3 = 0.26 ppm

4-hr AEGL-2: 0.5 ppm ÷ 3 = 0.17 ppm

8-hr AEGL-2: 0.25 ppm ÷ 3 = 0.083 ppm

DERIVATION OF AEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE

Key study: Stauffer, 1983

Toxicity Endpoint: Estimated 4-hr rat lethality threshold of 15 ppm (⅓ the LC_{50} of 45 ppm)

Scaling: 30-minutes and 1-hour

$C^3 \times t = k$

$(15\ ppm)^3 \times 4\ hr = 13{,}500\ ppm^{"}hr$

8-hours

$C^1 \times t = k$

$(15\ ppm)^1 \times 4\ hr = 60\ ppm^{"}hr$

Uncertainty Factors:

3 for interspecies variability

10 for intraspecies variability

10-min AEGL-3:

30-minute value adopted as 10-minute value because POD was 4-hours = 1.0 ppm

30-min AEGL-3

$C^3 \times 0.5\ hr = 13{,}500\ ppm^{"}hr$

$C^3 = 27{,}000\ ppm$

$C = 30\ ppm$

30-min AEGL-3 = 30/30 = 1.0 ppm

1-hr AEGL-3

$C^3 \times 1\ hr = 13{,}500\ ppm^{"}hr$

$C^3 = 13{,}500\ ppm$

$C = 23.8\ ppm$

1-hr AEGL-3 = 23.8/30 = 0.79 ppm

4-hr AEGL-3

15 ppm ÷ 30 = 0.50

8-hr AEGL-3

$C^1 \times 8\ hr = 60\ ppm^{"}hr$

$C^1 = 7.5\ ppm$

$C = 7.5\ ppm$

8-hr AEGL-3 = 7.5/30 = 0.25 ppm

APPENDIX XI-B:

Derivation Summary for Ethyl Chlorothioformate AEGLS

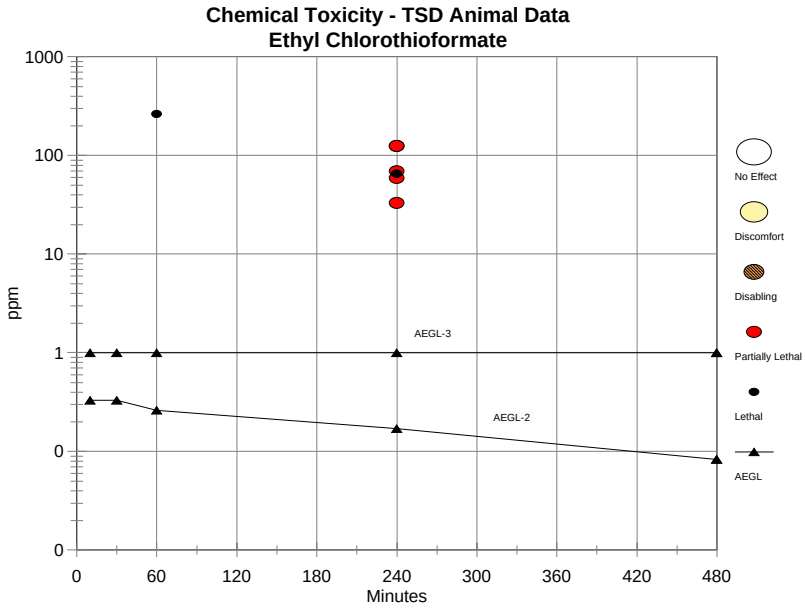
AEGL-1 VALUES FOR ETHYL CHLOROTHIOFORMATE				
10 minutes	**30 minutes**	**1 hour**	**4 hour**	**8 hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: Chemical-specific data were insufficient for deriving AEGL-1 values.				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
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 ethyl chlorothioformate.				

AEGL-2 VALUES FOR ETHYL CHLOROTHIOFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
0.33 ppm	**0.33 ppm**	**0.26 ppm**	**0.17 ppm**	**0.083 ppm**
Key Reference: Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.				
Test Species/Strain/Number: See AEGL-3 Derivation summary table				
Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table				
Effects: See AEGL-3 Derivation summary table				
Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. This approach is justified based on the steep concentration curve with regard to lethality (4-hour rat mortality incidence: 4/20 at 33 ppm; 14/20 at 59 ppm; 20/20 at 65 ppm; Stauffer, 1983).				
Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table				
Modifying Factor: See AEGL-3 Derivation summary table				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: See AEGL-3 Derivation summary table				
Data quality and research needs: See AEGL-3 Derivation summary table.				

AEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
1.0 ppm	**1.0 ppm**	**0.79 ppm**	**0.50 ppm**	**0.25 ppm**
Key Reference: Stauffer. 1983. Acute inhalation toxicity of ethyl chlorothioformate in rats (T-10710). Environmental Health Center Inhalation Facility. Staufffer Chemical Company. 400 Farmington Avenue. Farmington, CT. OTS0538464.				
Test Species/Strain/Sex/Number: Sprague Dawley rats/ 10/sex/group				
Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours (Estimated lethality threshold of ⅓ the 4-hr rat LC_{50} of 45 ppm (⅓ x 45 ppm = 15 ppm) is the point-of-departure for AEGL-3)				
Endpoint/Concentration/Rationale: ⅓ the 4-hr rat LC_{50} of 45 ppm (⅓ x 45 ppm = 15 ppm)/ 15 ppm/Estimated threshold for death for 4 hour exposure in rats				
Effects: LC_{50} =51 ppm (male); 41 ppm (female); 45 ppm (combined male and female)				
Uncertainty Factors/Rationale: Interspecies = 3: Ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Intraspecies = 10: Protect against potential delayed systemic effects from the thio- moiety				
Modifying Factor:				
Animal to Human Dosimetric Adjustment: Insufficient data				
Time Scaling: $c^n \times t = k$, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute value was adopted as the 10-minute value because the point-of-departure was 4-hours.				
Data Quality and Research Needs: Data limited to rat lethality studies.				

APPENDIX XI-C:

Category Plot for Ethyl Chlorothioformate


Chemical Toxicity - TSD Animal Data
Ethyl Chlorothioformate
1000
100
10
1
0
0
ppm
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Lethal
Lethal
AEGL