INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR
SELECTED CHLOROFORMATES

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

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

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

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

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

n-Butyl Chloroformate
C₅H₁₀ClO₂ (CAS Reg. No. 592-34-7)

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

sec-Butyl Chloroformate
C₅H₁₀ClO₂ (CAS Reg. No. 17462-58-7)

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

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

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

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

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

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

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

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

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

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

1  PREFACE .............................................................................................................................................. ii

4  CHAPTER I: GENERAL INFORMATION FOR SELECTED CHLOROFORMATES ............................. 1

5  CHAPTER II. METHYL CHLOROFORMATE .................................................................................... 1

6  CHAPTER III. ETHYL CHLOROFORMATE ....................................................................................... 1

7  CHAPTER IV: PROPYL CHLOROFORMATE .................................................................................. 23

8  CHAPTER V: ISOPROPYL CHLOROFORMATE .............................................................................. 23

9  CHAPTER VI: ALLYL CHLOROFORMATE ..................................................................................... 25

10  CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-...

11  BUTYL CHLOROFORMATE ........................................................................................................ 22

12  CHAPTER VIII: BENZYL CHLOROFORMATE ............................................................................. 1

13  CHAPTER IX: PHENYL CHLOROFORMATE .................................................................................. 19

14  CHAPTER X: 2-ETHYLHEXYL CHLOROFORMATE ...................................................................... 1

15  CHAPTER XI: ETHYL CHLOROTHIOFORMATE .......................................................................... 21

16
CHAPTER I: GENERAL INFORMATION FOR SELECTED CHLOROFORMATES
TABLE OF CONTENTS: CHAPTER I: GENERAL INFORMATION
FOR SELECTED CHLOROFORMATES

LIST OF TABLES: CHAPTER I. GENERAL INFORMATION
I.1. General Chemical and Physical Properties
I.2. Production and Use
I.3. Absorption, Metabolism, Disposition and Excretion
I.4. Mechanism of Toxicity
I.5. Concurrent Exposure Issues
I.6. Species Sensitivity
I.7. Temporal Extrapolation
I.8. References
LIST OF TABLES: CHAPTER I. GENERAL INFORMATION

1  TABLE I-1. Chemical and Physical Data for Methyl Chloroformate ......................................................... I-4
2  TABLE I-2. Chemical and Physical Data for Ethyl Chloroformate ............................................................... I-5
3  TABLE I-3. Chemical and Physical Data for Propyl Chloroformate ............................................................. I-5
4  TABLE I-4. Chemical and Physical Data for Isopropyl Chloroformate ......................................................... I-6
5  TABLE I-5. Chemical and Physical Data for Allyl Chloroformate ............................................................... I-6
6  TABLE I-6. Chemical and Physical Data for n-Butyl Chloroformate ............................................................ I-7
7  TABLE I-7. Chemical and Physical Data for Isobutyl Chloroformate ........................................................... I-7
8  TABLE I-8. Chemical and Physical Data for sec-Butyl Chloroformate .......................................................... I-8
9  TABLE I-9. Chemical and Physical Data for Benzyl Chloroformate ............................................................ I-8
10 TABLE I-10. Chemical and Physical Data for Phenyl Chloroformate .......................................................... I-9
11 TABLE I-11. Chemical and Physical Data for 2-Ethylhexyl Chloroformate .................................................... I-9
12 TABLE I-12. Chemical and Physical Data for Ethyl Chlorothioformate ......................................................... I-10
I.1. General Chemical and Physical Properties

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

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                | C₂H₅ClO₂         | HSDB, 2005a   |
| Molecular Weight                | 94.5            | HSDB, 2005a   |
| Physical State                  | Colorless liquid | HSDB, 2005a   |
| Vapor Pressure                  | 108.5 mm Hg at 25°C | HSDB, 2005a |
| Vapor Density                   | 3.26 g/L (air = 1) | HSDB, 2005a |
| Density/Specific Gravity        | 1.223 g/cm³     | HSDB, 2005a   |
| Melting/Boiling/Flash Point     | -61°C/71.0°C/12.2°C | HSDB, 2005a |
| Solubility                      | Slightly soluble (hydrolyzes) in water; Soluble in chloroform, benzene, alcohol, ether | HSDB, 2005a |
| Conversion factors in air       | 1 mg/m³ = 0.26 ppm |
|                                 | 1 ppm = 3.9 mg/m³ |
### TABLE I-2. Chemical and Physical Data for Ethyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Ethyl Chloroformate</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Ethyl chlorocarbonate</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>541-41-3</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₃H₅ClO₂</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>108.53</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Physical State</td>
<td>Water-white liquid</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>22.4 mm Hg at 25°C</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>3.7 g/L (air = 1)</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.403 g/cm³</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Melting/Boiling/Flash Point</td>
<td>-80.6°C/95°C/27.8°C</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Solubility</td>
<td>Gradually decomposes in water</td>
<td>HSDB, 2005b</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.23 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 4.4 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Propyl Chloroformate</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloridic acid, propyl ester; Formic acid, chloro-, propyl ester; Propyl chlorocarbonate; N-Propyl chloroformate</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>109-61-5</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₄H₇ClO₂</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>122.55</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Physical State</td>
<td>Colorless liquid</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>20 mm Hg at 25°C</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>4.2 g/L (air = 1)</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.09 g/cm³</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>112.4°C/34.4°C</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Solubility</td>
<td>Miscible in chloroform, benzene, ether</td>
<td>HSDB, 2005c</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.20 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 5.0 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>
TABLE I-4. Chemical and Physical Data for Isopropyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Isopropyl Chloroformate</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloride acid, 1-methylethyl ester; Carbonochloridic acid, 1-methylethyl ester; Chloroformic acid isopropyl ester; Formic acid, chloro-, isopropyl ester; Isopropyl chlorocarbonate; Isopropyl chloromethonate</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>108-23-6</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₄H₇ClO₂</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>122.55</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Physical State</td>
<td>Colorless liquid</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>100 mm Hg at 47°C</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>4.2 g/L (air = 1)</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.08 g/cm³</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>104.6°C/27.8°C</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in ether; hydrolyzes in water</td>
<td>HSDB, 2005d</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.20 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 5.0 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

TABLE I-5. Chemical and Physical Data for Allyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Allyl Chloroformate</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Chloroformic acid, allyl ester; Allyl Chlorocarbonate</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>2937-50-0</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₄H₅ClO₂</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>120.54</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Physical State</td>
<td>Colorless liquid</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>20 mm Hg at 25°C</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>4.2 g/L (air = 1)</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.14 g/cm³</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>110°C/31.1°C</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Solubility</td>
<td>Hydrolyzes in water</td>
<td>HSDB, 2005e</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.20 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 4.9 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>
TABLE I-6. Chemical and Physical Data for n-Butyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>n-Butyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Butyl chlorocarbonate; Butoxycarbonyl chloride; Chloroformic acid, butyl ester</td>
<td>BG Chemie, 2005</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>592-34-7</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₅H₉ClO₂</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>136.58</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
<td>BG Chemie, 2005</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>7 hPa at 20°C</td>
<td>BG Chemie, 2005</td>
</tr>
<tr>
<td>Vapor Density</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.06 g/cm³</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Solubility</td>
<td>Poorly soluble (hydrolyzes) in water; Miscible in ether; soluble in acetone and ethanol</td>
<td>BG Chemie, 2005</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>77.6°C/46.0°C</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.18 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 5.6 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

TABLE I-7. Chemical and Physical Data for Isobutyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Isobutyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloridic acid, 2-methylpropyl ester; Isobutyl chlorocarbonate</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>543-27-1</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₅H₁₀ClO₂</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>136.58</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Physical State</td>
<td>Clear liquid</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Vapor Density</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.04 g/cm³</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>130°C/39.4°C</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Solubility</td>
<td>Miscible in chloroform, benzene, ether; Gradually decomposes in water</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.18 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 5.6 mg/m³</td>
<td></td>
</tr>
<tr>
<td>Characteristic/Property</td>
<td>Data</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Common Name</td>
<td>sec-Butyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloridic acid, 1-methylpropyl ester</td>
<td>NLM, 2005</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>17462-58-7</td>
<td>NLM, 2005</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₅H₉ClO₂</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>136.58</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Physical State</td>
<td>Colorless liquid</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.049 g/cm³</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>NA/35.6°C</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Solubility</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.18 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 5.6 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Benzyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloridic acid phenyl methyl ester; Carbobenzyloxy chloroide; Chloroformic acid benzyl ester; Benzyl carbonyl chloride</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>501-53-1</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₈H₇ClO₂</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>170.60</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Physical State</td>
<td>Clear to pale yellow liquid</td>
<td>HSDB, 2006</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>0.009 kPa at 85-87°C</td>
<td>IPCS, 1999</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>1 g/L (air = 1)</td>
<td>IPCS, 1999</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.22 g/cm³</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>103°C/80°C</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Solubility</td>
<td>Decomposes in water</td>
<td>O’Neil et al., 2001</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.14 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 7.0 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE I-10. Chemical and Physical Data for Phenyl Chloroformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Phenyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Carbonochloridic acid phenyl ester; Phenyl chlorocarbonate; Phenoxycarbonyl chloride; Formic acid, chloro-, phenyl ester</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>1885-14-9</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₇H₅ClO₂</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>156.6</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Physical State</td>
<td>Colorless liquid</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>90 Pa at 20°C</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>5.41 g/L (air = 1)</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.25 g/cm³</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>188-189°C/69°C</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Solubility</td>
<td>Decomposes in water</td>
<td>IPCS, 2005</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.16 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 6.4 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>2-Ethylhexyl Chloroformate</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Chloroformic acid 2-ethylhexyl ester; Carbonochloridic acid, 2-ethylhexyl ester; 2-Ethylhexyl chlorocarbonate; Formic acid, chloro-, 2-ethylhexyl ester</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>24468-13-1</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₉H₁₇ClO₂</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>192.71</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Physical State</td>
<td>Clear, colorless liquid</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>1 mm Hg at 45°C</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>&gt;1 g/L (air = 1)</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>0.9914 g/cm³</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Boiling/Flash Point</td>
<td>208°C/NA</td>
<td>Kreutzberger, 2003</td>
</tr>
<tr>
<td>Solubility</td>
<td>Decomposes in water</td>
<td>RTECS, 2005</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.13 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ppm = 7.9 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>
TABLE I-12. Chemical and Physical Data for Ethyl Chlorothioformate

<table>
<thead>
<tr>
<th>Characteristic/Property</th>
<th>Data</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Name</td>
<td>Ethyl Chlorothioformate</td>
<td>HSDB, 2005f</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Ethylthiol chloroformate; Ethylthiocarbonyl chloride; Formin acid, chlorothio-, S-ethyl ester</td>
<td>HSDB, 2005f</td>
</tr>
<tr>
<td>CAS Registry No.</td>
<td>2941-64-2</td>
<td>HSDB, 2005f</td>
</tr>
<tr>
<td>Chemical Formula</td>
<td>C₃H₅ClO-S</td>
<td>HSDB, 2005f</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>124.59</td>
<td>HSDB, 2005f</td>
</tr>
<tr>
<td>Physical State</td>
<td>Amber liquid</td>
<td>Stauffer Chemical Company, 1983</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>8.3 mm Hg at 21°C</td>
<td>Stauffer Chemical Company, 1983</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Density/Specific Gravity</td>
<td>1.19 g/cm³</td>
<td>Stauffer Chemical Company, 1983</td>
</tr>
<tr>
<td>Freezing/Boiling/Flash Point</td>
<td>-60°C/132°C/51.7°C</td>
<td>Stauffer Chemical Company, 1983</td>
</tr>
<tr>
<td>Solubility</td>
<td>Decomposes in water</td>
<td>Stauffer Chemical Company, 1983</td>
</tr>
<tr>
<td>Conversion factors in air</td>
<td>1 mg/m³ = 0.20 ppm, 1 ppm = 5.1 mg/m³</td>
<td></td>
</tr>
</tbody>
</table>

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 RD₅₀ data for methyl, ethyl, propyl, isopropyl, isooctyl, sec-butyl, and phenyl chloroformates seem to suggest that the mouse may be more sensitive than the rat. However, this is likely an artifact of the RD₅₀ procedure stressing the mice (restrained with collar), and is not likely indicative of an increased sensitivity to chloroformates.

I.7. Temporal Extrapolation

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

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

I.8. References


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


CHAPTER II. METHYL CHLOROFORMATE
## TABLE OF CONTENTS: CHAPTER II: METHYL CHLOROFORMATE

1. LIST OF TABLES: CHAPTER II. METHYL CHLOROFORMATE ..................................................... II-3
2. EXECUTIVE SUMMARY: METHYL CHLOROFORMATE .......................................................... II-4

### II.1. HUMAN TOXICITY DATA................................................................................................II-5

1. II.1.1. Acute Lethality ........................................................................................................ II-5
2. II.1.2. Non-lethal Toxicity .................................................................................................. II-5
3. II.1.2.1. Case Reports ..................................................................................................... II-5
4. II.1.3. Developmental/Reproductive Toxicity ....................................................................... II-6
5. II.1.4. Genotoxicity .......................................................................................................... II-6
6. II.1.5. Carcinogenicity ...................................................................................................... II-7
7. II.1.6. Summary ............................................................................................................... II-7

### II.2. ANIMAL TOXICITY DATA............................................................................................... II-7

1. II.2.1. Lethality ................................................................................................................ II-7
2. II.2.1.1. Rats ....................................................................................................................... II-7
3. II.2.1.2. Mice ....................................................................................................................... II-11
4. II.2.2. Repeated-Exposure .................................................................................................. II-11
5. II.2.3. Developmental/Reproductive Toxicity ...................................................................... II-13
6. II.2.4. Genotoxicity .......................................................................................................... II-13
7. II.2.5. Carcinogenicity ...................................................................................................... II-13
8. II.2.6. Summary ............................................................................................................... II-13

### II.3. DATA ANALYSIS AND AEGL-1 .................................................................................. II-16

1. II.3.1. Human Data Relevant to AEGL-1 .......................................................................... II-16
2. II.3.2. Animal Data Relevant to AEGL-1 .......................................................................... II-16
3. II.3.3. Derivation of AEGL-1 .......................................................................................... II-16

### II.4. DATA ANALYSIS AND AEGL-2 ................................................................................. II-17

1. II.4.1. Human Data Relevant to AEGL-2 .......................................................................... II-17
2. II.4.2. Animal Data Relevant to AEGL-2 .......................................................................... II-17
3. II.4.3. Derivation of AEGL-2 .......................................................................................... II-17
INTERIM 1: 05/2008
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Iso-butyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

II.5. DATA ANALYSIS AND AEGL-3
II.5.1. Human Data Relevant to AEGL-3
II.5.2. Animal Data Relevant to AEGL-3
II.5.3. Derivation of AEGL-3

II.6. SUMMARY OF AEGL
II.6.1. AEGL Values and Toxicity Endpoints
II.6.2. Other Exposure Criteria
II.6.3. Data Adequacy and Research Needs

II.7. REFERENCES

APPENDIX II-A: TIME SCALING CALCULATIONS FOR METHYL CHLOROFORMATE
APPENDIX II-B: DERIVATION SUMMARY FOR METHYL CHLOROFORMATE
APPENDIX II-C: CATEGORY PLOT FOR METHYL CHLOROFORMATE
APPENDIX II-D: BENCHMARK CONCENTRATION CALCULATION FOR METHYL CHLOROFORMATE
# LIST OF TABLES: CHAPTER II. METHYL CHLOROFORMATE

1. Summary of AEGL Values For Methyl Chloroformate .......................................................... II-5
2. Mortality of Rats Exposed to Methyl Chloroformate for 1-hour ............................................. II-7
3. Mortality of Rats Exposed to Methyl Chloroformate for 1-hour ............................................. II-8
4. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours ............................................ II-9
5. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours ............................................ II-10
6. Exposure of Male Swiss-Webster Mice to Methyl Chloroformate for 30 minutes ............ II-11
7. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate .................. II-14
8. AEGL-1 Values for Methyl Chloroformate ........................................................................... II-16
9. AEGL-2 Values for Methyl Chloroformate ........................................................................... II-17
10. AEGL-3 Values for Methyl Chloroformate ........................................................................... II-18
11. Summary of AEGL Values For Methyl Chloroformate ...................................................... II-19
EXECUTIVE SUMMARY: METHYL CHLOROFORMATE

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

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

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient Data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm (16 mg/m³)</td>
<td>2.8 ppm (11 mg/m³)</td>
<td>2.2 ppm (8.6 mg/m³)</td>
<td>1.4 ppm (5.5 mg/m³)</td>
<td>0.70 ppm (2.7 mg/m³)</td>
<td>1/3 the AEGL-3 values (Hoechst, 1986)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm (47 mg/m³)</td>
<td>8.5 ppm (33 mg/m³)</td>
<td>6.7 ppm (26 mg/m³)</td>
<td>4.2 ppm (16 mg/m³)</td>
<td>2.1 ppm (8.2 mg/m³)</td>
<td>Estimated lethality threshold (BMCL₀₅) in the rat after a 4-hour exposure (Hoechst, 1986)</td>
</tr>
</tbody>
</table>

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:


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.
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 37.2°C. 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 methyl chloroformate 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 for 1-hour* |
|-----------------------------|-----------------|-----------------|
| Concentration (ppm)         | Male            | Female          |
| 0                           | 0/5             | 0/5             |
| 145                         | 4/5             | 0/5             |
| 173                         | 5/5             | 2/5             |
| 233                         | 5/5             | 4/5             |
| 274                         | 5/5             | 1/5             |
| BMCL$_{05}$                 |                 | 74 ppm          |
| LC$_{50}$                   |                 | 163 ppm         |

* Bio Test Laboratories, Inc. (1975)

In another study, groups of ten male Sprague Dawley rats were exposed to 735, 2947, 9610, or 66,235 ppm (nominal concentrations) methyl chloroformate for 1 hour (WARF Institute,
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>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>735</td>
<td>10/10 dead at 20 minutes into exposure</td>
</tr>
<tr>
<td>2,947</td>
<td>9/10 dead at end of 1-hour exposure; 1/10 dead 2 minutes post-exposure</td>
</tr>
<tr>
<td>9,610</td>
<td>5/10 dead at end of 1-hour exposure; 5/10 dead 10 minutes post-exposure</td>
</tr>
<tr>
<td>66,235</td>
<td>All 10 animals survived the 1 hour exposure. 7/10 dead 3 hours post-exposure; 3/10 dead within 18 hours post-exposure</td>
</tr>
</tbody>
</table>

*WARF Institute, Inc. (1972)

Groups of five male and five female Fischer 344 rats (main group) were exposed to 0, 26, 110, 133, 159, or 192 ppm methyl chloroformate vapor for 1 hour in a 3-foot wide Hinner-style chamber (Fisher et al., 1981). Methyl chloroformate chamber concentrations were monitored by real time variable pathlength infrared photospectrometry. In addition 10, 10, and 20 rats/sex (satellite rats) were concurrently exposed to 26, 110, or 133 ppm methyl chloroformate, respectively. One satellite rat/sex/concentration and 2 rats/sex at the lower three concentrations of the main group were sacrificed at 4 and 24 hours and 9 or 10 days post-exposure. All other surviving animals were sacrificed 14 days post-exposure. The LC50 values were 100 ppm for female rats, and between 92 and 123 ppm for male rats at 14 days post-exposure. Respiratory distress occurred in all main group rats at 110, 133, 159, and 192 ppm during the first 24 hours following exposure. The respiratory distress resolved within 24 hours in the 110 ppm group; 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 LC₅₀ of 88 (64-123) ppm for male Sprague-Dawley rats and a value of 103 (90-118) ppm for female Sprague-Dawley rats. Experiments were performed in bell jars using groups of five rats per exposure level and concentrations were analytically determined. No further experimental details were available.

Groups of five male and five female SPF Wistar rats were exposed to 35, 45, 57, or 73 ppm (analytical concentrations) methyl chloroformate for 4-hours followed by a 14-day observation period (Hoechst, 1986). The whole body exposures were performed in a 2.25 m³ exposure chamber operated under dynamic flow conditions. Methyl chloroformate concentrations were measured every 15 minutes during exposure using a single beam photometer, and were analytically measured every 120 minutes using gas chromatography. Clinical signs noted in all 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 LC₅₀ values of 51 ppm and 53 ppm were calculated for males and females, respectively. A combined male and female BMCL₀₅ value of 42.4 ppm and combined male and female BMC₀₁ value of 47.8 ppm were calculated. Mortality data are summarized in Table II-3.

| TABLE II-3. Mortality of Rats Exposed to Methyl Chloroformate for 4-hours* |
|-----------------|-----------------|-----------------|
| Concentration (ppm) | Male | Female |
| 35 | 0/5 | 0/5 |
| 45 | 0/5 | 0/5 |
| 57 | 5/5 | 3/5 |
| 73 | 5/5 | 5/5 |
| LC₅₀ | 51 ppm | 53 ppm |
| BMCL₀₅ | 42.4 ppm |  |
| BMC₀₁ | 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>
<thead>
<tr>
<th>Nominal Concentration (ppm)</th>
<th>Analytical Concentration (ppm)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>1.5</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>65</td>
<td>13.7</td>
<td>5/10</td>
<td>3/10</td>
</tr>
<tr>
<td>96</td>
<td>33.6</td>
<td>10/10</td>
<td>7/10</td>
</tr>
<tr>
<td>127</td>
<td>31.0</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>$LC_{50}$</td>
<td></td>
<td>13 ppm</td>
<td>18 ppm</td>
</tr>
</tbody>
</table>

*BASF, 1980

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

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

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

The following oral 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).
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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

*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 mediastinal 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>
<thead>
<tr>
<th>Species</th>
<th>Concentration (ppm)</th>
<th>Exposure Duration</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>37,500</td>
<td>3 min</td>
<td>12/12 dead</td>
<td>BASF, 1978</td>
</tr>
<tr>
<td>Rat</td>
<td>735 (nominal)</td>
<td>20 min</td>
<td>10/10 dead</td>
<td>WARF Institute, Inc., 1972</td>
</tr>
<tr>
<td>Rat</td>
<td>26</td>
<td>1 hr</td>
<td>No effects</td>
<td>Fisher et al., 1981</td>
</tr>
<tr>
<td>Rat</td>
<td>74 (nominal)</td>
<td>1 hr</td>
<td>BMCL_05</td>
<td>Bio-Test Labs, Inc., 1975</td>
</tr>
<tr>
<td>Rat-male</td>
<td>88</td>
<td>1 hr</td>
<td>LC_50</td>
<td>Vernot et al., 1977</td>
</tr>
<tr>
<td>Rat-male</td>
<td>92-123</td>
<td>1 hr</td>
<td>LC_50</td>
<td>Fisher et al., 1981</td>
</tr>
<tr>
<td>Rat-female</td>
<td>100</td>
<td>1 hr</td>
<td>LC_50</td>
<td>Fisher et al., 1981</td>
</tr>
<tr>
<td>Rat-female</td>
<td>103</td>
<td>1 hr</td>
<td>LC_50</td>
<td>Vernot et al., 1977</td>
</tr>
<tr>
<td>Rat</td>
<td>163 (nominal)</td>
<td>1 hr</td>
<td>LC_50</td>
<td>Bio-Test Labs Inc., 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>2974 (nominal)</td>
<td>1 hr</td>
<td>10/10 dead</td>
<td>WARF Institute, Inc., 1972</td>
</tr>
<tr>
<td>Rat</td>
<td>15</td>
<td>4 hrs</td>
<td>LC_50</td>
<td>BASF, 1980</td>
</tr>
<tr>
<td>Rat</td>
<td>42.4 ppm</td>
<td>4 hrs</td>
<td>BMCL_05</td>
<td>Hoechst, 1986</td>
</tr>
<tr>
<td>Rat-male</td>
<td>51</td>
<td>4 hrs</td>
<td>LC_50</td>
<td>Hoechst, 1986</td>
</tr>
<tr>
<td>Rat-female</td>
<td>53</td>
<td>4 hrs</td>
<td>LC_50</td>
<td>Hoechst, 1986</td>
</tr>
<tr>
<td>Mouse</td>
<td>52.4</td>
<td>30 minutes</td>
<td>RD_50</td>
<td>Carpenter, 1982</td>
</tr>
<tr>
<td><strong>Repeated Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>0.40</td>
<td>6 hr/d, 3 ds</td>
<td>No effects</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>2.15</td>
<td>6 hr/d, 3 ds</td>
<td>Histopathology</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>3.98</td>
<td>6 hr/d, 3 ds</td>
<td>Histopathology, decreased body weight</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>7.83</td>
<td>6 hr/d, 3 ds</td>
<td>Clinical signs, histopathology, decreased body weight</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>1.9</td>
<td>6 hr/d, 5 ds</td>
<td>No effects</td>
<td>HRC, 1992</td>
</tr>
<tr>
<td>Rat</td>
<td>6.2</td>
<td>6 hr/d, 5 ds</td>
<td>Clinical signs consistent with irritation, focal epithelia hyperplasia; petechial lung bleeding</td>
<td>HRC, 1992</td>
</tr>
<tr>
<td>Rat</td>
<td>19.5</td>
<td>6 hr/d, 5 ds</td>
<td>Clinical signs consistent with irritation, focal epithelia hyperplasia; inflammatory and erosive mucous membrane changes, petechial lung bleeding, increased lung</td>
<td>HRC, 1992</td>
</tr>
</tbody>
</table>
### TABLE II-6. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration (ppm)</th>
<th>Exposure Duration</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>0.40</td>
<td>6 hr/d, 5 ds/wk, 2 wks</td>
<td>No effects</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>2.15</td>
<td>6 hr/d, 5 ds/wk, 2 wks</td>
<td>Histopathology</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>3.98</td>
<td>6 hr/d, 5 ds/wk, 2 wks</td>
<td>Histopathology, cell proliferation</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>7.83</td>
<td>6 hr/d, 5 ds/wk, 2 wks</td>
<td>Clinical signs, histopathology, cell proliferation, increased lung weight</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>1</td>
<td>6 hr, 15 exposures</td>
<td>No effects</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>5</td>
<td>6 hr, 15 exposures</td>
<td>Nasal irritation, lethargy</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>20</td>
<td>6 hr, 15 exposures</td>
<td>Nasal irritation, respiratory difficulty, lethargy, lung pathology, kidney congestion</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>0.13</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>No effects</td>
<td>BASF, 1993</td>
</tr>
<tr>
<td>Rat</td>
<td>0.38</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>No effects</td>
<td>BASF, 1993</td>
</tr>
<tr>
<td>Rat</td>
<td>0.40</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>No effects</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>1.01</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>Larynx lesions</td>
<td>BASF, 1993</td>
</tr>
<tr>
<td>Rat</td>
<td>2.15</td>
<td>6 hr/d, 5 ds/wk, 4 weeks</td>
<td>Histopathology, cell proliferation</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>3.1</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>Nasal turbinate histopathology; larynx lesions</td>
<td>BASF, 1993</td>
</tr>
<tr>
<td>Rat</td>
<td>3.98</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>Histopathology, cell proliferation</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>7.83</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>Clinical signs, histopathology, cell proliferation, increased lung weight</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>8.8</td>
<td>6 hr/d, 5 ds/wk, 4 wks</td>
<td>3/10 deaths in final week of exposure; clinical signs; decreased BW; hematological effects; lung congestion; increased lung weight; nasal turbinate</td>
<td>BASF, 1993</td>
</tr>
</tbody>
</table>
TABLE II-6. Summary of Inhalation Data of Animals Exposed to Methyl Chloroformate

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration (ppm)</th>
<th>Exposure Duration</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>0.40</td>
<td>6 hr/d, 5 ds/wk, 13 wks</td>
<td>No effects</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>2.15</td>
<td>6 hr/d, 5 ds/wk, 13 wks</td>
<td>Histopathology, cell proliferation</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>3.98</td>
<td>6 hr/d, 5 ds/wk, 13 wks</td>
<td>Histopathology, cell proliferation, decreased body weight</td>
<td>BASF, 1999</td>
</tr>
<tr>
<td>Rat</td>
<td>7.83</td>
<td>6 hr/d, 5 ds/wk, 13 weeks</td>
<td>4/10 deaths-males (occurred after 24, 32, 36, or 41 exposures), clinical signs, histopathology, cell proliferation, increased lung weight, decreased body weight</td>
<td>BASF, 1999</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>4.0 ppm (16 mg/m$^3$)</td>
<td>2.8 ppm (11 mg/m$^3$)</td>
<td>2.2 ppm (8.6 mg/m$^3$)</td>
<td>1.4 ppm (5.5 mg/m$^3$)</td>
<td>0.70 ppm (2.7 mg/m$^3$)</td>
</tr>
</tbody>
</table>

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 LC₅₀ 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 LC₅₀ values of 51 ppm and 53 ppm were calculated for male and female Wistar rats, respectively; a combined male and female BMCL₀₅ value of 42.4 ppm and combined male and female BMC₀₁ value of 47.8 ppm were also calculated (Hoechst, 1986).

II.5.3. Derivation of AEGL-3

The calculated 4-hr BMCL₀₅ 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 cⁿ x t = k, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (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 LC₅₀ study (Bio-Test, 1975); utilizing the BMCL₀₅ from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986). The AEGL-3 values for methyl chloroformate are presented in Table II-9, and the calculations for these AEGL-3 values are presented in Appendix II-A.

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>12 ppm</td>
<td>8.5 ppm</td>
<td>6.7 ppm</td>
<td>4.2 ppm</td>
<td>2.1 ppm</td>
</tr>
<tr>
<td></td>
<td>(47 mg/m³)</td>
<td>(33 mg/m³)</td>
<td>(26 mg/m³)</td>
<td>(16 mg/m³)</td>
<td>(8.2 mg/m³)</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm (16 mg/m³)</td>
<td>2.8 ppm (11 mg/m³)</td>
<td>2.2 ppm (8.6 mg/m³)</td>
<td>1.4 ppm (5.5 mg/m³)</td>
<td>0.70 ppm (2.7 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm (47 mg/m³)</td>
<td>8.5 ppm (33 mg/m³)</td>
<td>6.7 ppm (26 mg/m³)</td>
<td>4.2 ppm (16 mg/m³)</td>
<td>2.1 ppm (8.2 mg/m³)</td>
</tr>
</tbody>
</table>

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 RD₅₀ study. Support provided by the repeated-exposure studies adds to confidence in the derived AEGL values.

II.7. REFERENCES


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


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


APPENDIX II-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: 1/3 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 BMCL₀₅ (42.4 ppm) from a 4-hour exposure in rats.

Scaling: 10-min, 30-min, and 1-hour
\[ C^3 \times t = k \]
\[ (42.4 \text{ ppm})^3 \times 4 \text{ hr} = 304900 \text{ ppm-hr} \]

8-hours
\[ C^1 \times t = k \]
\[ (42.4 \text{ ppm})^1 \times 4 \text{ hr} = 170 \text{ ppm-hr} \]

Uncertainty Factors:
3 for interspecies variability
3 for intraspecies variability

10-min AEGL-3
\[ C^3 \times 0.167 \text{ hr} = 304900 \text{ ppm-hr} \]
\[ C^3 = 1825748 \text{ ppm} \]
\[ C = 122 \text{ ppm} \]
\[ 10\text{-min AEGL-3} = 122/10 = 12 \text{ ppm} \]

30-min AEGL-3
\[ C^3 \times 0.5 \text{ hr} = 304900 \text{ ppm-hr} \]
\[ C^3 = 609800 \text{ ppm} \]
\[ C = 84.8 \text{ ppm} \]
\[ 30\text{-min AEGL-3} = 84.8/10 = 8.5 \text{ ppm} \]

1-hr AEGL-3
\[ C^3 \times 1 \text{ hr} = 304900 \text{ ppm-hr} \]
\[ C^3 = 304900 \text{ ppm} \]
\[ C = 67.3 \text{ ppm} \]
\[ 1\text{-hr AEGL-3} = 67.3/10 = 6.7 \text{ ppm} \]

4-hr AEGL-3
\[ 4\text{-hr AEGL-3} = 42.4/10 = 4.2 \text{ ppm} \]

8-hr AEGL-3
\[ C^1 \times 8 \text{ hr} = 170 \text{ ppm-hr} \]
\[ C^1 = 21.2 \text{ ppm} \]
\[ C = 21.2 \text{ ppm} \]
\[ 8\text{-hr AEGL-3} = 21/10 = 2.1 \text{ ppm} \]
APPENDIX II-B: DERIVATION SUMMARY FOR METHYL CHLOROFORMATE

ACUTE EXPOSURE GUIDELINES FOR METHYL CHLOROFORMATE

DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
<th>10-Minute</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>4.0 ppm</td>
<td>2.8 ppm</td>
<td>2.2 ppm</td>
<td>1.4 ppm</td>
<td>0.70 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**


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

### AEGL-3 VALUES FOR METHYL CHLOROFORMATE

<table>
<thead>
<tr>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 ppm</td>
<td>8.5 ppm</td>
<td>6.7 ppm</td>
<td>4.2 ppm</td>
<td>2.1 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

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

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

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

**Effects:**
Male rat LC50 = 51 ppm; female rat LC50 = 53 ppm
Male and Female BMCL05 = 42.4
Male and Female BMC01 = 47.8

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Male Mortality</th>
<th>Female Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 ppm</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>45 ppm</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>57 ppm</td>
<td>5/5</td>
<td>3/5</td>
</tr>
<tr>
<td>73 ppm</td>
<td>5/5</td>
<td>5/5</td>
</tr>
</tbody>
</table>

**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 LC50 study (Bio-Test, 1975); utilizing the BMCL05 from this study yields a 10-min AEGL-3 value of 13 ppm, which supports the time-scaled value of 12 ppm calculated from Hoechst (1986).

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

Chemical Toxicity - TSD Animal Data
Methyl Chloroformate

Minutes

ppm

No Effect
Discomfort
Disabling
Partially Lethal
Lethal
BMDS MODEL RUN

The form of the probability function is:

\[ P[\text{response}] = \text{Background} + (1-\text{Background}) \times \text{CumNorm(Intercept+Slope*Log(Dose))}, \]

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 )

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept</td>
<td>-71.9357</td>
<td>0.449759</td>
</tr>
<tr>
<td>Slope</td>
<td>18</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th>Deviance</th>
<th>Test DF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-5.00402</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-5.00722</td>
<td>0.00639048</td>
<td>3</td>
<td>0.9999</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-27.5256</td>
<td>45.04313</td>
<td>3</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC:12.0144

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

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0</td>
<td>10</td>
<td>-1.008e-007</td>
</tr>
<tr>
<td>45.0000</td>
<td>0.0003</td>
<td>0.003</td>
<td>0</td>
<td>10</td>
<td>-0.0564</td>
</tr>
<tr>
<td>57.0000</td>
<td>0.7993</td>
<td>7.993</td>
<td>8</td>
<td>10</td>
<td>0.005272</td>
</tr>
<tr>
<td>73.0000</td>
<td>1.0000</td>
<td>10.000</td>
<td>10</td>
<td>10</td>
<td>0.0007765</td>
</tr>
</tbody>
</table>

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

Probit Model with 0.95 Confidence Level

Methyl Chloroformate II-30
CHAPTER III. ETHYL CHLOROFORMATE
# TABLE OF CONTENTS: CHAPTER III: ETHYL CHLOROFORMATE

## LIST OF TABLES: ETHYL CHLOROFORMATE

III-4

## EXECUTIVE SUMMARY: ETHYL CHLOROFORMATE

III-5

### III.1. HUMAN TOXICITY DATA

III-6

#### III.1.1. Acute Lethality

III-6

#### III.1.2. Non-lethal Toxicity

III-6

##### III.1.2.1. Case Report

III-6

#### III.1.3. Developmental/Reproductive Toxicity

III-7

#### III.1.4. Genotoxicity

III-7

#### III.1.5. Carcinogenicity

III-7

#### III.1.6. Summary

III-7

### III.2. ANIMAL TOXICITY DATA

III-7

#### III.2.1. Acute Lethality

III-7

##### III.2.1.1. Rats

III-7

##### III.2.1.2. Mice

III-9

#### III.2.2. Developmental/Reproductive Toxicity

III-9

#### III.2.3. Genotoxicity

III-9

#### III.2.4. Carcinogenicity

III-9

#### III.2.5. Summary

III-10

### III.3. DATA ANALYSIS AND AEGL-1

III-10

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

III-10

#### III.3.2. Animal Data Relevant to AEGL-1

III-10

#### III.3.3. Derivation of AEGL-1

III-11

### III.4. DATA ANALYSIS AND AEGL-2

III-11

#### III.4.1. Human Data Relevant to AEGL-2

III-11

#### III.4.2. Animal Data Relevant to AEGL-2

III-11

#### III.4.3. Derivation of AEGL-2

III-11
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

III.5. DATA ANALYSIS AND AEGL-3

III.5.1. Human Data Relevant to AEGL-3

III.5.2. Animal Data Relevant to AEGL-3

III.5.3. Derivation of AEGL-3

III.6. SUMMARY OF AEGLS

III.6.1. AEGL Values and Toxicity Endpoints

III.6.2. Comparison with Other Standards and Guidelines

III.6.3. Data Quality and Research Needs

III.7. REFERENCES

APPENDIX III-A: DERIVATION OF AEGL VALUES FOR ETHYL CHLOROFORMATE

APPENDIX III-B: DERIVATION SUMMARY FOR ETHYL CHLOROFORMATE

APPENDIX III-C: CATEGORY PLOT FOR ETHYL CHLOROFORMATE
LIST OF TABLES: ETHYL CHLOROFORMATE

1. Summary of AEGL Values For Ethyl Chloroformate ................................................................. III-6
2. Exposure of Male Swiss-Webster Mice to Ethyl Chloroformate for 30 minutes* ............... III-9
3. Summary of Acute Inhalation Data of Animals Exposed to Ethyl Chloroformate ............... III-10
4. AEGL-1 Values for Ethyl Chloroformate ................................................................................. III-11
5. AEGL-2 Values for Ethyl Chloroformate ................................................................................. III-11
6. AEGL-3 Values for Ethyl Chloroformate ................................................................................. III-12
7. Summary of AEGL Values for Ethyl Chloroformate ............................................................... III-13
EXECUTIVE 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 1/3 = 48 ppm) (Vernot et al., 1977) was used as the point-of-departure for ethyl chloroformate AEGL-3 values. This concentration is considered a threshold for lethality and is supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981). Interspecies and intraspecies uncertainty factors of 3 each were applied because ethyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, interspecies 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).
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

The calculated values are listed in the table below.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>2.9 ppm(13 mg/m³)</td>
<td>2.0 ppm(8.8 mg/m³)</td>
<td>1.6 ppm(7.0 mg/m³)</td>
<td>0.40 ppm(1.8 mg/m³)</td>
<td>0.20 ppm(0.88 mg/m³)</td>
<td>1/3 the AEGL-3 values (Vernot et al., 1977)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>8.8 ppm(39 mg/m³)</td>
<td>6.1 ppm(27 mg/m³)</td>
<td>4.8 ppm(21 mg/m³)</td>
<td>1.2 ppm(5.3 mg/m³)</td>
<td>0.60 ppm(2.6 mg/m³)</td>
<td>Estimated lethality threshold in the rat after a 1-hour exposure (Vernot et al., 1977)</td>
</tr>
</tbody>
</table>

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:

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 LC50 values were 189 (164-216) ppm for male rats, and 200 (173-232) ppm for female rats at 14 days post-exposure. Controls and rats in the 47 ppm group were clinically normal and showed no treatment-related effects at necropsy. Body weight gain was decreased for surviving males and females in the 153 and 180 ppm groups at day 7 and at termination. All rats in the 245 and 270 ppm groups died prior to scheduled sacrifice. Average relative lung weight of animals in the 245 and 270 ppm groups was approximately three-times greater than that of controls, and corroborating lesions indicative of acute alveolar hemorrhage were noted. Relative lung weight was also increased (magnitude not specified) in the 153 and 180 ppm groups. Red lung coloration was noted in one male and one female in the 153 ppm group, and two females and one male in the 180 ppm group.

Vernot et al. (1977) reported a 1-hour LC50 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 20°C 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 LD50 values were reported for male rats: 470 mg/kg (Vernot et al., 1977) and 411 mg/kg (WARF Institute, Inc., 1978). An oral LD50 value of 614 mg/kg was reported for female Wistar rats (Hoechst, 1975); an oral LD50 of 244 mg/kg was reported for an unspecified sex and strain of rat (BASF, 1970c). A dermal LD50 value of >2 mL/kg was reported for male rats (WARF Institute, Inc., 1978), and a dermal LD50 value of 7120 mg/kg was reported for New Zealand white rabbits (Vernot et al., 1977).

Ethyl Chloroformate III-8
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>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory rates (control/exposed)</th>
<th>% Decrease in respiratory rate</th>
<th>Mortality Within 24-hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>285/255</td>
<td>11</td>
<td>0/4</td>
</tr>
<tr>
<td>50</td>
<td>280/235</td>
<td>52</td>
<td>0/4</td>
</tr>
<tr>
<td>100</td>
<td>260/120</td>
<td>54</td>
<td>3/4</td>
</tr>
<tr>
<td>200</td>
<td>215/55</td>
<td>74</td>
<td>4/4</td>
</tr>
</tbody>
</table>

*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.

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

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-Min | 30-Min | 1-Hr   | 4-Hr   | 8-Hr   |
| AEGL-1          | NR     | NR     | NR     | NR     | NR     |

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

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-Min | 30-Min | 1-Hr   | 4-Hr   | 8-Hr   |
| AEGL-2          | 2.9 ppm | 2.0 ppm | 1.6 ppm | 0.40 ppm | 0.20 ppm |
|                  | (13 mg/m$^3$) | (8.8 mg/m$^3$) | (7.0 mg/m$^3$) | (1.8 mg/m$^3$) | (0.88 mg/m$^3$) |

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>8.8 ppm (39 mg/m$^3$)</td>
<td>6.1 ppm (27 mg/m$^3$)</td>
<td>4.8 ppm (21 mg/m$^3$)</td>
<td>1.2 ppm (5.3 mg/m$^3$)</td>
<td>0.60 ppm (2.6 mg/m$^3$)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-min</th>
<th>30-min</th>
<th>1-hr</th>
<th>4-hr</th>
<th>8-hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>2.9 ppm (13 mg/m³)</td>
<td>2.0 ppm (8.8 mg/m³)</td>
<td>1.6 ppm (7.0 mg/m³)</td>
<td>0.40 ppm (1.8 mg/m³)</td>
<td>0.20 ppm (0.88 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>8.8 ppm (39 mg/m³)</td>
<td>6.1 ppm (27 mg/m³)</td>
<td>4.8 ppm (21 mg/m³)</td>
<td>1.2 ppm (5.3 mg/m³)</td>
<td>0.60 ppm (2.6 mg/m³)</td>
</tr>
</tbody>
</table>

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 RD₅₀ study. The consistency observed in the rat LC₅₀ studies adds to confidence in the derived AEGL values.

III.7. REFERENCES


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


SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000


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: 1/3 of the AEGL-3 values

<table>
<thead>
<tr>
<th>Duration</th>
<th>AEGL-2 Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-min</td>
<td>8.8 ppm ÷ 3  = 2.9 ppm</td>
</tr>
<tr>
<td>30-min</td>
<td>6.1 ppm ÷ 3  = 2.0 ppm</td>
</tr>
<tr>
<td>1-hr</td>
<td>4.8 ppm ÷ 3  = 1.6 ppm</td>
</tr>
<tr>
<td>4-hr</td>
<td>1.2 ppm ÷ 3  = 0.40 ppm</td>
</tr>
<tr>
<td>8-hr</td>
<td>0.60 ppm ÷ 3  = 0.20 ppm</td>
</tr>
</tbody>
</table>
DERIVATION OF AEGL-3 VALUES FOR ETHYL CHLOROFORMATE

Key study: Vernot et al., 1977

Toxicity Endpoint: Estimated LC\(_{01}\) (1/3 the LC\(_{50}\)) from a 1-hour exposure in male rats.

LC\(_{50}\) = 145 ppm; 1/3 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:

\[ C^3 \times 0.167 \text{ hr} = 112769 \text{ ppm-hr} \]
\[ C^3 = 675263 \text{ ppm} \]
\[ C = 87.7 \text{ ppm} \]
\[ 10\text{-min AEGL-3} = 87.7/10 = 8.8 \text{ ppm} \]

30-min AEGL-3:

\[ C^3 \times 0.5 \text{ hr} = 112769 \text{ ppm-hr} \]
\[ C^3 = 225538 \text{ ppm} \]
\[ C = 60.9 \text{ ppm} \]
\[ 30\text{-min AEGL-3} = 60.9/10 = 6.1 \text{ ppm} \]

1-hr AEGL-3:

\[ 1\text{-hr AEGL-3} = 48.3/10 = 4.8 \text{ ppm} \]

4-hr AEGL-3:

\[ C^1 \times 4 \text{ hr} = 48.3 \text{ ppm-hr} \]
\[ C^1 = 12 \text{ ppm} \]
\[ C = 12 \text{ ppm} \]
\[ 4\text{-hr AEGL-3} = 12/10 = 1.2 \text{ ppm} \]
<table>
<thead>
<tr>
<th></th>
<th>8-hr AEGL-3:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( C^1 \times 8 \text{ hr} = 48.3 \text{ ppm} \cdot \text{hr} )</td>
</tr>
<tr>
<td>2</td>
<td>( C^1 = 6.0 \text{ ppm} )</td>
</tr>
<tr>
<td>3</td>
<td>( C = 6.0 \text{ ppm} )</td>
</tr>
<tr>
<td>4</td>
<td>8-hr AEGL-3 = ( 6.0/10 = 0.60 \text{ ppm} )</td>
</tr>
</tbody>
</table>
APPENDIX III-B: DERIVATION SUMMARY FOR
ETHYL CHLOROFORMATE

ACUTE EXPOSURE GUIDELINES FOR
ETHYL CHLOROFORMATE

DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>AEGL-1 VALUES FOR ETHYL CHLOROFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Min</td>
</tr>
<tr>
<td>NR</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Time Period</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>2.9</td>
<td>2.0</td>
<td>1.6</td>
<td>0.40</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Key Reference:

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 LC₅₀: 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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.8 ppm</td>
<td>6.1 ppm</td>
<td>4.8 ppm</td>
<td>1.2 ppm</td>
<td>0.60 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

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

**Exposure Route/Concentrations/Durations:** Rats/Inhalation/ 1 hour

(1/3 the 1-hour male rat LC$_{50}$ was the point-of-departure for AEGL-3) (1/3 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:
- Intraspaces = 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:** $c^n x t = k$, where $n = 3$ when extrapolating to shorter time points (10-minutes and 30-minutes) and $n = 1$ when extrapolating to longer time points (4-hours and 8-hours).

**Data Quality and Research Needs:** 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

- No Effect
- Discomfort
- Disabling
- Some Lethality
- Lethal

AEGL-3
AEGL-2

ppm

Minutes
CHAPTER IV: PROPYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER IV: PROPYL CHLOROFORMATE

LIST OF TABLES: PROPYL CHLOROFORMATE ................................................................. IV-4

EXECUTIVE SUMMARY: PROPYL CHLOROFORMATE ................................................... IV-5

IV.1. HUMAN TOXICITY DATA ....................................................................................... IV-6

   IV.1.1. Acute Lethality ............................................................................................... IV-6

   IV.1.2. Non-lethal Toxicity ........................................................................................ IV-6

   IV.1.3. Developmental/Reproductive Toxicity ........................................................... IV-6

   IV.1.4. Genotoxicity .................................................................................................. IV-6

   IV.1.5. Carcinogenicity ............................................................................................ IV-6

   IV.1.6. Summary ....................................................................................................... IV-6

IV.2. ANIMAL TOXICITY DATA ....................................................................................... IV-7

   IV.2.1. Acute Lethality ............................................................................................... IV-7

       IV.2.1.1. Rats ........................................................................................................ IV-7

       IV.2.1.2. Mice ....................................................................................................... IV-8

   IV.2.2. Nonlethal Toxicity ......................................................................................... IV-8

       IV.2.2.1. Rabbits .................................................................................................. IV-8

   IV.2.3. Developmental/Reproductive Toxicity ........................................................... IV-9

   IV.2.4. Genotoxicity .................................................................................................. IV-9

   IV.2.5. Carcinogenicity ............................................................................................ IV-9

   IV.2.6. Summary ....................................................................................................... IV-9

IV.3. DATA ANALYSIS AND AEGL-1 ............................................................................ IV-10

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

   IV.3.2. Animal Data Relevant to AEGL-1 ................................................................. IV-10

   IV.3.3. Derivation of AEGL-1 .................................................................................. IV-10

IV.4. DATA ANALYSIS AND AEGL-2 ............................................................................ IV-10

   IV.4.1. Human Data Relevant to AEGL-2 ................................................................. IV-10

   IV.4.2. Animal Data Relevant to AEGL-2 ................................................................. IV-10

   IV.4.3. Derivation of AEGL-2 .................................................................................. IV-10

IV.5. DATA ANALYSIS AND AEGL-3 ............................................................................ IV-10

   IV.5.1. Human Data Relevant to AEGL-3 ................................................................. IV-10

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

IV.5.2. Animal Data Relevant to AEGL-3 ................................................................. IV-10
IV.5.3. Derivation of AEGL-3 ....................................................................................... IV-11
IV.6. SUMMARY OF AEGLS ....................................................................................... IV-11
IV.6.1. AEGL Values and Toxicity Endpoints ............................................................... IV-11
IV.6.2. Comparison with Other Standards and Guidelines ........................................... IV-12
IV.6.3. Data Quality and Research Needs ..................................................................... IV-12
IV.7. REFERENCES ...................................................................................................... IV-12
APPENDIX IV-A: DERIVATION OF AEGL VALUES FOR PROPYL CHLOROFORMATE .... IV-13
APPENDIX IV-B: DERIVATION SUMMARY FOR PROPYL CHLOROFORMATE AEGLS .... IV-17
APPENDIX IV-C: CATEGORY PLOT FOR PROPYL CHLOROFORMATE ....................... IV-20
APPENDIX IV-D: BENCHMARK CONCENTRATION CALCULATION FOR PROPYL CHLOROFORMATE ............................................................. IV-21
LIST OF TABLES: PROPYL CHLOROFORMATE

1. Summary of AEGL Values For Propyl Chloroformate ........................................ IV-5
2. Exposure of Albino Rats to Propyl Chloroformate 1 hour ................................ IV-7
3. Exposure of Male Swiss-Webster Mice to Propyl Chloroformate for 30 minutes ...... IV-8
4. AEGL-1 Values for Propyl Chloroformate............................................................... IV-10
5. AEGL-2 Values for Propyl Chloroformate............................................................... IV-10
6. AEGL-3 Values for Propyl Chloroformate............................................................... IV-11
7. Summary of AEGL Values for Propyl Chloroformate ........................................ IV-11
EXECUTIVE 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<sub>05</sub> 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.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient Data</td>
</tr>
<tr>
<td>AEGL-2 (Disabiling)</td>
<td>6.7 ppm (34 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>4.7 ppm (24 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>3.7 ppm (19 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>0.90 ppm (4.5 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>0.47 ppm (2.4 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>⅓ the AEGL-3 values (Bio-Test Laboratories, Inc., 1970)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>20 ppm (100 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>14 ppm (70 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>11 ppm (55 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>2.7 ppm (14 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>1.4 ppm (7.0 mg/m&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>1-hour rat BMCL&lt;sub&gt;05&lt;/sub&gt; (Bio-Test Laboratories, Inc., 1970)</td>
</tr>
</tbody>
</table>

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


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

*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 20°C for 3 minutes. (BASF, 1970b). Clinical signs included vigorous escape behavior, extremely severe mucous membrane irritation, and gasping. Lung congestion and edema were noted at necropsy.

An oral 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>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory Rates (control/exposed)</th>
<th>% Decrease in Respiratory rate</th>
<th>Mortality Within 24-hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>255/225</td>
<td>12</td>
<td>0/4</td>
</tr>
<tr>
<td>50</td>
<td>280/205</td>
<td>27</td>
<td>1/4</td>
</tr>
<tr>
<td>75</td>
<td>270/150</td>
<td>44</td>
<td>2/4</td>
</tr>
<tr>
<td>100</td>
<td>245/95</td>
<td>61</td>
<td>0/4</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>6.7 ppm (34 mg/m³)</td>
<td>4.7 ppm (24 mg/m³)</td>
<td>3.7 ppm (19 mg/m³)</td>
<td>0.90 ppm (4.5 mg/m³)</td>
<td>0.47 ppm (2.4 mg/m³)</td>
</tr>
</tbody>
</table>

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 LC₅₀ of 410 ppm and BMCL₀₅ 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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>20 ppm (100 mg/m$^3$)</td>
<td>14 ppm (70 mg/m$^3$)</td>
<td>11 ppm (55 mg/m$^3$)</td>
<td>2.7 ppm (14 mg/m$^3$)</td>
<td>1.4 ppm (7.0 mg/m$^3$)</td>
</tr>
</tbody>
</table>

**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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>6.7 ppm (34 mg/m$^3$)</td>
<td>4.7 ppm (24 mg/m$^3$)</td>
<td>3.7 ppm (19 mg/m$^3$)</td>
<td>0.90 ppm (4.5 mg/m$^3$)</td>
<td>0.47 ppm (2.4 mg/m$^3$)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>20 ppm (100 mg/m$^3$)</td>
<td>14 ppm (70 mg/m$^3$)</td>
<td>11 ppm (55 mg/m$^3$)</td>
<td>2.7 ppm (14 mg/m$^3$)</td>
<td>1.4 ppm (7.0 mg/m$^3$)</td>
</tr>
</tbody>
</table>

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


Propyl Chloroformate

IV-12
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: 1/3 of the AEGL-3 values

10-min AEGL-2: \( 20 \text{ ppm} \div 3 = 6.7 \text{ ppm} \)

30-min AEGL-2: \( 14 \text{ ppm} \div 3 = 4.7 \text{ ppm} \)

1-hr AEGL-2: \( 11 \text{ ppm} \div 3 = 3.7 \text{ ppm} \)

4-hr AEGL-2: \( 2.7 \text{ ppm} \div 3 = 0.90 \text{ ppm} \)

8-hr AEGL-2: \( 1.4 \text{ ppm} \div 3 = 0.47 \text{ ppm} \)
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)\(^3\) x 1 hr = 10077696 ppm·hr

4-hours and 8-hours
\[ C^1 \times t = k \]
(216 ppm)\(^1\) x 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:
\[ C^3 \times 0.167 \text{ hr} = 10,077,696 \text{ ppm·hr} \]
\[ C^3 = 60345485 \text{ ppm} \]
\[ C = 392 \text{ ppm} \]
10-min AEGL-3 = 392/20 = 20 ppm

30-min AEGL-3
\[ C^3 \times 0.5 \text{ hr} = 10,077,696 \text{ ppm·hr} \]
\[ C^3 = 20155392 \text{ ppm} \]
\[ C = 272 \text{ ppm} \]
30-min AEGL-3 = 272/20 = 14 ppm

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

4-hr AEGL-3
\[ C^1 \times 4 \text{ hr} = 216 \text{ ppm·hr} \]
\[ C^1 = 54 \text{ ppm} \]
4-hr AEGL-3 = 54/20 = 2.7 ppm
INTERIM 1: 05/2008
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 8-hr AEGL-3
2 \( C^1 \times 8 \text{ hr} = 216 \text{ ppm/hr} \)
3 \( C^1 = 27 \text{ ppm} \)
4 \( C = 27 \text{ ppm} \)
5 \( 8\text{-hr AEGL-3} = \frac{27}{20} = 1.4 \text{ ppm} \)
APPENDIX IV-B: DERIVATION SUMMARY FOR
PROPYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR
PROPYL CHLOROFORMATE
DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>AEGL-1 VALUES FOR PROPYL CHLOROFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Min</td>
</tr>
<tr>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propyl Chloroformate</strong></td>
<td>6.7 ppm</td>
<td>4.7 ppm</td>
<td>3.7 ppm</td>
<td>0.90 ppm</td>
<td>0.47 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

**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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>20 ppm</td>
<td>14 ppm</td>
<td>11 ppm</td>
<td>2.7 ppm</td>
<td>1.4 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

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

**Exposure Route/Concentrations/Durations:** Rats/Inhalation/1 hour
(Calculated BMCL<sub>05</sub> of 216 ppm was the point-of-departure for AEGL-3)

**Endpoint/Concentration/Rationale:** BMCL<sub>05</sub> in rats after a 1 hr-exposure/ 216 ppm/Estimated threshold for death for 1 hour exposure in rats

**Effects:** LC<sub>50</sub> = 410 ppm; BMC<sub>01</sub> = 229 ppm; BMCL<sub>05</sub> = 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

Minutes

No Effect
Discomfort
Disabling
Partially Lethal
Lethal

AEGL-3
AEGL-2
APPENDIX IV-D: BENCHMARK CONCENTRATION CALCULATION
FOR PROPYL CHLOROFORMATE

BMDS MODEL RUN

The form of the probability function is:

\[ \text{[response]} = \text{Background} + (1-\text{Background}) \times \text{CumNorm(Intercept+Slope*Log(Dose))}, \]

where \( \text{CumNorm(.)} \) 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 )

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Slope</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept</td>
<td>-99.4462</td>
<td>20016.9</td>
</tr>
<tr>
<td>Slope</td>
<td>16.977</td>
<td>3446.36</td>
</tr>
</tbody>
</table>

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.
INTERIM 1: 05/2008
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th>Deviance</th>
<th>Test DF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-5.00402</td>
<td>7.62052e-008</td>
<td>1</td>
<td>0.9998</td>
</tr>
<tr>
<td>Fitted model</td>
<td>-5.00402</td>
<td>7.62052e-008</td>
<td>1</td>
<td>0.9998</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-20.1904</td>
<td>30.3727</td>
<td>2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AIC: 14.008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>249.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0</td>
<td>10</td>
<td>-0.0001952</td>
</tr>
<tr>
<td>333.0000</td>
<td>0.2000</td>
<td>2.0000</td>
<td>2</td>
<td>10</td>
<td>4.115e-007</td>
</tr>
<tr>
<td>1000.0000</td>
<td>1.0000</td>
<td>10.0000</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

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

![Probit Model with 0.95 Confidence Level](image-url)
CHAPTER V: ISOPROPYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER V: ISOPROPYL CHLOROFORMATE

LIST OF TABLES: ISOPROPYL CHLOROFORMATE ............................................................ V-4

EXECUTIVE SUMMARY: ISOPROPYL CHLOROFORMATE ........................................ V-5

V.1. HUMAN TOXICITY DATA .......................................................................................... V-6
  V.1.1. Acute Lethality ...................................................................................................... V-6
  V.1.2. Non-lethal Toxicity .............................................................................................. V-6
  V.1.3. Developmental/Reproductive Toxicity ............................................................... V-6
  V.1.4. Genotoxicity ........................................................................................................ V-6
  V.1.5. Carcinogenicity ................................................................................................... V-6
  V.1.6. Summary ............................................................................................................... V-6

V.2. ANIMAL TOXICITY DATA ....................................................................................... V-6
  V.2.1. Acute Lethality ...................................................................................................... V-6
  V.2.1.1. Rats .................................................................................................................. V-6
  V.2.1.2. Mice .................................................................................................................. V-8
  V.2.2. Nonlethal Toxicity ............................................................................................... V-9
  V.2.3. Developmental/Reproductive Toxicity ............................................................... V-10
  V.2.4. Genotoxicity ........................................................................................................ V-10
  V.2.5. Carcinogenicity ................................................................................................... V-10
  V.2.6. Summary ............................................................................................................... V-10

V.3. DATA ANALYSIS AND AEGL-1 ............................................................................ V-11
  V.3.1. Human Data Relevant to AEGL-1 ....................................................................... V-11
  V.3.2. Animal Data Relevant to AEGL-1 ....................................................................... V-12
  V.3.3. Derivation of AEGL-1 ....................................................................................... V-12

V.4. DATA ANALYSIS AND AEGL-2 ............................................................................ V-12
  V.4.1. Human Data Relevant to AEGL-2 ....................................................................... V-12
  V.4.2. Animal Data Relevant to AEGL-2 ....................................................................... V-12
  V.4.3. Derivation of AEGL-2 ....................................................................................... V-12
LIST OF TABLES: ISOPROPYL CHLOROFORMATE

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

Isopropyl Chloroformate

V-4
EXECUTIVE SUMMARY: ISOPROPYL CHLOROFORMATE

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

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

One-third of the 1-hr LC50 value in rats (300 ppm x 1/3 = 100 ppm) (Bio Test Laboratories, Inc., 1970) was used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because isopropyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor is 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, 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).

TABLE V-S 1. Summary of AEGL Values For Isopropyl Chloroformate

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient Data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>6.0 ppm (30 mg/m³)</td>
<td>4.3 ppm (22 mg/m³)</td>
<td>3.3 ppm (17 mg/m³)</td>
<td>0.83 ppm (4.2 mg/m³)</td>
<td>0.43 ppm (2.2 mg/m³)</td>
<td>1/3 the AEGL-3 values (Bio Test Laboratories, Inc., 1970)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>18 ppm (90 mg/m³)</td>
<td>13 ppm (65 mg/m³)</td>
<td>10 ppm (50 mg/m³)</td>
<td>2.5 ppm (13 mg/m³)</td>
<td>1.3 ppm (6.5 mg/m³)</td>
<td>Estimated lethality threshold in the rat after a 1-hr exposure (Bio Test Laboratories, Inc., 1970)</td>
</tr>
</tbody>
</table>

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


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.

V.2.  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 °C) in a water bath. The resulting vapor was mixed with additional dry air to obtain the desired vapor concentration. The test atmosphere was then introduced into the top of a 70 L Plexiglass inhalation chamber, dispersed by a baffle plate, and exhausted at the bottom of the chamber. Average nominal concentrations were calculated by dividing the total weight of the isopropyl chloroformate vaporized by the total volume of air used during each inhalation exposure. Animals in the mid- and high-exposure groups started gasping for breath within 15 minutes after the initiation of exposure and exhibited convulsions and salivation. Low-concentration animals exhibited gasping and slight salivation. Necropsy of animals that died revealed moderate to severe lung hyperemia. Rats that survived the 14-day observation period exhibited no gross abnormalities at necropsy. The 1-hour LC\textsubscript{50} was determined to be 300 ppm. Data are summarized in Table V-1.

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

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).

Isopropyl Chloroformate
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 LD₅₀ of 177.8 mg/kg was calculated. An approximate oral LD₅₀ of 800 mm³ was reported in rats (BASF, 1968c).

V.2.1.2. Mice

Following a 10-minute fresh air control period, groups of four male Swiss-Webster mice were exposed head only to nominal concentrations of 0, 50, 75, 100, 200, or 500 ppm isopropyl chloroformate aerosol for 30 minutes (Carpenter, 1982). The mice were then removed to fresh air for a 10 minute recovery period, while respiratory rates were monitored continuously. Undiluted isopropyl chloroformate was delivered to a Pitt #1 aerosol generator via a 2 cc syringe, driven by a pump at a known rate. Aerosol was directed into a 9 L stainless steel chamber which was continuously evacuated at 20 L/min. An RD₅₀ of 104 ppm was calculated. Data are summarized in Table V-2.

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory Rates(control/exposed)</th>
<th>% Decrease in Respiratory rate</th>
<th>Mortality within 24 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>320/260</td>
<td>19</td>
<td>1/4</td>
</tr>
<tr>
<td>75</td>
<td>225/150</td>
<td>33</td>
<td>3/4</td>
</tr>
<tr>
<td>100</td>
<td>260/110</td>
<td>58</td>
<td>4/4</td>
</tr>
<tr>
<td>200</td>
<td>275/55</td>
<td>80</td>
<td>4/4</td>
</tr>
<tr>
<td>500</td>
<td>–</td>
<td>100</td>
<td>4/4 (died in exposure)</td>
</tr>
</tbody>
</table>

Data are summarized in Table V-2.

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 had a capacity of 2.2 L, and air flow was 8.8 L/min. Baseline respiratory rates of each mouse were recorded for 10 minutes before exposure. Respiratory rates were recorded at 5 and 10 minutes into the 15 minute exposure period, and percent respiratory depression was calculated from these values. Lung weights were obtained at necropsy following death from exposure or scheduled sacrifice. In this study, the RD₅₀ is calculated to be 375 ppm, and a 15-min. LC₅₀ is estimated to be between 283...
and 345 ppm. Concentration-related increases in lung weight, indicative of pulmonary edema, were observed in treated animals compared to controls. Data are summarized in Table V-3.

<table>
<thead>
<tr>
<th>TABLE V-3. Exposure of Male Swiss-Webster Mice to Isopropyl Chloroformate for 15 minutes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (ppm)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Nominal</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>177</td>
</tr>
<tr>
<td>306</td>
</tr>
<tr>
<td>443</td>
</tr>
<tr>
<td>883</td>
</tr>
</tbody>
</table>

*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. Development/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 \textit{Salmonella typhimurium} strains TA 98, TA 100, TA 1535, and TA 1537 and in \textit{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

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration (ppm)</th>
<th>Exposure Duration</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>15,600 (nominal)</td>
<td>17-41 minutes</td>
<td>10/10 dead</td>
<td>Bio Test Labs, Inc., 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>1640 (nominal)</td>
<td>40-60 minutes</td>
<td>10/10 dead</td>
<td>Bio Test Labs, Inc., 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>200 (approximate)</td>
<td>1 hr</td>
<td>0/12 dead</td>
<td>BASF, 1968a</td>
</tr>
<tr>
<td>Rat</td>
<td>300 (nominal)</td>
<td>1 hr</td>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Bio Test Labs, Inc., 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>200</td>
<td>5 hrs</td>
<td>2/8 dead</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Mouse</td>
<td>283-345</td>
<td>15 min</td>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Anderson, 1984</td>
</tr>
<tr>
<td>Mouse</td>
<td>375</td>
<td>15 min</td>
<td>RD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Anderson, 1984</td>
</tr>
<tr>
<td>Mouse</td>
<td>104</td>
<td>30 min</td>
<td>RD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Carpenter, 1982</td>
</tr>
<tr>
<td>Repeated Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>20</td>
<td>6 hr/d, 20 d</td>
<td>Nasal irritation</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>50</td>
<td>6 hr/d, 11 d</td>
<td>Respiratory difficulty, weight loss, lung hemorrhage, 1/8 dead</td>
<td>Gage, 1970</td>
</tr>
<tr>
<td>Rat</td>
<td>22</td>
<td>6 hr/d, 5 d</td>
<td>Decreased body weight gain, increased lung weight, enlarged bronchial lymph nodes, peribroncholar mononuclear cell infiltrate, focal pulmonary emphysema</td>
<td>Collins &amp; Proctor, 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>42</td>
<td>6 hr/d, 5 d</td>
<td>Body weight loss, increased lung weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, peribronchiolar mononuclear cell infiltrate, focal pulmonary emphysema</td>
<td>Collins &amp; Proctor, 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>86</td>
<td>6 hr/d, 5 d</td>
<td>Body weight loss, increased lung weight, enlarged bronchial lymph nodes, focal alveolar edema, bronchiolitis, focal pulmonary emphysema 3/4 males dead: deaths after 2, 4, and 5 d treatment 3/4 females dead: deaths after 3, 3, and 5 d treatment</td>
<td>Collins &amp; Proctor, 1984</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>6.0 ppm</td>
<td>4.3 ppm</td>
<td>3.3 ppm</td>
<td>0.83 ppm</td>
<td>0.43 ppm</td>
</tr>
</tbody>
</table>

(30 mg/m³)  (22 mg/m³)  (17 mg/m³)  (4.2 mg/m³)  (2.2 mg/m³)

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

V.5.3. Derivation of AEGL-3

One-third of the 1-hr LC₅₀ value in rats (300 ppm x 1/3 = 100 ppm) (Bio-Test Laboratories, Inc., 1970) will be used as the point-of-departure for isopropyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality and is supported by the fact that 0/12 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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>18 ppm</td>
<td>13 ppm</td>
<td>10 ppm</td>
<td>2.5 ppm</td>
<td>1.3 ppm</td>
</tr>
<tr>
<td></td>
<td>(90 mg/m³)</td>
<td>(65 mg/m³)</td>
<td>(50 mg/m³)</td>
<td>(13 mg/m³)</td>
<td>(6.5 mg/m³)</td>
</tr>
</tbody>
</table>

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 insufficient 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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>6.0 ppm (30 mg/m³)</td>
<td>4.3 ppm (22 mg/m³)</td>
<td>3.3 ppm (17 mg/m³)</td>
<td>0.83 ppm (4.2 mg/m³)</td>
<td>0.43 ppm (2.2 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>18 ppm (90 mg/m³)</td>
<td>13 ppm (65 mg/m³)</td>
<td>10 ppm (50 mg/m³)</td>
<td>2.5 ppm (13 mg/m³)</td>
<td>1.3 ppm (6.5 mg/m³)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 Min</td>
</tr>
<tr>
<td>AEGL-1</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2</td>
<td>6.0 ppm (30 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3</td>
<td>18 ppm (90 mg/m³)</td>
</tr>
<tr>
<td>ERPG-1*</td>
<td>Insufficient Data</td>
</tr>
<tr>
<td>ERPG-2*</td>
<td>5 ppm</td>
</tr>
<tr>
<td>ERPG-3*</td>
<td>20 ppm</td>
</tr>
<tr>
<td>Dutch MACb</td>
<td>1 ppm</td>
</tr>
</tbody>
</table>

*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.

bMAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA.
V.6.3. Data Quality and Research Needs

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

V.7. REFERENCES


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


2. Toxicology Research Laboratory, Midland, MI.


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: 1/3 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 LC01 (1/3 the LC50) from a 1-hour exposure in male rats.

LC50 = 300 ppm; 1/3 x 300 ppm = 100 ppm (point of departure)

Scaling:

10-minutes and 30-minutes

\[ C^3 \times t = k \]
\[ (100 \text{ ppm})^3 \times 1 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr} \]

4-hours and 8-hours

\[ C^1 \times t = k \]
\[ (100 \text{ ppm})^1 \times 1 \text{ hr} = 100 \text{ ppm} \cdot \text{hr} \]

Uncertainty Factors:

3 for interspecies variability
3 for intraspecies variability

10-min AEGL-3:

\[ C^3 \times 0.167 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr} \]
\[ C^3 = 59,880,24 \text{ ppm} \]
\[ C = 182 \text{ ppm} \]
\[ 10\text{-min AEGL-3} = 182/10 = 18 \text{ ppm} \]

30-min AEGL-3

\[ C^3 \times 0.5 \text{ hr} = 1,000,000 \text{ ppm} \cdot \text{hr} \]
\[ C^3 = 2,000,000 \text{ ppm} \]
\[ C = 126 \text{ ppm} \]
\[ 30\text{-min AEGL-3} = 126/10 = 13 \text{ ppm} \]

1-hr AEGL-3

\[ 1\text{-hr AEGL-3} = 100/10 = 10 \text{ ppm} \]

4-hr AEGL-3

\[ C^1 \times 4 \text{ hr} = 100 \text{ ppm} \cdot \text{hr} \]
\[ C^1 = 25 \text{ ppm} \]
\[ C = 25 \text{ ppm} \]
\[ 4\text{-hr AEGL-3} = 25/10 = 2.5 \text{ ppm} \]

8-hr AEGL-3

\[ C^1 \times 8 \text{ hr} = 100 \text{ ppm} \cdot \text{hr} \]
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1. $C^1 = 12.5 \text{ ppm}$
2. $C = 12.5 \text{ ppm}$
3. $8\text{-hr AEGL-3} = 12.5/10 = 1.3 \text{ ppm}$
**APPENDIX V-B: DERIVATION SUMMARY FOR ISOPROPYL CHLOROFORMATE AEGL**

**ACUTE EXPOSURE GUIDELINES FOR PROPYL CHLOROFORMATE**

**DERIVATION SUMMARY**

<table>
<thead>
<tr>
<th>AEGL-1 VALUES FOR ISOPROPYL CHLOROFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10-Min</strong></td>
</tr>
<tr>
<td>NR</td>
</tr>
</tbody>
</table>

- **Reference:** NA
- **Test Species/Strain/Number:** NA
- **Exposure Route/Concentrations/Durations:** NA
- **Effects:** 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.
Isopropyl Chloroformate

<table>
<thead>
<tr>
<th>Time Duration</th>
<th>AEGL-2 Values for Isopropyl Chloroformate</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Min</td>
<td>6.0 ppm</td>
</tr>
<tr>
<td>30-Min</td>
<td>4.3 ppm</td>
</tr>
<tr>
<td>1-Hr</td>
<td>3.3 ppm</td>
</tr>
<tr>
<td>4-Hr</td>
<td>0.83 ppm</td>
</tr>
<tr>
<td>8-Hr</td>
<td>0.43 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

**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.

**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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 ppm</td>
<td>13 ppm</td>
<td>10 ppm</td>
<td>2.5 ppm</td>
<td>1.3 ppm</td>
<td></td>
</tr>
</tbody>
</table>


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

Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour

(1/3 the 1-hour rat LC50 was the point-of-departure for AEGL-3) (1/3 x 300 ppm = 100 ppm)

Endpoint/Concentration/Rationale: 1/3 the 1-hour rat LC50 / 100 ppm/Estimated threshold for death for 1 hour exposure in rats

Effects: LC50 = 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 x t = k, where n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

Data Quality and Research Needs: Sparse 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

Chemical Toxicity - TSD Animal Data
Isopropyl Chloroformate

- No Effect
- Discomfort
- Disabling
- Some Lethality
- Lethal
CHAPTER VI: ALLYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER VI: ALLYL CHLOROFORMATE

LIST OF TABLES: ALLYL CHLOROFORMATE ................................................................. VI-4

EXECUTIVE SUMMARY: ALLYL CHLOROFORMATE ........................................ VI-5

VI.1. HUMAN TOXICITY DATA ................................................................................ VI-6

V.1.1. Acute Lethality ............................................................................................... VI-6
V.1.2. Non-lethal Toxicity ....................................................................................... VI-6
V.1.3. Developmental/Reproductive Toxicity ....................................................... VI-6
V.1.4. Genotoxicity ................................................................................................. VI-6
V.1.5. Carcinogenicity ......................................................................................... VI-6
V.1.6. Summary ....................................................................................................... VI-6

VI.2. ANIMAL TOXICITY DATA ............................................................................ VI-6

VI.2.1. Acute Lethality ............................................................................................... VI-6
VI.2.1.1. Rats ........................................................................................................ VI-6
VI.2.2 Developmental/Reproductive Toxicity ....................................................... VI-7
VI.2.3. Genotoxicity ............................................................................................... VI-7
VI.2.4. Carcinogenicity ....................................................................................... VI-7
VI.2.5. Summary ....................................................................................................... VI-8

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

VI.3.1. Human Data Relevant to AEGL-1 .......................................................... VI-8
VI.3.2. Animal Data Relevant to AEGL-1 .......................................................... VI-8
VI.3.3. Derivation of AEGL-1 ............................................................................... VI-8

VI.4. DATA ANALYSIS AND AEGL-2 ............................................................... VI-8

VI.4.1. Human Data Relevant to AEGL-2 .......................................................... VI-8
VI.4.2. Animal Data Relevant to AEGL-2 .......................................................... VI-8
VI.4.3 Derivation of AEGL-2 ............................................................................... VI-8
INTERIM 1: 05/2008
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

1 VI.5. DATA ANALYSIS AND AEGL-3 .................................................................................................................. VI-9
2 VI.5.1. Human Data Relevant to AEGL-3 ........................................................................................................ VI-9
3 VI.5.2. Animal Data Relevant to AEGL-3 ........................................................................................................ VI-9
4 VI.5.3. Derivation of AEGL-3 .......................................................................................................................... VI-9
5 VI.6. SUMMARY OF AEGLS ................................................................................................................................ VI-10
6 VI.6.1. AEGL Values and Toxicity Endpoints ................................................................................................. VI-10
7 VI.6.2. Comparison with Other Standards and Guidelines ................................................................................ VI-10
8 VI.6.3. Data Quality and Research Needs ......................................................................................................... VI-10
9 VI.7. REFERENCES ........................................................................................................................................ VI-10
10 APPENDIX VI-A: DERIVATION OF AEGL VALUES FOR ALLYL CHLOROFORMATE ........ VI-11
11 APPENDIX VI-B: DERIVATION SUMMARY FOR ALLYL CHLOROFORMATE AEGLS ...... VI-15
12 APPENDIX VI-C: CATEGORY PLOT FOR ALLYL CHLOROFORMATE ....................................................... VI-18
13 APPENDIX VI-D: BENCHMARK CONCENTRATION CALCULATION FOR ALLYL CHLOROFORMATE .................................................................................................................................................. VI-19

Allyl Chloroformate VI-3
LIST OF TABLES: ALLYL CHLOROFORMATE

1. Summary of AEGL Values For Allyl Chloroformate ................................................................. VI-5
2. Exposure of Sprague Dawley Rats to Allyl Chloroformate 1 hour ............................................. VI-7
3. AEGL-1 Values for Allyl Chloroformate .................................................................................... VI-8
4. AEGL-2 Values for Allyl Chloroformate .................................................................................... VI-9
5. AEGL-3 Values for Allyl Chloroformate .................................................................................... VI-9
6. Summary of AEGL Values for Allyl Chloroformate ................................................................. VI-10
EXECUTIVE SUMMARY: ALLOYL 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_{0.05} 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).

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min (Nondisabling)</th>
<th>30-Min (Nondisabling)</th>
<th>1-Hr (Disabling)</th>
<th>4-Hr (Lethality)</th>
<th>8-Hr (Lethality)</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2</td>
<td>1.3 ppm (6.4 mg/m³)</td>
<td>0.87 ppm (4.3 mg/m³)</td>
<td>0.70 ppm (3.4 mg/m³)</td>
<td>0.18 ppm (0.88 mg/m³)</td>
<td>0.090 ppm (0.44 mg/m³)</td>
<td>1/3 the AEGL-3 values (Stillmeadow Inc., 1987)</td>
</tr>
<tr>
<td>AEGL-3</td>
<td>3.8 ppm (19 mg/m³)</td>
<td>2.6 ppm (13 mg/m³)</td>
<td>2.1 ppm (10 mg/m³)</td>
<td>0.53 ppm (2.6 mg/m³)</td>
<td>0.26 ppm (1.3 mg/m³)</td>
<td>1-hour rat BMCL_{0.05} (Stillmeadow Inc., 1987)</td>
</tr>
</tbody>
</table>

*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

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
dynamic 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>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Mortality- Males</th>
<th>Mortality- Females</th>
<th>Mortality- Combined Males &amp; Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.7</td>
<td>0/5</td>
<td>0/5</td>
<td>0/10</td>
</tr>
<tr>
<td>65.0</td>
<td>3/5</td>
<td>3/5</td>
<td>6/10</td>
</tr>
<tr>
<td>77.7</td>
<td>3/5</td>
<td>4/5</td>
<td>7/10</td>
</tr>
<tr>
<td>134.5</td>
<td>5/5</td>
<td>4/5</td>
<td>9/10</td>
</tr>
<tr>
<td>175.7</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>233.3</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>LC$_{50}$</td>
<td></td>
<td></td>
<td>65.1 ppm</td>
</tr>
<tr>
<td>BMCL$_{05}$</td>
<td></td>
<td></td>
<td>21 ppm</td>
</tr>
<tr>
<td>BMC$_{01}$</td>
<td></td>
<td></td>
<td>25.7 ppm</td>
</tr>
</tbody>
</table>

*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 LC₅₀ of 65.1 ppm, a BMCL₀₅ of 21 ppm, and a BMC₀₁ of 25.7 ppm and showing clinical signs consistent with severe irritation. 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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>1.3 ppm (6.4 mg/m³)</td>
<td>0.87 ppm (4.3 mg/m³)</td>
<td>0.70 ppm (3.4 mg/m³)</td>
<td>0.18 ppm (0.88 mg/m³)</td>
<td>0.090 ppm (0.44 mg/m³)</td>
</tr>
</tbody>
</table>

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 LC₅₀ of 65.1 ppm and a BMCL₀₅ of 21 ppm were calculated (Stillmeadow Inc., 1987).

VI.5.3. Derivation of AEGL-3

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>3.8 ppm (19 mg/m³)</td>
<td>2.6 ppm (13 mg/m³)</td>
<td>2.1 ppm (10 mg/m³)</td>
<td>0.53 ppm (2.6 mg/m³)</td>
<td>0.26 ppm (1.3 mg/m³)</td>
</tr>
</tbody>
</table>
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 BMCL05 from a 1-hour rat study.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>1.3 ppm (6.4 mg/m³)</td>
<td>0.87 ppm (4.3 mg/m³)</td>
<td>0.70 ppm (3.4 mg/m³)</td>
<td>0.18 ppm (0.88 mg/m³)</td>
<td>0.090 ppm (0.44 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>3.8 ppm (19 mg/m³)</td>
<td>2.6 ppm (13 mg/m³)</td>
<td>2.1 ppm (10 mg/m³)</td>
<td>0.53 ppm (2.6 mg/m³)</td>
<td>0.26 ppm (1.3 mg/m³)</td>
</tr>
</tbody>
</table>

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 BMCL05 from a well-conducted rat study.

VI.7. REFERENCES


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 ALLOYL CHLOROFORMATE**

Key study: Stillmeadow Inc., 1987

Toxicity Endpoint: 1/3 of the AEGL-3 values

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>AEGL-2 Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-min</td>
<td>3.8 ppm ÷ 3 = 1.3 ppm</td>
</tr>
<tr>
<td>30-min</td>
<td>2.6 ppm ÷ 3 = 0.87 ppm</td>
</tr>
<tr>
<td>1-hr</td>
<td>2.1 ppm ÷ 3 = 0.70 ppm</td>
</tr>
<tr>
<td>4-hr</td>
<td>0.53 ppm ÷ 3 = 0.18 ppm</td>
</tr>
<tr>
<td>8-hr</td>
<td>0.26 ppm ÷ 3 = 0.090 ppm</td>
</tr>
</tbody>
</table>
DERIVATION OF AEGL-3 VALUES FOR ALLYL CHLOROFORMATE

Key study: Stillmeadow Inc., 1987

Toxicity Endpoint: 1-hour rat BMCL_{0.05} (21 ppm)

Scaling:

10-min and 30-min

$C^3 \times t = k$

$(21 \text{ ppm})^3 \times 1 \text{ hr} = 9261 \text{ ppm-hr}$

4-hrs and 8-hrs

$C^1 \times t = k$

$(21 \text{ ppm})^1 \times 1 \text{ hr} = 21 \text{ ppm-hr}$

Uncertainty Factors:

3 for interspecies variability
3 for intraspecies variability

10-min AEGL-3:

$C^3 \times 0.167 \text{ hr} = 9261 \text{ ppm-hr}$

$C^3 = 55455 \text{ ppm}$

$C = 38 \text{ ppm}$

10-min AEGL-3 = $38/10 = 3.8 \text{ ppm}$

30-min AEGL-3

$C^3 \times 0.5 \text{ hr} = 9261 \text{ ppm-hr}$

$C^3 = 18522 \text{ ppm}$

$C = 26.4 \text{ ppm}$

30-min AEGL-3 = $26.4/10 = 2.6 \text{ ppm}$

1-hr AEGL-3

1-hr AEGL-3 = $21/10 = 2.1 \text{ ppm}$

4-hr AEGL-3

$C^1 \times 4 \text{ hr} = 21 \text{ ppm-hr}$

$C^1 = 5.25 \text{ ppm}$

$C = 5.25 \text{ ppm}$

4-hr AEGL-3 = $5.25/10 = 0.53 \text{ ppm}$
### Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

<table>
<thead>
<tr>
<th></th>
<th>8-hr AEGL-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C = 2.63 ppm</td>
</tr>
<tr>
<td>2</td>
<td>C x 8 hr = 21 ppm-hr</td>
</tr>
<tr>
<td>3</td>
<td>8-hr AEGL-3 = 2.63/10 = 0.26 ppm</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

8-hr AEGL-3 = 2.63/10 = 0.26 ppm
APPENDIX VI-B: DERIVATION SUMMARY FOR ALLYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR PROPYL CHLOROFORMATE
DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>10 min</th>
<th>30 Min</th>
<th>1 Hr</th>
<th>4 Hour</th>
<th>8 Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (ppm)</td>
<td>1.3 ppm</td>
<td>0.87 ppm</td>
<td>0.70 ppm</td>
<td>0.18 ppm</td>
<td>0.090 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

**Test Species/Strain/Number:** See AEGL-3 Derivation summary table

**Exposure Route/Concentrations/Durations:** See AEGL-3 Derivation summary table

**Effects:**
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**

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8 ppm</td>
<td>2.6 ppm</td>
<td>2.1 ppm</td>
<td>0.53 ppm</td>
<td>0.26 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

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

**Exposure Route/Concentrations/Durations:** Rats/Inhalation/1 hour
(Calculated BMCL05 of 21 ppm was the point-of-departure for AEGL-3)

**Endpoint/Concentration/Rationale:** BMCL05 in rats after a 1 hr-exposure/ 21 ppm/Estimated threshold for death for 1 hour exposure in rats

**Effects:**
LC50 = 65.1 ppm; BMC01 = 25.7 ppm; BMCL05 = 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 x t=k, where n=3 when extrapolating to shorter time points (10-minutes and 30-minutes) and n = 1 when extrapolating to longer time points (4-hours and 8-hours).

**Data Quality and Research Needs:** Sparse data set.
APPENDIX VI-C: CATEGORY PLOT FOR ALLYL CHLOROFORMATE
APPENDIX VI-D: BENCHMARK CONCENTRATION CALCULATION FOR
ALLYL CHLOROFORMATE

BMDS MODEL RUN

The form of the probability function is: 

\[ P[\text{response}] = \text{Background} + (1 - \text{Background}) \times \text{CumNorm} (\text{Intercept} + \text{Slope} \times \log(\text{Dose})) \]

where \(\text{CumNorm}(.)\) 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)

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>Slope</td>
<td>-1</td>
<td>1</td>
</tr>
</tbody>
</table>

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept</td>
<td>-10.3866</td>
<td>2.68182</td>
</tr>
<tr>
<td>Slope</td>
<td>2.48392</td>
<td>0.621724</td>
</tr>
</tbody>
</table>

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

### Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th>Deviance</th>
<th>Test DF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-16.0896</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-17.3239</td>
<td>2.46858</td>
<td>4</td>
<td>0.6503</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-36.6519</td>
<td>41.1245</td>
<td>5</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 38.6478

### Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.7000</td>
<td>0.0495</td>
<td>0.495</td>
<td>0</td>
<td>10</td>
<td>-0.7219</td>
</tr>
<tr>
<td>65.0000</td>
<td>0.4929</td>
<td>4.929</td>
<td>6</td>
<td>10</td>
<td>0.6774</td>
</tr>
<tr>
<td>77.7000</td>
<td>0.6648</td>
<td>6.648</td>
<td>7</td>
<td>10</td>
<td>0.236</td>
</tr>
<tr>
<td>134.5000</td>
<td>0.9632</td>
<td>9.632</td>
<td>9</td>
<td>10</td>
<td>-1.06</td>
</tr>
<tr>
<td>175.7000</td>
<td>0.9929</td>
<td>9.929</td>
<td>10</td>
<td>10</td>
<td>0.2674</td>
</tr>
<tr>
<td>233.3000</td>
<td>0.9992</td>
<td>9.992</td>
<td>10</td>
<td>10</td>
<td>0.08938</td>
</tr>
</tbody>
</table>

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

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

BMD = 33.7621
BMDL = 21.098
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
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: CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE ........................................................... VII-4

EXECUTIVE SUMMARY: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE ....................................................................................................... VII-5

VII.1. HUMAN TOXICITY DATA ............................................................................................... VII-6
VII.1.1. Acute Lethality ....................................................................................................... VII-6
VII.1.2. Non-lethal Toxicity ................................................................................................... VII-6
VII.1.3. Developmental/Reproductive Toxicity ........................................................................ VII-6
VII.1.4. Genotoxicity .......................................................................................................... VII-6
VII.1.5. Carcinogenicity ....................................................................................................... VII-6
VII.1.6. Summary ............................................................................................................... VII-7

VII.2. ANIMAL TOXICITY DATA .............................................................................................. VII-7
VII.2.1. Acute Lethality ....................................................................................................... VII-7
VII.2.2. Non-lethal Toxicity ................................................................................................... VII-7
VII.2.3. Developmental/Reproductive Toxicity ........................................................................ VII-9
VII.2.4. Genotoxicity .......................................................................................................... VII-9
VII.2.5. Carcinogenicity ....................................................................................................... VII-9
VII.2.6. Summary ............................................................................................................... VII-9

VII.3. DATA ANALYSIS AND AEGL-1 ..................................................................................... VII-9
VII.3.1. Human Data Relevant to AEGL-1 ................................................................................... VII-9
VII.3.2. Animal Data Relevant to AEGL-1 ................................................................................. VII-9
VII.3.3. Derivation of AEGL-1 ................................................................................................ VII-9

VII.4. DATA ANALYSIS AND AEGL-2.................................................................................... VII-10
VII.4.1. Human Data Relevant to AEGL-2 ................................................................................. VII-10
VII.4.2. Animal Data Relevant to AEGL-2 ................................................................................. VII-10
VII.4.3. Derivation of AEGL-2 ................................................................................................ VII-10

VII.5. DATA ANALYSIS AND AEGL-3.................................................................................... VII-11
VII.5.1. Human Data Relevant to AEGL-3 ................................................................................... VII-11

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

VII.5.2. Animal Data Relevant to AEGL-3 ................................................................................. VII-11
VII.5.3. Derivation of AEGL-3 ................................................................................................. VII-11
VII.6. SUMMARY OF AEGLS.................................................................................................... VII-12
VII.6.1. AEGL Values and Toxicity Endpoints......................................................................... VII-12
VII.6.2. Comparison with Other Standards and Guidelines ....................................................... VII-13
VII.6.3 Data Quality and Research Needs ............................................................................... VII-13
II.7. REFERENCES ................................................................................................................ VII-13

APPENDIX VII-A: DERIVATION OF AEGL VALUES FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE................................................................ VII-15
APPENDIX VII-B: DERIVATION SUMMARY FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE AEGLS ........................................ VII-18
APPENDIX VII-C: CATEGORY PLOT FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, AND sec-BUTYL CHLOROFORMATE ...................................................... VII-24
# LIST OF TABLES: CHAPTER VII: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII-S 1</td>
<td>Summary of AEGL Values for n-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-S 2</td>
<td>Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-1</td>
<td>Exposure of Male Swiss-Webster Mice to Isobutyl Chloroformate for 30 minutes</td>
</tr>
<tr>
<td>VII-2</td>
<td>Exposure of Male Swiss-Webster Mice to sec-butyl Chloroformate for 30 minutes</td>
</tr>
<tr>
<td>VII-3</td>
<td>AEGL-1 Values for n-Butyl Chloroformate, Isobutyl Chloroformate, and sec Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-4</td>
<td>AEGL-2 Values for n-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-5</td>
<td>AEGL-2 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-6</td>
<td>AEGL-3 Values for n-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-7</td>
<td>AEGL-3 Values for Isobutyl Chloroformate and sec-Butyl Chloroformate</td>
</tr>
<tr>
<td>VII-8</td>
<td>Summary of AEGL Values for n-butyl Chloroformate</td>
</tr>
<tr>
<td>VII-9</td>
<td>Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY: n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE

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

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

One-third of the concentration where 4/10 rats died after a 1-hr exposure to n-butyl chloroformate (200 ppm x 1/3 = 66.7 ppm) (BASF, 1970) was used as the point-of-departure for n-butyl chloroformate AEGL-3 values. This concentration is considered an estimated threshold for lethality. Interspecies and intraspecies uncertainty factors of 3 each were applied because n-butyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Thus, the total uncertainty factor was 10. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, 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).

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm</td>
<td>2.8 ppm</td>
<td>2.2 ppm</td>
<td>0.57 ppm</td>
<td>0.28 ppm</td>
<td>1/3 AEGL-3 values</td>
</tr>
<tr>
<td></td>
<td>(22 mg/m³)</td>
<td>(33 mg/m³)</td>
<td>(27 mg/m³)</td>
<td>(6.7 mg/m³)</td>
<td>(3.3 mg/m³)</td>
<td></td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm</td>
<td>8.4 ppm</td>
<td>6.7 ppm</td>
<td>1.7 ppm</td>
<td>0.83 ppm</td>
<td>Estimated 1-hr lethality threshold in rats (BASF, 1970)</td>
</tr>
<tr>
<td></td>
<td>(68 mg/m³)</td>
<td>(100 mg/m³)</td>
<td>(80 mg/m³)</td>
<td>(20 mg/m³)</td>
<td>(10 mg/m³)</td>
<td></td>
</tr>
</tbody>
</table>

NR: Not Recommended. However, absence of a derived AEGL-1 value does not imply that exposure below the AEGL-2 is without adverse effects.
Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD₅₀ 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.

### TABLE VII-S 2. Summary of AEGL Values for Isobutyl Chloroformate and sec-Butyl Chloroformate

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>By analogy to n-butyl chloroformate</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm (22 mg/m³)</td>
<td>2.8 ppm (33 mg/m³)</td>
<td>2.2 ppm (27 mg/m³)</td>
<td>0.57 ppm (6.7 mg/m³)</td>
<td>0.28 ppm (3.3 mg/m³)</td>
<td>By analogy to n-butyl chloroformate</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm (68 mg/m³)</td>
<td>8.4 ppm (100 mg/m³)</td>
<td>6.7 ppm (80 mg/m³)</td>
<td>1.7 ppm (20 mg/m³)</td>
<td>0.83 ppm (10 mg/m³)</td>
<td>By analogy to n-butyl chloroformate</td>
</tr>
</tbody>
</table>

### 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 20°C. (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 RD50 of 97.0± 5.82 ppm was calculated. Results are summarized in Table VII-1.

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory rates (control/exposed)</th>
<th>% Decrease in respiratory rate</th>
<th>Mortality Within 24-hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>265/20</td>
<td>25</td>
<td>0/4</td>
</tr>
<tr>
<td>50</td>
<td>260/155</td>
<td>40</td>
<td>0/4</td>
</tr>
<tr>
<td>100</td>
<td>310/155</td>
<td>50</td>
<td>0/4</td>
</tr>
<tr>
<td>150</td>
<td>290/145</td>
<td>50</td>
<td>0/4</td>
</tr>
<tr>
<td>200</td>
<td>295/85</td>
<td>71</td>
<td>0/4</td>
</tr>
</tbody>
</table>

*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 RD50 of 117± 1.64 ppm was calculated. Results are summarized in Table VII-2.

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory rates (control/exposed)</th>
<th>% Decrease in respiratory rate</th>
<th>Mortality Within 24-hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>195/175</td>
<td>10</td>
<td>0/4</td>
</tr>
<tr>
<td>100</td>
<td>280/165</td>
<td>41</td>
<td>0/4</td>
</tr>
<tr>
<td>150</td>
<td>295/130</td>
<td>55</td>
<td>0/4</td>
</tr>
<tr>
<td>200</td>
<td>225/40</td>
<td>82</td>
<td>¼</td>
</tr>
</tbody>
</table>

*Carpenter, 1982
VII.2.3. Development/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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>4.0 ppm (22 mg/m³)</td>
<td>2.8 ppm (33 mg/m³)</td>
<td>2.2 ppm (27 mg/m³)</td>
<td>0.57 ppm (6.7 mg/m³)</td>
<td>0.28 ppm (3.3 mg/m³)</td>
</tr>
</tbody>
</table>

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

Isobutyl Chloroformate and sec-Butyl Chloroformate

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>4.0 ppm (22 mg/m³)</td>
<td>2.8 ppm (33 mg/m³)</td>
<td>2.2 ppm (27 mg/m³)</td>
<td>0.57 ppm (6.7 mg/m³)</td>
<td>0.28 ppm (3.3 mg/m³)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>12 ppm (68 mg/m³)</td>
<td>8.4 ppm (100 mg/m³)</td>
<td>6.7 ppm (80 mg/m³)</td>
<td>1.7 ppm (20 mg/m³)</td>
<td>0.83 ppm (10 mg/m³)</td>
</tr>
</tbody>
</table>
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 RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD₅₀ values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate. 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**

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>12 ppm</td>
<td>8.4 ppm</td>
<td>6.7 ppm</td>
<td>1.7 ppm</td>
<td>0.83 ppm</td>
</tr>
<tr>
<td></td>
<td>(68 mg/m³)</td>
<td>(100 mg/m³)</td>
<td>(80 mg/m³)</td>
<td>(20 mg/m³)</td>
<td>(10 mg/m³)</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm</td>
<td>2.8 ppm</td>
<td>2.2 ppm</td>
<td>0.57 ppm</td>
<td>0.28 ppm</td>
</tr>
<tr>
<td></td>
<td>(22 mg/m³)</td>
<td>(33 mg/m³)</td>
<td>(27 mg/m³)</td>
<td>(6.7 mg/m³)</td>
<td>(3.3 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm</td>
<td>8.4 ppm</td>
<td>6.7 ppm</td>
<td>1.7 ppm</td>
<td>0.83 ppm</td>
</tr>
<tr>
<td></td>
<td>(68 mg/m³)</td>
<td>(100 mg/m³)</td>
<td>(80 mg/m³)</td>
<td>(20 mg/m³)</td>
<td>(10 mg/m³)</td>
</tr>
</tbody>
</table>

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\textsubscript{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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>4.0 ppm (22 mg/m\textsuperscript{3})</td>
<td>2.8 ppm (33 mg/m\textsuperscript{3})</td>
<td>2.2 ppm (27 mg/m\textsuperscript{3})</td>
<td>0.57 ppm (6.7 mg/m\textsuperscript{3})</td>
<td>0.28 ppm (3.3 mg/m\textsuperscript{3})</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>12 ppm (68 mg/m\textsuperscript{3})</td>
<td>8.4 ppm (100 mg/m\textsuperscript{3})</td>
<td>6.7 ppm (80 mg/m\textsuperscript{3})</td>
<td>1.7 ppm (20 mg/m\textsuperscript{3})</td>
<td>0.83 ppm (10 mg/m\textsuperscript{3})</td>
</tr>
</tbody>
</table>

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


n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-13


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: 1/3 of the AEGL-3 values

10-min AEGL-2: $12 \text{ ppm} \div 3 = 4.0 \text{ ppm}$

30-min AEGL-2: $8.4 \text{ ppm} \div 3 = 2.8 \text{ ppm}$

1-hr AEGL-2: $6.7 \text{ ppm} \div 3 = 2.2 \text{ ppm}$

4-hr AEGL-2: $1.7 \text{ ppm} \div 3 = 0.57 \text{ ppm}$

8-hr AEGL-2: $0.83 \text{ ppm} \div 3 = 0.28 \text{ ppm}$

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

\[ C^3 \times t = k \]
\[ (66.7 \text{ ppm})^3 \times 1 \text{ hr} = 296,741 \text{ ppm/hr} \]

4-hours and 8-hours

\[ C^1 \times t = k \]
\[ (66.7 \text{ ppm})^1 \times 1 \text{ hr} = 66.7 \text{ ppm/hr} \]

Uncertainty Factors:
3 for interspecies variability
3 for intraspecies variability

10-min AEGL-3:

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

30-min AEGL-3

\[ C^3 \times 0.5 \text{ hr} = 296,741 \text{ ppm/hr} \]
\[ C^3 = 593482 \text{ ppm} \]
\[ C = 84.0 \text{ ppm} \]
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

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

8-hr AEGL-3

\[ C^1 \times 8 \text{ hr} = 66.7 \text{ ppm/hr} \]
\[ C^1 = 8.34 \text{ ppm} \]
\[ C = 8.34 \text{ ppm} \]
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.

n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-17
APPENDIX VII-B: DERIVATION SUMMARY FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, and sec-BUTYL CHLOROFORMATE AEGLS

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

<table>
<thead>
<tr>
<th>10 min</th>
<th>30 min</th>
<th>1 hr</th>
<th>4 hr</th>
<th>8 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10 min</th>
<th>30 min</th>
<th>1 hr</th>
<th>4 hr</th>
<th>8 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Reference:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Species/Strain/Number:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Route/Concentrations/Durations:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint/Concentration/Rationale:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertainty Factors/Rationale:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modifying Factor:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal to Human Dosimetric Adjustment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Scaling:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data Quality and Research Needs:</td>
<td>No chemical-specific data were available for derivation of AEGL-1 values.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No data were available to derive values by analogy to n-butyl chloroformate.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Duration</td>
<td>10-Min</td>
<td>30-Min</td>
<td>1-Hr</td>
<td>4-Hr</td>
<td>8-Hr</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>4.0 ppm</td>
<td>2.8 ppm</td>
<td>2.2 ppm</td>
<td>0.57 ppm</td>
<td>0.28 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

**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 to 1.8 ppm n-butyl chloroformate for 6 hours/day, 5 days/week for 4 weeks (HRC 1990), and when exposed to 2.9 ppm 6 hours/day for 5 days (HRC 1990).
AEGL-2 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>4.0</td>
<td>2.8</td>
<td>2.2</td>
<td>0.57</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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

1

AEGL-3 VALUES FOR n-BUTYL CHLOROFORMATE

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 ppm</td>
<td>8.4 ppm</td>
<td>6.7 ppm</td>
<td>1.7 ppm</td>
<td>0.83 ppm</td>
<td></td>
</tr>
</tbody>
</table>

Key Reference:
BASF. 1970. BASF AG, Gewerbehygienisch-Pharmakologisches Institut. N-Butylchlorokohlensaureester-

Test Species/Strain/Sex/Number: Sprague Dawley rats/5/sex/group
Exposure Route/Concentrations/Durations: Rats/Inhalation/1 hour
(1/3 the concentration causing death in 4/10 rats was the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: 1/3 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: \( c^n x t = k \), where \( n=3 \) when extrapolating to shorter time points (10-minutes and 30-minutes) and
\( n = 1 \) when extrapolating to longer time points (4-hours and 8-hours).

Data Quality and Research Needs: Sparse data set. 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).

2

n-Butyl, Isobutyl, sec-Butyl Chloroformates VII-22
### AEGL-3 VALUES FOR ISOBUTYL CHLOROFORMATE and sec-BUTYL CHLOROFORMATE

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 ppm</td>
<td>8.4 ppm</td>
<td>6.7 ppm</td>
<td>1.7 ppm</td>
<td>0.83 ppm</td>
<td></td>
</tr>
</tbody>
</table>

**Key Reference:**
Derived by analogy to n-butyl chloroformate. n-Butyl chloroformate AEGL-3 values adopted as AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate.

**Test Species/Strain/Number:**

**Exposure Route/Concentrations/Durations:**

**Effects:**

**Endpoint/Concentration/Rationale:**

**Uncertainty Factors/Rationale:**

**Modifying Factor:** NA

**Animal to Human Dosimetric Adjustment:** NA

**Time Scaling:**

**Data quality and research needs:** Sparse data set. Chemical-specific data were insufficient for the derivation of AEGL-3 values for isobutyl chloroformate and sec-butyl chloroformate. However, isobutyl chloroformate and sec-butyl chloroformate are structural analogs of n-butyl chloroformate and mouse RD₅₀ data suggest that isobutyl chloroformate and sec-butyl chloroformate are of similar toxicity (Carpenter, 1982) (male Swiss-Webster mouse RD₅₀ values are 97 ppm for isobutyl chloroformate and 117 ppm for sec-butyl chloroformate). Thus, the AEGL-3 values for n-butyl chloroformate were adopted as surrogates for isobutyl chloroformate and sec-butyl chloroformate.
APPENDIX VII-C: CATEGORY PLOT FOR n-BUTYL CHLOROFORMATE, ISOBUTYL CHLOROFORMATE, AND sec-BUTYL CHLOROFORMATE
CHAPTER VIII: BENZYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER VIII: BENZYL CHLOROFORMATE

LIST OF TABLES: BENZYL CHLOROFORMATE ........................................................................ VIII-4

EXECUTIVE SUMMARY: BENZYL CHLOROFORMATE ............................................................ VIII-5

VIII.1. HUMAN TOXICITY DATA .............................................................................................. VIII-6
  VIII.1.1. Acute Lethality ......................................................................................................... VIII-6
  VIII.1.2. Non-lethal Toxicity .................................................................................................. VIII-6
  VIII.1.3. Developmental/Reproductive Toxicity ...................................................................... VIII-6
  VIII.1.4. Genotoxicity ......................................................................................................... VIII-6
  VIII.1.5. Carcinogenicity ...................................................................................................... VIII-6
  VIII.1.6. Summary .............................................................................................................. VIII-6

VIII.2. ANIMAL TOXICITY DATA ............................................................................................. VIII-6
  VIII.2.1. Acute Lethality ......................................................................................................... VIII-6
  VIII.2.2. Non-lethal Toxicity .................................................................................................. VIII-7
  VIII.2.3. Developmental/Reproductive Toxicity ...................................................................... VIII-7
  VIII.2.4. Genotoxicity ......................................................................................................... VIII-7
  VIII.2.5. Carcinogenicity ...................................................................................................... VIII-7
  VIII.2.6. Summary .............................................................................................................. VIII-8

VIII.3. DATA ANALYSIS AND AEGL-1 .................................................................................... VIII-8
  VIII.3.1. Human Data Relevant to AEGL-1 ................................................................................ VIII-8
  VIII.3.2. Animal Data Relevant to AEGL-1 ................................................................................ VIII-8
  VIII.3.3. Derivation of AEGL-1 ............................................................................................. VIII-8

VIII.4. DATA ANALYSIS AND AEGL-2 .................................................................................... VIII-8
  VIII.4.1. Human Data Relevant to AEGL-2 ................................................................................ VIII-8
  VIII.4.2. Animal Data Relevant to AEGL-2 ................................................................................ VIII-8
  VIII.4.3. Derivation of AEGL-2 ............................................................................................. VIII-8

VIII.5. DATA ANALYSIS AND AEGL-3 .................................................................................... VIII-9
  VIII.5.1. Human Data Relevant to AEGL-3 ................................................................................ VIII-9
  VIII.5.2. Animal Data Relevant to AEGL-3 ................................................................................ VIII-9
  VIII.5.3. Derivation of AEGL-3 ............................................................................................. VIII-9
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate
LIST OF TABLES: CHAPTER VIII: BENZYL CHLOROFORMATE

1. Summary of AEGL Values For Benzyl Chloroformate ............................................................... 5
2. Mortality in Rats Exposed to Benzyl Chloroformate for 4 hours .................................................. 7
3. AEGL-1 Values for Benzyl Chloroformate .................................................................................... 8
4. AEGL-2 Values for Benzyl Chloroformate .................................................................................... 9
5. AEGL-3 Values for Benzyl Chloroformate .................................................................................... 9
6. Summary of AEGL Values for Benzyl Chloroformate ............................................................... 10
EXECUTIVE SUMMARY: BENZYL CHLOROFORMATE

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

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

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.

### TABLE VIII-S 1. Summary of AEGL Values For Benzyl Chloroformate

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>0.97 ppm (6.7 mg/m³)</td>
<td>0.63 ppm (4.3 mg/m³)</td>
<td>0.31 ppm (2.2 mg/m³)</td>
<td>1/3 the AEGL-3 values (BASF, 1990)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>3.7 ppm (26 mg/m³)</td>
<td>3.7 ppm (26 mg/m³)</td>
<td>2.9 ppm (20 mg/m³)</td>
<td>1.9 ppm (13 mg/m³)</td>
<td>0.93 ppm (6.5 mg/m³)</td>
<td>Concentration causing no death in rats; 4-hr exposure (BASF, 1990)</td>
</tr>
</tbody>
</table>

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

Benzyl Chloroformate
VIII.1. HUMAN TOXICITY DATA

VIII.1.1. Acute Lethality

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

VIII.1.2. Non-lethal Toxicity

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

VIII.1.3. Developmental/Reproductive Toxicity

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

VIII.1.4. Genotoxicity

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

VIII.1.5. Carcinogenicity

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

VIII.1.6. Summary

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

VIII.2. ANIMAL TOXICITY DATA

VIII.2.1. Acute Lethality

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

<table>
<thead>
<tr>
<th>Cumulative lethality on day</th>
<th>18.6 ppm</th>
<th>84.6 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total at end of study</td>
<td>0/10</td>
<td></td>
</tr>
</tbody>
</table>

* 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 20°C 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 typhimurium* 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 for 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.

VIII.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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

Benzyl Chloroformate  
VIII-8
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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>0.97 ppm (6.7 mg/m³)</td>
<td>0.63 ppm (4.3 mg/m³)</td>
<td>0.31 ppm (2.2 mg/m³)</td>
</tr>
</tbody>
</table>

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 LC₅₀ 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 $c^n x t = k$, where the exponent, $n$, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using $n=3$ when extrapolating to shorter time points (30-minutes and 1-hour) and $n = 1$ when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value. The AEGL-3 values for benzyl chloroformate are presented in Table VIII-4, and the calculations for these AEGL-3 values are presented in Appendix VIII-A.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl Chloroformate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

<table>
<thead>
<tr>
<th>AEGL-3</th>
<th>3.7 ppm (26 mg/m³)</th>
<th>3.7 ppm (26 mg/m³)</th>
<th>2.9 ppm (20 mg/m³)</th>
<th>1.9 ppm (13 mg/m³)</th>
<th>0.93 ppm (6.5 mg/m³)</th>
</tr>
</thead>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>1.2 ppm (8.7 mg/m³)</td>
<td>0.97 ppm (6.7 mg/m³)</td>
<td>0.63 ppm (4.3 mg/m³)</td>
<td>0.31 ppm (2.2 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>3.7 ppm (26 mg/m³)</td>
<td>3.7 ppm (26 mg/m³)</td>
<td>2.9 ppm (20 mg/m³)</td>
<td>1.9 ppm (13 mg/m³)</td>
<td>0.93 ppm (6.5 mg/m³)</td>
</tr>
</tbody>
</table>

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


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


APPENDIX 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: 1/3 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

\[ C^3 \times t = k \]

\[ (18.6 \text{ ppm})^3 \times 4 \text{ hr} = 25739 \text{ ppm-hr} \]

8-hours

\[ C_1 \times t = k \]

\[ (18.6 \text{ ppm})^1 \times 4 \text{ hr} = 74.4 \text{ ppm-hr} \]

Uncertainty Factors:

3 for interspecies variability
3 for intraspecies variability

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

30-min AEGL-3

\[ C^3 \times 0.5 \text{ hr} = 25739 \text{ ppm-hr} \]

\[ C^3 = 51478 \text{ ppm} \]

\[ C = 37.2 \text{ ppm} \]

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

1-hr AEGL-3

\[ C^3 \times 1 \text{ hr} = 25739 \text{ ppm-hr} \]

\[ C^3 = 25739 \text{ ppm} \]

\[ C = 29.5 \text{ ppm} \]

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

4-hr AEGL-3

\[ 4\text{-hr AEGL-3} = 18.6/10 = 1.9 \text{ ppm} \]

8-hr AEGL-3

\[ C^1 \times 8 \text{ hr} = 74.4 \text{ ppm-hr} \]

\[ C^1 = 9.3 \text{ ppm} \]

\[ C = 9.3 \text{ ppm} \]

8-hr AEGL-3 = 9.3/10 = 0.93 ppm
APPENDIX VIII-B: DERIVATION SUMMARY FOR BENZYL CHLOROFORMATE

AEGLS

ACUTE EXPOSURE GUIDELINES FOR
BENZYL CHLOROFORMATE

DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>Time</th>
<th>AEGL-1 Values (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min</td>
<td>NR</td>
</tr>
<tr>
<td>30 Min</td>
<td>NR</td>
</tr>
<tr>
<td>1 Hr</td>
<td>NR</td>
</tr>
<tr>
<td>4 Hr</td>
<td>NR</td>
</tr>
<tr>
<td>8 Hr</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>1.2</td>
<td>1.2</td>
<td>0.97</td>
<td>0.63</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**Key Reference:**

**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**

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>3.7 ppm</td>
<td>3.7 ppm</td>
<td>2.9 ppm</td>
<td>1.9 ppm</td>
<td>0.93 ppm</td>
</tr>
</tbody>
</table>

**Key Reference:**

**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

Chemical Toxicity - TSD Animal Data
Benzyl Chloroformate

Minutes

ppm

No Effect
Discomfort
Disabling
Partially Lethal
Lethal

Benzyl Chloroformate
CHAPTER IX: PHENYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER IX: PHENYL CHLOROFORMATE

LIST OF TABLES CHAPTER IX: PHENYL CHLOROFORMATE ................................................... IX-4

EXECUTIVE SUMMARY: PHENYL CHLOROFORMATE .............................................................. IX-5

IX.1. HUMAN TOXICITY DATA..................................................................................................... IX-6
IX.1.1. Acute Lethality ................................................................................................................ IX-6
IX.1.2. Non-lethal Toxicity ........................................................................................................ IX-6
IX.1.3. Developmental/Reproductive Toxicity ......................................................................... IX-6
IX.1.4. Genotoxicity ................................................................................................................ IX-6
IX.1.5. Carcinogenicity ............................................................................................................. IX-6
IX.1.6. Summary ....................................................................................................................... IX-6

IX.2. ANIMAL TOXICITY DATA................................................................................................... IX-6
IX.2.1. Acute Lethality ................................................................................................................ IX-6
IX.2.1.1. Rats ............................................................................................................................. IX-6
IX.2.2. Non-lethal Toxicity ....................................................................................................... IX-9
IX.2.2.1. Mice ........................................................................................................................ IX-9
IX.2.3. Developmental/Reproductive Toxicity ..................................................................... IX-9
IX.2.4. Genotoxicity ................................................................................................................ IX-9
IX.2.5. Carcinogenicity ............................................................................................................ IX-10
IX.2.6. Summary ....................................................................................................................... IX-10

IX.3. DATA ANALYSIS AND AEGL-1 ....................................................................................... IX-10
IX.3.1. Human Data Relevant to AEGL-1 ................................................................................ IX-10
IX.3.2. Animal Data Relevant to AEGL-1 ................................................................................ IX-10
IX.3.3. Derivation of AEGL-1 ................................................................................................ IX-10

IX.4. DATA ANALYSIS AND AEGL-2 ....................................................................................... IX-10
IX.4.1. Human Data Relevant to AEGL-2 ................................................................................ IX-10
IX.4.2. Animal Data Relevant to AEGL-2 ................................................................................ IX-10
IX.4.3. Derivation of AEGL-2 ................................................................................................ IX-11

IX.5. DATA ANALYSIS AND AEGL-3 ....................................................................................... IX-11
IX.5.1. Human Data Relevant to AEGL-3 ................................................................................ IX-11
IX.5.2. Animal Data Relevant to AEGL-3 ................................................................................ IX-11
Phenyl Chloroformate

IX–3
### LIST OF TABLES CHAPTER IX: PHENYL CHLOROFORMATE

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX-S 1</td>
<td>Summary of AEGL Values For Phenyl Chloroformate</td>
<td>IX-5</td>
</tr>
<tr>
<td>IX-1</td>
<td>Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours</td>
<td>IX-7</td>
</tr>
<tr>
<td>IX-2</td>
<td>Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours</td>
<td>IX-8</td>
</tr>
<tr>
<td>IX-3</td>
<td>Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours</td>
<td>IX-8</td>
</tr>
<tr>
<td>IX-4</td>
<td>Exposure of Male Swiss-Webster Mice to Phenyl Chloroformate for 30 minutes</td>
<td>IX-9</td>
</tr>
<tr>
<td>IX-5</td>
<td>AEGL-1 Values for Phenyl Chloroformate</td>
<td>IX-10</td>
</tr>
<tr>
<td>IX-6</td>
<td>AEGL-2 Values for Phenyl Chloroformate</td>
<td>IX-11</td>
</tr>
<tr>
<td>IX-7</td>
<td>AEGL-3 Values for Phenyl Chloroformate</td>
<td>IX-12</td>
</tr>
<tr>
<td>IX-8</td>
<td>Summary of AEGL Values for Phenyl Chloroformate</td>
<td>IX-12</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY: PHENYL CHLOROFORMATE

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

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

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.19 ppm (1.2 mg/m³)</td>
<td>0.12 ppm (0.77 mg/m³)</td>
<td>0.060 ppm (0.38 mg/m³)</td>
<td>1/3 the AEGL-3 values (BASF, 1990; Hoechst, 1989)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.57 ppm (3.6 mg/m³)</td>
<td>0.36 ppm (2.3 mg/m³)</td>
<td>0.18 ppm (1.2 mg/m³)</td>
<td>4-hr rat BMCL05 (BASF, 1990; Hoechst, 1989)</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Combined Males and Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.76 ppm</td>
<td>0/5</td>
<td>0/5</td>
<td>0/10</td>
</tr>
<tr>
<td>44.5 ppm</td>
<td>4/5</td>
<td>3/5</td>
<td>7/10</td>
</tr>
<tr>
<td>97 ppm</td>
<td>5/5</td>
<td>4/5</td>
<td>9/10</td>
</tr>
<tr>
<td>156 ppm</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>311 ppm</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>LC$_{50}$</td>
<td>38.9 ppm</td>
<td>43 ppm</td>
<td>39.6 ppm</td>
</tr>
<tr>
<td>BMCL$_{05}$</td>
<td>0.68 ppm</td>
<td>1.9 ppm</td>
<td>1.33 ppm</td>
</tr>
<tr>
<td>BMC$_{01}$</td>
<td>27 ppm</td>
<td>31 ppm</td>
<td>5.3 ppm</td>
</tr>
</tbody>
</table>

*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 mortality data are similar for both studies.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Combined Males and Females</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.76 ppm</td>
<td>0/5</td>
<td>0/5</td>
<td>0/10</td>
<td>Hoechst, 1989</td>
</tr>
<tr>
<td>15.6 ppm</td>
<td>0/5</td>
<td>2/5</td>
<td>2/10</td>
<td>BASF, 1990</td>
</tr>
<tr>
<td>44.5 ppm</td>
<td>4/5</td>
<td>3/5</td>
<td>7/10</td>
<td>Hoechst, 1989</td>
</tr>
<tr>
<td>74.9 ppm</td>
<td>4/5</td>
<td>5/5</td>
<td>9/10</td>
<td>BASF, 1990</td>
</tr>
<tr>
<td>97 ppm</td>
<td>5/5</td>
<td>4/5</td>
<td>9/10</td>
<td>Hoechst, 1989</td>
</tr>
<tr>
<td>156 ppm</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
<td>Hoechst, 1989</td>
</tr>
<tr>
<td>159.3 ppm</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
<td>BASF, 1990</td>
</tr>
<tr>
<td>311 ppm</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
<td>Hoechst, 1989</td>
</tr>
<tr>
<td>LC$_{50}$</td>
<td>37.6 ppm</td>
<td>24.2 ppm</td>
<td>30.0 ppm</td>
<td></td>
</tr>
<tr>
<td>BMCL$_{05}$</td>
<td>6.3 ppm</td>
<td>0.82 ppm</td>
<td>3.6 ppm</td>
<td></td>
</tr>
<tr>
<td>BMC$_{01}$</td>
<td>12.4 ppm</td>
<td>2.6 ppm</td>
<td>5.4 ppm</td>
<td></td>
</tr>
</tbody>
</table>

*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 20°C 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>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Respiratory rates (control/exposed)</th>
<th>% Decrease in respiratory rate</th>
<th>Mortality Within 24-hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>285/240</td>
<td>16.1</td>
<td>0/4</td>
</tr>
<tr>
<td>6.25</td>
<td>250/180</td>
<td>26.0</td>
<td>0/4</td>
</tr>
<tr>
<td>12.5</td>
<td>265/145</td>
<td>45.3</td>
<td>0/4</td>
</tr>
<tr>
<td>17.5</td>
<td>265/140</td>
<td>47.2</td>
<td>0/4</td>
</tr>
<tr>
<td>25</td>
<td>250/90</td>
<td>64.0</td>
<td>0/4</td>
</tr>
<tr>
<td>50</td>
<td>200/70</td>
<td>65.0</td>
<td>0/4</td>
</tr>
<tr>
<td>100</td>
<td>245/50</td>
<td>79.6</td>
<td>0/4</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.19 ppm (1.2 mg/m³)</td>
<td>0.12 ppm (0.77 mg/m³)</td>
<td>0.060 ppm (0.38 mg/m³)</td>
</tr>
</tbody>
</table>

IX.5. DATA ANALYSIS AND AEGL-3

IX.5.1. Human Data Relevant to AEGL-3

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

IX.5.2. Animal Data Relevant to AEGL-3

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

IX.5.3. Derivation of AEGL-3

The 4-hour rat BMCL₀₅ of 3.6 ppm from the combined BASF (1990) and Hoechst (1989) studies will be used as the point-of-departure for phenyl chloroformate AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each will be applied because phenyl chloroformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species or among individuals. Furthermore, inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate (Section II.5.3), isopropyl chloroformate (Section V.5.3), and n-butyl chloroformate (Section VII.5.3), and these resulting AEGL values were considered protective when compared with 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

Phenyl Chloroformate
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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.57 ppm (3.6 mg/m³)</td>
<td>0.36 ppm (2.3 mg/m³)</td>
<td>0.18 ppm (1.2 mg/m³)</td>
</tr>
</tbody>
</table>

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 BMCL₀₅ value.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.24 ppm (1.5 mg/m³)</td>
<td>0.19 ppm (1.2 mg/m³)</td>
<td>0.12 ppm (0.77 mg/m³)</td>
<td>0.060 ppm (0.38 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.72 ppm (4.6 mg/m³)</td>
<td>0.57 ppm (3.6 mg/m³)</td>
<td>0.36 ppm (2.3 mg/m³)</td>
<td>0.18 ppm (1.2 mg/m³)</td>
</tr>
</tbody>
</table>

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 RD₅₀ study in male Swiss Webster mice.
IX.7. REFERENCES


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: 1/3 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 BMCL05 (3.6 ppm)

Scaling:

\[
\begin{align*}
30\text{-minutes and 1-hr} & \quad C^3 \times t = k \\
(3.6 \text{ ppm})^3 \times 4 \text{ hr} & = 186.7 \text{ ppm} \cdot \text{hr} \\
8\text{-hours} & \quad C^1 \times t = k \\
(3.6 \text{ ppm})^1 \times 4 \text{ hr} & = 14.4 \text{ ppm} \cdot \text{hr}
\end{align*}
\]

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

\[
\begin{align*}
C^3 \times 0.5 \text{ hr} & = 186.7 \text{ ppm} \cdot \text{hr} \\
C^3 & = 373.4 \text{ ppm} \\
C & = 7.2 \text{ ppm} \\
30\text{-min AEGL-3} & = \frac{7.2}{10} = 0.72 \text{ ppm}
\end{align*}
\]

1-hr AEGL-3

\[
\begin{align*}
C^3 \times 1 \text{ hr} & = 186.7 \text{ ppm} \cdot \text{hr} \\
C^3 & = 186.7 \text{ ppm} \\
C & = 5.7 \text{ ppm} \\
1\text{-hr AEGL-3} & = \frac{5.7}{10} = 0.57 \text{ ppm}
\end{align*}
\]

4-hr AEGL-3

\[
\begin{align*}
4\text{-hr AEGL-3} & = \frac{3.6}{10} = 0.36 \text{ ppm}
\end{align*}
\]

8-hr AEGL-3

\[
\begin{align*}
C^1 \times 8 \text{ hr} & = 14.4 \text{ ppm} \cdot \text{hr} \\
C^1 & = 1.8 \text{ ppm} \\
C & = 1.8 \text{ ppm} \\
8\text{-hr AEGL-3} & = \frac{1.8}{10} = 0.18 \text{ ppm}
\end{align*}
\]
APPENDIX IX-B: DERIVATION SUMMARY FOR
PHENYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR
PHENYL CHLOROFORMATE
DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>AEGL-1 VALUES FOR PHENYL CHLOROFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min</td>
</tr>
<tr>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (ppm)</td>
<td>0.24</td>
<td>0.24</td>
<td>0.19</td>
<td>0.12</td>
<td>0.060</td>
</tr>
</tbody>
</table>

**Key References:**


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

**AEGL-3 VALUES FOR PHENYL CHLOROFORMATE**

<table>
<thead>
<tr>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72 ppm</td>
<td>0.72 ppm</td>
<td>0.57 ppm</td>
<td>0.36 ppm</td>
<td>0.18 ppm</td>
</tr>
</tbody>
</table>

**Key References:**


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

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

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

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

**Effects: Concentration Mortality**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.76 ppm</td>
<td>0/10</td>
</tr>
<tr>
<td>15.6 ppm</td>
<td>2/10</td>
</tr>
<tr>
<td>44.5 ppm</td>
<td>7/10</td>
</tr>
<tr>
<td>74.9 ppm</td>
<td>9/10</td>
</tr>
<tr>
<td>97 ppm</td>
<td>9/10</td>
</tr>
<tr>
<td>156 ppm</td>
<td>10/10</td>
</tr>
<tr>
<td>159.3 ppm</td>
<td>10/10</td>
</tr>
<tr>
<td>311 ppm</td>
<td>10/10</td>
</tr>
</tbody>
</table>

**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

Minutes

No Effect
Discomfort
Disabling
Partially Lethal
Lethal

AEGL-3
AEGL-2
APPENDIX IX-D: BENCHMARK CONCENTRATION CALCULATION FOR PHENYL CHLOROFORMATE

BMDS MODEL RUN

The form of the probability function is:

\[ P[\text{response}] = \text{Background} + (1-\text{Background}) \times \text{CumNorm(Intercept+Slope}\times\text{Log(Dose)}), \]

where \text{CumNorm(.)} is the cumulative normal distribution function.

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

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

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
- background = 0
- intercept = -2.32244
- slope = 0.759796

Asymptotic Correlation Matrix of Parameter Estimates

( *** 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 )

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-0.98</td>
</tr>
<tr>
<td>slope</td>
<td>-0.98</td>
<td>1</td>
</tr>
</tbody>
</table>

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept</td>
<td>-4.60327</td>
<td>1.20324</td>
</tr>
<tr>
<td>Slope</td>
<td>1.35407</td>
<td>0.307109</td>
</tr>
</tbody>
</table>

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

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th>Deviance</th>
<th>Test DF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-17.6143</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-18.0291</td>
<td>0.829451</td>
<td>6</td>
<td>0.9913</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-47.9918</td>
<td>60.755</td>
<td>7</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 40.0581

Goodness of Fit

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est_Prob</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7600</td>
<td>0.0001</td>
<td>0.001</td>
<td>0</td>
<td>10</td>
<td>-0.02491</td>
</tr>
<tr>
<td>15.6000</td>
<td>0.1885</td>
<td>1.885</td>
<td>2</td>
<td>10</td>
<td>0.09264</td>
</tr>
<tr>
<td>44.5000</td>
<td>0.7040</td>
<td>7.040</td>
<td>7</td>
<td>10</td>
<td>-0.02802</td>
</tr>
<tr>
<td>74.9000</td>
<td>0.8927</td>
<td>8.927</td>
<td>9</td>
<td>10</td>
<td>0.07446</td>
</tr>
<tr>
<td>97.0000</td>
<td>0.9442</td>
<td>9.442</td>
<td>9</td>
<td>10</td>
<td>-0.0692</td>
</tr>
<tr>
<td>156.0000</td>
<td>0.9873</td>
<td>9.873</td>
<td>10</td>
<td>10</td>
<td>0.359</td>
</tr>
<tr>
<td>159.3000</td>
<td>0.9882</td>
<td>9.882</td>
<td>10</td>
<td>10</td>
<td>0.3459</td>
</tr>
<tr>
<td>311.0000</td>
<td>0.9992</td>
<td>9.992</td>
<td>10</td>
<td>10</td>
<td>0.08752</td>
</tr>
</tbody>
</table>

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

Probit Model with 0.95 Confidence Level

Phenyl Chloroformate

IX–22
CHAPTER X: 2-ETHYLHEXYL CHLOROFORMATE
TABLE OF CONTENTS: CHAPTER IX: 2-ETHYLHEXYL CHLOROFORMATE

LIST OF TABLES: 2-ETHYLHEXYL CHLOROFORMATE

EXECUTIVE SUMMARY: 2-ETHYLHEXYL CHLOROFORMATE

X.1. HUMAN TOXICITY DATA
X.1.1. Acute Lethality
X.1.2. Non-lethal Toxicity
X.1.3. Developmental/Reproductive Toxicity
X.1.4. Genotoxicity
X.1.5. Carcinogenicity
X.1.6. Summary

X.2. ANIMAL TOXICITY DATA
X.2.1. Acute Lethality
X.2.1.1. Rats
X.2.2. Non-lethal Toxicity
X.2.3. Developmental/Reproductive Toxicity
X.2.4. Genotoxicity
X.2.5. Carcinogenicity
X.2.6. Summary

X.3. DATA ANALYSIS AND AEGL-1
X.3.1. Human Data Relevant to AEGL-1
X.3.2. Animal Data Relevant to AEGL-1
X.3.3. Derivation of AEGL-1

X.4. DATA ANALYSIS AND AEGL-2
X.4.1. Human Data Relevant to AEGL-2
X.4.2. Animal Data Relevant to AEGL-2
X.4.3. Derivation of AEGL-2

X.5. DATA ANALYSIS AND AEGL-3
X.5.1. Human Data Relevant to AEGL-3
X.5.2. Animal Data Relevant to AEGL-3
X.5.3. Derivation of AEGL-3
X.6. SUMMARY OF AEGLS ............................................................................................................ X-10
X.6.1. AEGL Values and Toxicity Endpoints ............................................................................. X-10
X.6.2. Comparison with Other Standards and Guidelines .......................................................... X-10
X.6.3. Data Quality and Research Needs ................................................................................... X-10
X.7. REFERENCES ..................................................................................................................... 11

APPENDIX X-A: DERIVATION OF AEGL VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE
APPENDIX X-B: DERIVATION SUMMARY FOR 2-ETHYLHEXYL CHLOROFORMATE
APPENDIX X-C: CATEGORY PLOT FOR 2-ETHYLHEXYL CHLOROFORMATE
APPENDIX X-D: BENCHMARK CONCENTRATION CALCULATION FOR 2-ETHYLHEXYL CHLOROFORMATE
LIST OF TABLES: 2-ETHYLHEXYL CHLOROFORMATE

1. Summary of AEGL Values For 2-Ethylhexyl Chloroformate ........................................X-5
2. Mortality in Rats Exposed to 2-Ethylhexyl Chloroformate for 4 hours .........................X-7
3. AEGL-1 Values for 2-Ethylhexyl Chloroformate ...........................................................X-8
4. AEGL-2 Values for 2-Ethylhexyl Chloroformate ...........................................................X-9
5. AEGL-3 Values for 2-Ethylhexyl Chloroformate ........................................................X-10
6. Summary of AEGL Values for 2-Ethylhexyl Chloroformate ........................................X-10
EXECUTIVE SUMMARY: 2-ETHYLHEXYL CHLOROFORMATE

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

No acute inhalation data consistent with the definition of AEGL-2 with both concentration and duration information were available. Therefore, the AEGL-2 values for 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.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>1.2 ppm (9.5 mg/m^3)</td>
<td>1.2 ppm (9.5 mg/m^3)</td>
<td>0.97 ppm (7.7 mg/m^3)</td>
<td>0.60 ppm (4.7 mg/m^3)</td>
<td>0.30 ppm (2.4 mg/m^3)</td>
<td>1/3 the AEGL-3 values (BASF, 1985)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>3.6 ppm (28 mg/m^3)</td>
<td>3.6 ppm (28 mg/m^3)</td>
<td>2.9 ppm (23 mg/m^3)</td>
<td>1.8 ppm (14 mg/m^3)</td>
<td>0.91 ppm (7.2 mg/m^3)</td>
<td>4-hr rat BMCL_{05} (BASF, 1985)</td>
</tr>
</tbody>
</table>

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

2-Ethylhexyl Chloroformate X-5
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 2-ethylhexyl chloroformate
Methyl Chloroformate, Ethyl Chloroformate, Propyl Chloroformate, Isopropyl Chloroformate, Allyl Chloroformate, n-Butyl Chloroformate, Isobutyl Chloroformate, sec-Butyl Chloroformate, Ethyl Chlorothioformate, Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate

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>
<thead>
<tr>
<th>Time to death</th>
<th>Time to death</th>
<th>Combined Males and Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>22.8 ppm</td>
<td>0/10</td>
<td>–</td>
</tr>
<tr>
<td>26.6 ppm</td>
<td>4/10</td>
<td>2 dead: Day of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 dead: Day 1 post-exposure</td>
</tr>
<tr>
<td>34.3 ppm</td>
<td>7/10</td>
<td>2 dead: Day of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 dead: Day 1 post-exposure</td>
</tr>
<tr>
<td>46.9 ppm</td>
<td>10/10</td>
<td>8 dead: Day of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 dead: Day 1 post-exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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 |

*BASE, 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 20°C for 3 minutes, 10 minutes, 30 minutes, 1 hour, and 2 hours, respectively (BASE, 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.

2-Ethylhexyl Chloroformate X-7
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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-2</td>
<td>1.2 ppm (9.5 mg/m³)</td>
<td>1.2 ppm (9.5 mg/m³)</td>
<td>0.97 ppm (7.7 mg/m³)</td>
<td>0.60 ppm (4.7 mg/m³)</td>
<td>0.30 ppm (2.4 mg/m³)</td>
</tr>
</tbody>
</table>

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 LC₅₀ values of 29.9 ppm, 36.3 ppm, and 33.9 ppm were calculated for male rats, female rats, and male and female rats combined, respectively (BASF, 1985). Four-hour BMCL₀₅ values of 18.1 ppm, 26.0 ppm, and 20.1 ppm were calculated for male rats, female rats, and male and female rats combined, respectively (BASF, 1985).

X.5.3. Derivation of AEGL-3

The 4-hour male rat BMCL₀₅ 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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-3</td>
<td>3.6 ppm (28 mg/m³)</td>
<td>3.6 ppm (28 mg/m³)</td>
<td>2.9 ppm (23 mg/m³)</td>
<td>1.8 ppm (14 mg/m³)</td>
<td>0.91 ppm (7.2 mg/m³)</td>
</tr>
</tbody>
</table>

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 BMCL₀₅ value.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Non-disabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>1.2 ppm (9.5 mg/m³)</td>
<td>1.2 ppm (9.5 mg/m³)</td>
<td>0.97 ppm (7.7 mg/m³)</td>
<td>0.60 ppm (4.7 mg/m³)</td>
<td>0.30 ppm (2.4 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>3.6 ppm (28 mg/m³)</td>
<td>3.6 ppm (28 mg/m³)</td>
<td>2.9 ppm (23 mg/m³)</td>
<td>1.8 ppm (14 mg/m³)</td>
<td>0.91 ppm (7.2 mg/m³)</td>
</tr>
</tbody>
</table>

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


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

AEGL-1 values for 2-ethylhexyl chloroformate are not recommended.
Key studies: BASF, 1985

Toxicity Endpoint: 1/3 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 BMCL05 (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

\[ C^3 \times 0.5 \text{ hr} = 23,719 \text{ ppm-hr} \]
\[ C^3 = 47,438 \text{ ppm} \]
\[ C = 36.2 \text{ ppm} \]
\[ 30\text{-min AEGL-3} = 36.2/10 = 3.6 \text{ ppm} \]

1-hr AEGL-3

\[ C^3 \times 1 \text{ hr} = 23,719 \text{ ppm-hr} \]
\[ C^3 = 23,719 \text{ ppm} \]
\[ C = 28.7 \text{ ppm} \]
\[ 1\text{-hr AEGL-3} = 28.7/10 = 2.9 \text{ ppm} \]

4-hr AEGL-3

\[ 4\text{-hr AEGL-3} = 18.6/10 = 1.8 \text{ ppm} \]

8-hr AEGL-3

\[ C^1 \times 8 \text{ hr} = 72.4 \text{ ppm-hr} \]
\[ C^1 = 9.1 \text{ ppm} \]
\[ C = 9.1 \text{ ppm} \]
\[ 8\text{-hr AEGL-3} = 9.1/10 = 0.91 \text{ ppm} \]
APPENDIX X-B: DERIVATION SUMMARY FOR 2-ETHYLHEXYL CHLOROFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR 2-ETHYLHEXYL CHLOROFORMATE

<table>
<thead>
<tr>
<th>Duration</th>
<th>AEGL-1 Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min</td>
<td>NR</td>
</tr>
<tr>
<td>30 Min</td>
<td>NR</td>
</tr>
<tr>
<td>1 Hr</td>
<td>NR</td>
</tr>
<tr>
<td>4 Hr</td>
<td>NR</td>
</tr>
<tr>
<td>8 Hr</td>
<td>NR</td>
</tr>
</tbody>
</table>

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.
2-Ethylhexyl Chloroformate

AEGL-2 VALUES FOR 2-ETHYLHEXYL CHLOROFORMATE

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2 ppm</td>
<td>1.2 ppm</td>
<td>0.97 ppm</td>
<td>0.60 ppm</td>
<td>0.30 ppm</td>
</tr>
</tbody>
</table>

Key Reference:

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

<table>
<thead>
<tr>
<th>Exposure Duration</th>
<th>Concentration</th>
<th>Male Mortality</th>
<th>Female Mortality</th>
<th>Combined Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Min</td>
<td>3.6 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
<tr>
<td>30-Min</td>
<td>3.6 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
<tr>
<td>1-Hr</td>
<td>2.9 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
<tr>
<td>4-Hr</td>
<td>1.8 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
<tr>
<td>8-Hr</td>
<td>0.91 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
</tbody>
</table>

**Key Reference:**

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

**Exposure Route/Concentrations/Durations:** Rats/Inhalation/4 hours
(Male BMCL₀₅, 18.1 ppm, was the point-of-departure for AEGL-3)

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

**Effects:**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Male Mortality</th>
<th>Female Mortality</th>
<th>Combined Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.8 ppm</td>
<td>0/10</td>
<td>0/10</td>
<td>0/20</td>
</tr>
<tr>
<td>26.6 ppm</td>
<td>4/10</td>
<td>1/10</td>
<td>5/20</td>
</tr>
<tr>
<td>34.3 ppm</td>
<td>7/10</td>
<td>2/10</td>
<td>9/20</td>
</tr>
<tr>
<td>46.9 ppm</td>
<td>10/10</td>
<td>10/10</td>
<td>20/20</td>
</tr>
</tbody>
</table>

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

**Data Quality and Research Needs:** Sparse data set.
APPENDIX X-C: CATEGORY PLOT FOR 2-ETHYLHEXYL CHLOROFORMATE

Chemical Toxicity - TSD Animal Data
2-Ethylhexyl Chloroformate

- No Effect
- Discomfort
- Disabling
- Partially Lethal
- Lethal

AEGL-3
AEGL-2

ppm
Minutes
APPENDIX X-D: BENCHMARK CONCENTRATION CALCULATION FOR
2-ETHYLCHEXYL 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 )

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept</td>
<td>-18.7737</td>
<td>5.12639</td>
</tr>
<tr>
<td>Slope</td>
<td>5.52218</td>
<td>1.51755</td>
</tr>
</tbody>
</table>

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

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th>Deviance</th>
<th>Test DF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-12.8388</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-14.2231</td>
<td>2.76871</td>
<td>2</td>
<td>0.2505</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-27.6759</td>
<td>29.6742</td>
<td>3</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 32.4462

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Ethylhexyl Chloroformate</td>
<td>X-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interim 1: 05/2008

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Probit</th>
<th>Coefficient</th>
<th>Alpha</th>
<th>Beta</th>
<th>Gamma</th>
<th>Change</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.8000</td>
<td>0.0659</td>
<td>0.659</td>
<td>0</td>
<td>10</td>
<td>-0.8398</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.6000</td>
<td>0.2559</td>
<td>2.559</td>
<td>4</td>
<td>10</td>
<td>1.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34.3000</td>
<td>0.7728</td>
<td>7.728</td>
<td>7</td>
<td>10</td>
<td>-0.5491</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46.9000</td>
<td>0.9934</td>
<td>9.934</td>
<td>10</td>
<td>10</td>
<td>0.2587</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 = 8.0971

Probit Model with 0.95 Confidence Level

10:35 09/27 2006
CHAPTER XI: ETHYL CHLOROTHIOFORMATE
TABLE OF CONTENTS: CHAPTER XI: ETHYL CHLOROTHIOFORMATE

LIST OF TABLES: ETHYL CHLOROTHIOFORMATE ................................................................. XI-4

EXECUTIVE SUMMARY: ETHYL CHLOROTHIOFORMATE ................................................. XI-5

XI.1. HUMAN TOXICITY DATA ............................................................................................ XI-6
  XI.1.1. Acute Lethality ...................................................................................................... XI-6
  XI.1.2. Non-lethal Toxicity ................................................................................................ XI-6
  XI.1.3. Developmental/Reproductive Toxicity ................................................................. XI-6
  XI.1.4. Genotoxicity ......................................................................................................... XI-6
  XI.1.5. Carcinogenicity .................................................................................................... XI-6
  XI.1.6. Summary ............................................................................................................... XI-6

XI.2. ANIMAL TOXICITY DATA ......................................................................................... XI-7
  XI.2.1. Acute Lethality ...................................................................................................... XI-7
  XI.2.2. Non-lethal Toxicity ................................................................................................ XI-8
  XI.2.3. Developmental/Reproductive Toxicity ................................................................. XI-8
  XI.2.4. Genotoxicity ......................................................................................................... XI-8
  XI.2.5. Carcinogenicity .................................................................................................... XI-8
  XI.2.6. Summary ............................................................................................................... XI-9

XI.3. DATA ANALYSIS AND AEGL-1 .............................................................................. XI-9
  XI.3.1. Human Data Relevant to AEGL-1 ........................................................................ XI-9
  XI.3.2. Animal Data Relevant to AEGL-1 ......................................................................... XI-9
  XI.3.3. Derivation of AEGL-1 ........................................................................................ XI-9

XI.4. DATA ANALYSIS AND AEGL-2 .............................................................................. XI-9
  XI.4.1. Human Data Relevant to AEGL-2 ........................................................................ XI-9
  XI.4.2. Animal Data Relevant to AEGL-2 ......................................................................... XI-9
  XI.4.3. Derivation of AEGL-2 ........................................................................................ XI-9

XI.5. DATA ANALYSIS AND AEGL-3 .............................................................................. XI-10
  XI.5.1. Human Data Relevant to AEGL-3 ........................................................................ XI-10
  XI.5.2. Animal Data Relevant to AEGL-3 ......................................................................... XI-10
  XI.5.3. Derivation of AEGL-3 ........................................................................................ XI-10

Ethyl Chlorothioformate ......................................................... XI-2
LIST OF TABLES: ETHYL CHLOROTHIOFORMATE

1. TABLE XI-S 1. Summary of AEGL Values For Ethyl Chlorothioformate ........................................................ XI-5
2. TABLE XI-1. Mortality of Rats Exposed to Ethyl Chlorothioformate for 4-hours .............................................. XI-8
3. TABLE XI-2. AEGL-1 Values for Ethyl Chlorothioformate ................................................................................ XI-9
4. TABLE XI-3. AEGL-2 Values for Ethyl Chlorothioformate ................................................................................ XI-10
5. TABLE XI-4. AEGL-3 Values for Ethyl Chlorothioformate ................................................................................ XI-10
6. TABLE XI-5. Summary of AEGL Values for Ethyl Chlorothioformate .............................................................. XI-11
EXECUTIVE 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 (1/3 the 4-hr LC₅₀: 1/3 x 45 ppm = 15 ppm) (Stauffer, 1983) was used for deriving AEGL-3 values for ethyl chlorothioformate. An interspecies uncertainty factor of 3 was applied because ethyl chlorothioformate is highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of effect is not expected to vary greatly between species. An intraspecies uncertainty factor of 10 was applied to protect against potential delayed systemic effects that may occur due to the thio-moiety. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by \( c^n x t = k \), where the exponent, \( n \), ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using \( n=3 \) when extrapolating to shorter time points (30-minutes and 1-hour) and \( n = 1 \) when extrapolating to longer time points (8-hours). The 30-minute AEGL-3 value will be adopted as the 10-minute value due to the uncertainty in extrapolating from a 4-hour point-of-departure.

The calculated values are listed in the table below.

<table>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
<th>Endpoint (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>0.33 ppm (1.7 mg/m³)</td>
<td>0.33 ppm (1.7 mg/m³)</td>
<td>0.26 ppm (1.3 mg/m³)</td>
<td>0.17 ppm (0.87 mg/m³)</td>
<td>0.083 ppm (0.42 mg/m³)</td>
<td>1/3 the AEGL-3 values (Stauffer, 1983)</td>
</tr>
<tr>
<td>AEGL-3 (Lethality)</td>
<td>1.0 ppm (5.1 mg/m³)</td>
<td>1.0 ppm (5.1 mg/m³)</td>
<td>0.79 ppm (4.0 mg/m³)</td>
<td>0.50 ppm (2.6 mg/m³)</td>
<td>0.25 ppm (1.3 mg/m³)</td>
<td>Estimated 4-hour rat lethality threshold (Stauffer, 1983)</td>
</tr>
</tbody>
</table>

NR: Not Recommended. The lack of AEGL-1 values does not imply that concentrations below AEGL-2 will be without effect.
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. LC50 values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC50 value of 45 ppm was also calculated. Data are summarized in Table XI-1.
TABLE XI-1. Mortality of Rats Exposed to Ethyl Chlorothioformate for 4-hours *

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Incidence</th>
<th>Time of Death (Days Post-Exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7-14</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>2/10</td>
<td>0 2 0 0 0 0 0 0</td>
</tr>
<tr>
<td>59</td>
<td>6/10</td>
<td>0 5 1 0 0 0 0 0</td>
</tr>
<tr>
<td>65</td>
<td>10/10</td>
<td>0 8 2 0 0 0 0 0</td>
</tr>
<tr>
<td>69</td>
<td>8/10</td>
<td>1 7 0 0 0 0 0 0</td>
</tr>
<tr>
<td>124</td>
<td>10/10</td>
<td>6 4 0 0 0 0 0 0</td>
</tr>
<tr>
<td><strong>LC50</strong></td>
<td>51 ppm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Incidence</th>
<th>Time of Death (Days Post-Exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 0 0 0 0 1</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>2/10</td>
<td>0 1 0 0 0 0 1</td>
</tr>
<tr>
<td>59</td>
<td>8/10</td>
<td>0 3 3 1 0 0 0 1</td>
</tr>
<tr>
<td>65</td>
<td>10/10</td>
<td>0 6 2 2 0 0 0 0</td>
</tr>
<tr>
<td>69</td>
<td>10/10</td>
<td>0 6 4 0 0 0 0 0</td>
</tr>
<tr>
<td>124</td>
<td>10/10</td>
<td>4 6 0 0 0 0 0 0</td>
</tr>
<tr>
<td><strong>LC50</strong></td>
<td>41 ppm</td>
<td></td>
</tr>
<tr>
<td>Combined Male and Female LC50</td>
<td>45 ppm</td>
<td></td>
</tr>
</tbody>
</table>

*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 activation 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<sub>50</sub> values of 51 ppm and 41 ppm were calculated for male and female rats, respectively. A combined male and female LC<sub>50</sub> 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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

XI.4. DATA ANALYSIS AND AEGL-2

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

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-Min          | 30-Min          | 1-Hr            | 4-Hr            | 8-Hr            |
| AEGL-2          | 0.33 ppm        | 0.33 ppm        | 0.26 ppm        | 0.17 ppm        | 0.083 ppm       |
|                 | (1.7 mg/m³)     | (1.7 mg/m³)     | (1.3 mg/m³)     | (0.87 mg/m³)    | (0.42 mg/m³)    |

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

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

XI.5.2. Animal Data Relevant to AEGL-3

Four-hour LC₅₀ values of 51 ppm and 41 ppm were calculated for male and female rats, respectively, and the combined sexes LC₅₀ was 45 ppm (Stauffer, 1983).

XI.5.3. Derivation of AEGL-3

An estimated 4-hour rat lethality threshold of 15 ppm (1/3 the 4-hr LC₅₀: 1/3 x 45 ppm = 15 ppm) (Stauffer, 1983) will be used for deriving AEGL-3 values for ethyl chlorothioformate. 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 $c^n x = k$, 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-Min          | 30-Min          | 1-Hr            | 4-Hr            | 8-Hr            |
| AEGL-3          | 1.0 ppm         | 1.0 ppm         | 0.79 ppm        | 0.50 ppm        | 0.25 ppm        |
|                 | (5.1 mg/m³)     | (5.1 mg/m³)     | (4.0 mg/m³)     | (2.6 mg/m³)     | (1.3 mg/m³)     |
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>
<thead>
<tr>
<th>Classification</th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL-1 (Nondisabling)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AEGL-2 (Disabling)</td>
<td>0.33 ppm (1.7 mg/m³)</td>
<td>0.33 ppm (1.7 mg/m³)</td>
<td>0.26 ppm (1.3 mg/m³)</td>
<td>0.17 ppm (0.87 mg/m³)</td>
<td>0.083 ppm (0.42 mg/m³)</td>
</tr>
<tr>
<td>AEGL-3 (Lethal)</td>
<td>1.0 ppm (5.1 mg/m³)</td>
<td>1.0 ppm (5.1 mg/m³)</td>
<td>0.79 ppm (4.0 mg/m³)</td>
<td>0.50 ppm (2.6 mg/m³)</td>
<td>0.25 ppm (1.3 mg/m³)</td>
</tr>
</tbody>
</table>

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


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: 1/3 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 (1/3 the LC₅₀ of 45 ppm)

Scaling:

30-minutes and 1-hour

\[ C^3 \times t = k \]

(15 ppm)³ x 4 hr = 13,500 ppm-hr

8-hours

\[ C^1 \times t = k \]

(15 ppm)¹ x 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

\[ C^3 \times 0.5 \text{ hr} = 13,500 \text{ ppm-hr} \]

\[ C^3 = 27,000 \text{ ppm} \]

\[ C = 30 \text{ ppm} \]

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

1-hr AEGL-3

\[ C^3 \times 1 \text{ hr} = 13,500 \text{ ppm-hr} \]

\[ C^3 = 13,500 \text{ ppm} \]

\[ C = 23.8 \text{ ppm} \]

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

4-hr AEGL-3

15 ppm ÷ 30 = 0.50

8-hr AEGL-3

\[ C^1 \times 8 \text{ hr} = 60 \text{ ppm-hr} \]

\[ C^1 = 7.5 \text{ ppm} \]

\[ C = 7.5 \text{ ppm} \]

8-hr AEGL-3 = 7.5/30 = 0.25 ppm
APPENDIX XI-B: DERIVATION SUMMARY FOR 
ETHYL CHLOROTHIOFORMATE AEGLS

ACUTE EXPOSURE GUIDELINES FOR 
ETHYL CHLOROTHIOFORMATE 
DERIVATION SUMMARY

<table>
<thead>
<tr>
<th>AEGL-1 VALUES FOR ETHYL CHLOROTHIOFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Min</td>
</tr>
<tr>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10-Min</th>
<th>30-Min</th>
<th>1-Hr</th>
<th>4-Hr</th>
<th>8-Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.33 ppm</td>
<td>0.33 ppm</td>
<td>0.26 ppm</td>
<td>0.17 ppm</td>
<td>0.083 ppm</td>
</tr>
</tbody>
</table>

### Key Reference:

### 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.
1

<table>
<thead>
<tr>
<th>AEGL-3 VALUES FOR ETHYL CHLOROTHIOFORMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Min</td>
</tr>
<tr>
<td>1.0 ppm</td>
</tr>
</tbody>
</table>

Key Reference:

Test Species/Strain/Sex/Number: Sprague Dawley rats/ 10/sex/group

Exposure Route/Concentrations/Durations: Rats/Inhalation/4 hours
(Estimated lethality threshold of 1/3 the 4-hr rat LC₅₀ of 45 ppm (1/3 x 45 ppm = 15 ppm) is the point-of-departure for AEGL-3)

Endpoint/Concentration/Rationale: 1/3 the 4-hr rat LC₅₀ of 45 ppm (1/3 x 45 ppm = 15 ppm)/ 15 ppm/Estimated threshold for death for 4 hour exposure in rats

Effects: LC₅₀ =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 x t= k, where n=3 when extrapolating to shorter time points (30-minutes and 1-hour) and n = 1 when extrapolating to longer time points (8-hours). The 30-minute value was adopted as the 10-minute value because the point-of-departure was 4-hours.

Data Quality and Research Needs: Data limited to rat lethality studies.
APPENDIX XI-C: CATEGORY PLOT FOR ETHYL CHLOROTHIOFORMATE

Chemical Toxicity - TSD Animal Data
Ethyl Chlorothioformate

Minutes

ppm

No Effect
Discomfort
Disabling
Partially Lethal
Lethal
AEGL-3
AEGL-2
AEGL

Ethyl Chlorothioformate

XI-19