Integrated Laboratory Systems

Bis(2-chloroethoxy)methane [111-91-1]

Review of Toxicological Literature

Prepared for

Errol Zeiger, Ph.D. National Institute of Environmental Health Sciences P.O. Box 12233 Research Triangle Park, North Carolina 27709 Contract No. N01-ES-65402

Submitted by

Raymond Tice, Ph.D. (Principal Investigator) Brigette Brevard, M.A. (Co-Principal Investigator) Integrated Laboratory Systems P.O. Box 13501 Research Triangle Park, North Carolina 27709

September 1998

EXECUTIVE SUMMARY

Bis(2-chloroethoxy)methane was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing. Classified as a haloether, it is a colorless liquid that is heavier than water.

Bis(2-chloroethoxy)methane is produced by the reaction of ethylene chlorohydrin (a possible impurity) and formaldehyde under acid catalysis. It is analyzed by gas chromatography via several EPA-approved testing methods. Only one company is identified as a U.S. manufacturer. In 1977, ~10 to 50 million pounds were produced in the United States. No current data on production or import volumes were located. Bis(2-chloroethoxy)methane is used primarily as the starting compound in the production of polysulfide elastomers, and as a solvent.

Bis(2-chloroethoxy)methane is a synthetic organic compound that does not occur naturally. It is not taken up by plants; however, it can translocate through plants and be taken up by animals. In pure water, bis(2-chloroethoxy)methane hydrolyzes slowly with a half-life of six months to several years. Its half-life in a model pond was ~11 years. It is co-metabolically oxidized by the bacterium *Nitrosomonas europea* (known to be present in wastewater sludge from treatment facilities) via the enzyme, ammonia monooxygenase. Bis(2-chloroethoxy)methane has an estimated half-life of 10 hours in the atmosphere when reacted with photochemically produced hydroxy radicals.

No data on human exposure were found; however, exposure is presumed to be from its production and use in industrial environments. Human exposure can occur via inhalation, ingestion, or dermal contact. Symptoms of exposure include skin and eye irritation.

No data on chemical disposition, metabolism, or toxicokinetics were located.

The oral LD_{50} in rats is 65 mg/kg (0.38 mmol/kg). When exposed to 120 ppm (850 mg/m³; 4.91 mmol/m³) for 4 hours, 6 of 6 rats died. The dermal LD_{50} in guinea pigs is 170 mg/kg (0.98 mmol/kg). Bis(2-chloroethoxy)methane was essentially non-irritating to rabbits in ocular toxicity tests. In non-mammalian systems, a 48-hour LC_{50} of 201 mg/L (1.16 mmol/L) was found in *Daphnia magna* and a 96-hour LC_{50} of 184 mg/L (1.06 mmol/L) was found in *Pimephales promelas* (fathead minnows).

In a subchronic, 3-month oral toxicity study, 17 of 20 rats given 120 mg/kg (0.58 mmol/kg) bis(2-chloroethoxy)methane per day died within 76 days of exposure. Symptoms included emaciation, hypothermia, lethargy/prostration, dyspnea, moist rales, slight tremors, salivation, and brown-yellow stains on the paws, ventral surface, and anogenital area. Examination revealed degeneration of the myocardium in animals that died after day 14.

No data on reproductive and teratogenic effects, carcinogenicity, genotoxicity, or immunotoxicity were found.

Chlorinated alkyl ethers, such as bis(2-chloroethoxy)methane, show the same reactivity as their non-chlorinated analogs.

TABLE OF CONTENTS

1.0	BASIS FOR NOMINATION	1
2.0	INTRODUCTION	1
	2.1 Chemical Identification	1
	2.2 Physical-Chemical Properties	2
	2.3 Commercial Availability	2
	2.4 Production and Import Volumes	2
3.0	PRODUCTION PROCESSES AND ANALYSES	3
4.0	USES	4
5.0	ENVIRONMENTAL OCCURRENCE AND PERSISTENCE	4
6.0	HUMAN EXPOSURE	5
7.0	REGULATORY STATUS	5
8.0	TOXICOLOGICAL DATA	6
	8.1 General Toxicology	6
	8.1.1 Human Data	6
	8.1.2 Chemical Disposition, Metabolism, and Toxicokinetics	6
	8.1.3 Acute Exposure	7
	8.1.4 Short-Term and Subchronic Exposure	9
	8.1.5 Chronic Exposure	9
	8.2 Reproductive and Teratological Effects	9
	8.3 Carcinogenicity	9
	8.4 Genetic Toxicity	9
	8.5 Immunotoxicity	9
9.0	STRUCTURE-ACTIVITY RELATIONSHIPS	9
10.0	ONLINE DATABASES AND SECONDARY REFERENCES	10
	10.1 Online Databases	10
	10.2 Secondary References	11
11.0	REFERENCES	11
12.0	REFERENCES CONSIDERED BUT NOT CITED	13
ACK	NOWLEDGEMENTS	15

TABLES

Table 1	EPA-Approved Test Methods for Bis(2-chloroethoxy)methane	3
Table 2	Regulations Relevant to Bis(2-chlorethoxy)methane	5
Table 3	Acute Toxicity Values for Bis(2-chloroethoxy)methane	7
Table 4	Acute Exposure to Bis(2-chloroethoxy)methane	8

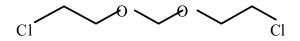
1.0 BASIS FOR NOMINATION

Bis(2-chloroethoxy)methane was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing.

2.0 INTRODUCTION

Bis(2-chloroethoxy)methane

[111-91-1]



2.1 Chemical Identification

Bis(2-chloroethoxy)methane ($C_5H_{10}Cl_2O_2$; mol. wt. = 173.04) is also called:

Dichloroethyl formal Dichlorodiethyl formal Ethane, 1,1 -[methylenebis(oxy)]bis[2-chloro-1,1 -[Methylenebis(oxy)]bis(2-chloroethane) Bis(2-chloroethoxy)methane Bis(2-chloroethyl)formal Bis(β -chloroethyl)formal Formaldehyde bis(β -chloroethyl) acetal Formaldehyde bis(2-chloroethyl) acetal 2,2-Dichloroethyl formal Di(2-chloroethyl) acetal

(NIST, 1998; HSDB, 1998)

Property	Information	Reference
Physical State	colorless liquid	Anon. (1986); Lewis (1993)
Flash Point (open cup)	230°C (110.0°F)	HSDB (1998)
Freezing Point (°C)	-32.8	Anon. (1986); Lewis (1993)
Boiling Point (°C)	218.1	Anon. (1986); Lewis (1993)
Specific Gravity (20°C/20°C)	1.2339	Anon. (1986); Lewis (1993)
Solubility (ppm in water @	78,000-81,000	Anon. (1986); Lewis (1993)
25°C)		
Vapor Pressure (mm Hg @ 25°C)	0.1	HSDB (1998)
Slightly Soluble in:	water	Anon. (1986); Lewis (1993)

2.2 Physical-Chemical Properties

Bis(2-chloroethoxy)methane is classified as a haloether. It is a colorless liquid that is heavier than water. In water, it can be decomposed by mineral acids (Lewis, 1993). Toxic chloride fumes are formed on contact with acid or acid fumes (Sax, 1984). Hydrolysis is relatively slow, with a minimum calculated half-life in pure water of six months to several years (pH=7 and 25°C) (HSDB, 1998). Haag and Mill (1989) showed that the minimum half-life of bis(2-chloroethoxy)methane in water was two years. Hydrolysis can occur at two sites on the molecule: the carbon-oxygen bonds of the acetal linkage and the carbon-chloride bonds (HSDB, 1998). The maximum calculated hydrolytic half-life is in the order of thousands of years for the acetal linkage and approximately six months for the carbon-chloride bonds.

Bis(2-chloroethoxy)methane is slightly flammable when exposed to heat or flame (Sax, 1984). Upon thermal decomposition, hydrogen chloride fumes are released.

2.3 Commercial Availability

In the United States, bis(2-chloroethoxy)methane is manufactured by Morton International, Inc. (Moss Point, MS) (Anon., 1986; HSDB, 1998). It is supplied by Chem Service, Inc. (West Chester, PA), Protocol Analytical Supplies, Inc. (Middlesex, NJ), Supelco, Inc. (Bellefonte, PA), ICN Biomedicals, Inc. (K&K Rare & Fine Chemicals) (Costa Mesa, CA), Karl Industries (Sapon Laboratories Division) (Aurora, OH), and Pfaltz & Bauer, Inc. (Waterbury, CT) (CSI, 1998).

No information on the technical purity of bis(2-chloroethoxy)methane was found; however, ethylene chlorohydrin is the main impurity and must be removed prior to the production of polysulfide polymers because it terminates chain polymerization (HSDB, 1998).

2.4 Production and Import Volumes

Approximately 10 to 50 million pounds of bis(2-chloroethoxy)methane were produced in the United States in 1977 (HSDB, 1998). No current data on import volumes were located.

3.0 PRODUCTION PROCESSES AND ANALYSES

Bis(2-chloroethoxy)methane is produced by the reaction of ethylene chlorohydrin and formaldehyde under acid catalysis (Grayson, 1984). The reaction is as follows:

 $\begin{array}{rl} & H^{+} \\ 2 \ \text{ClCH}_{2} \ \text{CH}_{2} \text{OH} + \text{HCHO} & \rightarrow & \text{Cl CH}_{2} \ \text{CH}_{2} \text{OCH}_{2} \text{O} \ \text{CH}_{2} \text{CH}_{2} \text{Cl} + H_{2} \text{O} \end{array}$

Bis(2-chloroethoxy)methane can be analyzed by the EPA-approved test methods listed in **Table 1**.

EPA Method	Test Type	Samples Analyzed	Detection Limit	Additional Information
611	Gas Chromatography	Municipal and industrial discharges	0.3 µg/L	 for analysis of haloethers precision of 0.33 times the average recovery + 0.11 working range is 1.0 to 626 μg/L
625	Gas Chromatography/ Mass Spectrometry (GC/MS)	Municipal and industrial discharges	5.3 μg/L	 for Acid/Base/Neutral extractables precision of 0.26 times the average recovery + 2.01 working range is 5 to 1300 μg/L
8250	GC/MS	Solid waste matrixes Soils Ground water	5.3 μg/L	 for analysis of most neutral, acidic and basic organic compounds soluble in methylene chloride standard deviation of 34.5 µg/L working range is 49.2 to 154.7 µg/L
8270	GC/MS	Solid waste matrixes Soils Ground water	10.0 μg/L	 for analysis of most neutral, acidic and basic organic compounds soluble in methylene chloride initial precision of 27 µg/L accuracy of 43 to 153 µg/L

 Table 1. EPA-Approved Test Methods for Bis(2-chloroethoxy)methane

Source: HSDB, 1998.

3

Because EPA Methods 611 and 625 are based on liquid-liquid extraction, they may result in sample loss due to the number of extraction/concentration procedures (Huang et al., 1997). Recovery percentages for haloethers can range from 40 to 80% with standard liquid-liquid extraction. Greater precision and lower detection limits were achieved utilizing the technique of solid phase micro-extraction (SPME).

Column retention times are usually used for determining the presence of chemical substances in a sample analyzed by gas chromatography; however, it has been shown that the emergence temperature can also be useful in identifying a chemical substance (Saxton, 1987). Saxton showed the emergence temperature of bis(2-chloroethoxy)methane to be 100.9° C, using programmed temperature gas chromatography (PTGC) with a methyl silicone column.

4.0 **USES**

Most of the bis(2-chloroethoxy)methane produced is used by Morton International Inc. as the starting compound to produce polysulfide elastomers (HSDB, 1998). Over 95% of polysulfide polymers are made from bis(2-chloroethoxy)methane and sodium polysulfide. These polysulfides are used extensively in a variety of sealant applications because of their resistance to degradation by many solvents and resistance to high temperatures (Vietti and Scherrer, 1992). Bis(2-chloro-ethoxy)methane is also used as a solvent (HSDB, 1998).

5.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Bis(2-chloroethoxy)methane is not believed to occur naturally (HSDB, 1998). Its release can occur by volatilization during its manufacture and formulation in polysulfides, or through its use as a solvent. Bis(2-chloroethoxy)methane was found (levels not provided) in the industrial wastes of metal finishing, plastics, chemical manufacturers, and steam electric power industries that discharge effluents to the combined sewerage system along the lower Passaic River in New Jersey (Shear et al., 1996).

The volatility of bis(2-chloroethoxy)methane does not contribute significantly to its environmental fate in water (HSDB, 1998). It is estimated that in a model pond, the half-life of

4

bis(2-chloroethoxy)methane would be 11 years. This is compared to a half life of 0.5 to 2.0 years for other similar haloethers. Bis(2-chloroethoxy)methane has been detected in water from inland waterways (Van Steenderen et al., 1987). Samples taken from a synthetic rubber plant s treated effluent revealed bis(2-chloroethoxy)methane levels of 140 mg/L (Webb et al., 1973). In the Chef Menteur River that flows from Lake Pontchartrain, Louisiana, to the Gulf of Mexico, clams had tissue levels (12 ng/g (ppb), wet weight)of bis(2-chloroethoxy)methane, even though the chemical was not detected in the lake s sediment samples (McFall et al., 1985). Bis(2-chloroethoxy)-methane was not detected in fish taken from fourteen Lake Michigan tributaries (Camanzo et al., 1987).

In soil, bis(2-chloroethoxy)methane is estimated to have a K_{oc} range of 7-115, suggesting that it is mobile to highly mobile. Because it has a vapor pressure of 1.4 x 10⁻⁴ and a Henry s Law constant of $1.7^{\circ}x^{\circ}10^{-7}$, volatilization from dry soil should occur slowly and volatilization from moist soil should not occur at all (HSDB, 1998). In normal soil (without the addition of sludge), bis(2-chloroethoxy)methane is predicted to not be taken up by plant roots or foliage; however, it may translocate through plants and be taken up by animals (Duarte-Davidson and Jones, 1996). Sludge may act to increase the organic matter content of soil, therefore reducing the amount of the compound volatilized and available for root and foliage uptake. GC/MS analysis of plants grown in sludge-treated coal refuse showed that they contained less than the minimum detection limit of 4 mg/kg dry weight of bis(2-chloroethoxy)methane (Webber et al., 1994).

Biodegradation is not a significant environmental fate of bis(2-chloroethoxy)methane (HSDB, 1998); however, one possible source of biodegradation or bioremediation of bis(2-chloroethoxy)methane in water has been suggested by Musafija-Jeknic and Hyman (1997). Their studies show that the bacterium, *Nitrosomonas europea*, can co-metabolically oxidize bis(2-chloroethoxy)methane via ammonia monooxygenase. A study by Patterson and Kodukala (1981) showed that when the influent of a sludge treatment facility was spiked with 0.24 g/L of bis(2-chloroethoxy)methane, 60% of the pollutant was removed.

In the atmosphere, bis(2-chloroethoxy)methane has an estimated half-life of 10 hours when reacted with photochemically produced hydroxy radicals (HSDB, 1998). Degradation by photolysis is not an important fate process in the atmosphere or in surface waters since bis(2chloroethoxy)methane does not contain chromophores that absorb light in the visible or ultraviolet regions of the electromagnetic spectrum.

6.0 HUMAN EXPOSURE

No human exposure data are available; however, it is believed to be limited to industrial sites where the production and use of bis(2-chloroethoxy)methane occurs (HSDB, 1998).

7.0 **REGULATORY STATUS**

U.S. government regulations pertaining to bis(2-chloroethoxy)methane are summarized in

6410 B

Table 2.

	8		•	
	Regulation	Summary of Regulation		
D O E	10 CFR Part 40	Bis(2-chloroethoxy)methane is listed as a hazardous constituent of groundwater in an Appendix table. The table identifies the constituents for which standards must be set and complied with if the specific constituent is reasonably expected to be in or derived from the byproduct material and has been detected in ground water.		
E P A	40 CFR Part 136	This section establishes guidelines for the analysis of pollutants and provides conditions and limits for the analysis of bis(2-chloroethoxy)methane by GC/M Test Type EPA Method Number GC 611 GC/MS 625, 1625		

 Table 2. Regulations Relevant to Bis(2-chlorethoxy)methane

Table 2. Regulations Relevant to Bis(2-chloroethoxy)methane (Continued)

Standard Method

	Regulation	Summary of Regulation		
E P A	40 CFR Part 264	Chemical storage units must be decontaminated at the close of use. The most reliable means of detection, approved by the EPA, is given along with the limits of detection for each test. Specific details about each test are contained in the EPA publication SW846. Bis (2-chlorethoxy)methane is best detected by GC/MS method 8270. The lowest concentration of analytes that can be reliably tested by this method is 10 mg/L.		
	40 CFR Part 258	Establishes criteria for pollutants in municipal solid waste landfills under the Resource Conservation and Recovery Act (RCRA) to ensure human health and safety. EPA approved methods of detection for bis(2-chloroethoxy)methane are 8110 and 8270. Their respective limits of detection are 5 and 10 mg/L.		

40 CFR Part 268.48	Establishes limits of pollutants in wastewater and non-wastewater. Bis(2- chloroethoxy)methane has a wastewater standard of 0.036 mg/L and a non- wastewater standard of 7.2 mg/kg. Exceeding these limits invokes non-compliance with the treatment standards set forth in Sec. 268.2(i). These limits were changed in 1994 (62 FR Part 7502; Feb. 19, 1994) to 0.036 mg/L ² and 7.2 mg/kg ³ .
40 CFR Part 302	Identifies substances that are considered hazardous under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980. The statutory source for this designation is Sec. 311(b)(4) of the Clean Water Act (CWA). The reportable quantity for bis(2-chloroethoxy)methane is 1000 pounds (454 kg) and the RCRA waste number is U024.
40 CFR Part 372	This section regulates the reporting of toxic chemical releases and the communities right-to-know. Bis(2-chloroethoxy)methane was added to the list of chemicals that fall under this regulation in January 1, 1994.
40 CFR Part 799.5055 Subpart D	Identifies chemical substances that are to be tested and the method of detection under the Toxic Substances Control Act (TSCA). For bis(2-chloroethoxy)- methane, two tests are required by the regulation. Testing is to be conducted on bis(2-chloroethoxy)methane to determine hydrolysis as a function of pH at 25°C. Also, an oral gavage subchronic toxicity test shall be conducted in the rat in accordance with 40 CFR Part 798.2650.

Source: CPI, 1998.

8.0 TOXICOLOGICAL DATA

8.1 General Toxicology

8.1.1 Human Data

No data on the effects of bis(2-chloroethoxy)methane in humans were located. Exposure can occur by inhalation, ingestion, and dermal contact (Radian, 1991) and symptoms can include skin and eye irritation (HSDB, 1998).

8.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No data on chemical disposition, metabolism, or toxicokinetics were located.

8.1.3 Acute Exposure

 LD_{50} values for bis(2-chloroethoxy)methane are presented in **Table 3**. The details of studies discussed in this section are presented in **Table 4**.

7

Route	Species (sex and strain)	LD_{50}	Reference				
Oral	Rat (sex n.p., Sherman)	$LD_{50} = 65 \text{ mg/kg} (0.38 \text{ mmol/kg})$	Smyth and Carpenter (1948)				
Dermal	Guinea Pig (sex and strain n.p.)	$LD_{50} = 170 \text{ mg/kg} (0.98 \text{ mmol/kg})$	Smyth and Carpenter (1948)				
Non-mam	Non-mammalian Species						
N/A Daphnia magna (Straus) and Pimephales promelas (Rafinesque)		48-h LD ₅₀ = 201 mg/L (1.16 mmol/L) in <i>D. magna</i> ; 96-h LD ₅₀ = 184 mg/L (1.06 mmol/L) in <i>P. promelas</i>	Gersich and Mayes (1986)				

 Table 3. Acute Toxicity Values for Bis(2-chloroethoxy)methane

Abbreviations: n.p. = not provided; N/A = not applicable; h = hour; LD_{50} = dose lethal to 50% of test animals.

Little data are available on the effects of bis(2-chloroethoxy)methane in animals. In a 4-hour inhalation study, 0 of 6 rats died when exposed to 60 ppm (425 mg/m³; 2.46 mmol/m³) and 6 of 6 rats died when exposed to 120 ppm (850 mg/m³; 4.91 mmol/m³) (Smyth and Carpenter, 1948). In another 4-hour study, 4 of 6 rats exposed to 62 ppm (440 mg/m³; 2.5 mmol/m³) bis(2-chloroethoxy)methane died; no other signs or symptoms of exposure were observed (Carpenter et al., 1949). A single oral dose of 60 mg/kg (0.35 mmol/kg) killed 2 of 5 female rats (Bio/dynamics, 1990). In the same study, it was also found that bis(2-chloroethoxy)methane was lethal at a concentration of 100 mg/mL (0.58 mmol/mL) following a single oral dose but essentially non-toxic at 10 mg/mL (0.06 mmol/mL). Bis(2-chloroethoxy)methane (0.5 mL, undiluted) was not irritating to the corneas of rabbits in an ocular toxicity study (Carpenter and Smyth, 1946).

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/ Observation Period	Results/Comments	Reference
Rat						
Rat, Albino Sherman, age n.p.	6 M or F per dose	bis(2-chloro- ethoxy)methane, purity n.p.	Inhalation: 60 and 120 ppm (425 and 850 mg/m ³ ; 2.46 and 4.91 mmol/m ³)	4 h exposure, observation period n.p.	0/6 rats died following exposure to 60 ppm. 6/6 rats died following exposure to 120 ppm.	Smyth and Carpenter (1948)
Rat, Albino Sherman, age n.p.	6 M or F	bis(2-chloro- ethoxy)methane, purity n.p.	Inhalation: 62 ppm (440 mg/m ³ ; 2.5 mmol/m ³)	4 h exposure, observation period n.p.	4/6 rats died. No other symptoms were reported.	Carpenter et al. (1949)
Rat, Sprague- Dawley CD, age n.p.	5 F	bis(2-chloro- ethoxy)methane, purity n.p.	Oral: 60 mg/kg (0.35 mmol/kg)	Single dose, observation period n.p.	2/5 rats died.	Bio/dynamics (1990)
	3 M and 3 F per dose		Oral: 10 or 100 mg/mL (0.06 or 0.58 mmol/mL)	Single dose, 24 h observa- tion period	All rats receiving 100 mg/mL died within 24 h of dosing. All rats receiving 10 mg/mL survived and exhibited no abnormalities within 24 h of dosing.	
Rabbit						
Rabbit, strain and age n.p.	5, sex n.p.	bis(2-chloro- ethoxy)methane, purity n.p.	Ocular: 0.5 mL, undiluted	Single dose, 24 h observa- tion period	Essentially non-irritating to the cornea (Grade 1).	Carpenter and Smyth (1946)

 Table 4. Acute Exposure to Bis(2-chloroethoxy)methane

Abbreviations: F = female; h = hour(s); M = male; n.p. = not provided.

8.1.4 Short-Term and Subchronic Exposure

In a subchronic, 3-month, oral toxicity study, Sprague-Dawley rats were given daily oral doses of 10, 20, 40, 80, and 120 mg/kg (0.06, 0.12, 0.23, 0.46, and 0.69 mmol/kg) bis(2-chloroethoxy)methane for at least 90 days (Bio/dynamics, 1989). Of the 20 rats that received the highest dose (120 mg/kg/day; 0.69 mmol/kg/day), all ten males and seven of ten females died or were killed in a moribund condition during the study. One death occurred after a single dose and seven more occurred during the first week. One female in the 80 mg/kg/day dose group died on day 78. No deaths were observed in the 10, 20, or 40 mg/kg/day dose groups. Rats that died exhibited emaciation, poor food consumption, hypothermia, lethargy/prostration, dyspnea, gasping, moist rales, ataxia, abnormal posture, slight tremors, salivation, and brown-yellow stains on the snout, paws, ventral surface, and anogenital area. Examination revealed degeneration of the myocardium in all animals that died after day 14; this was considered to be a possible cause of death.

8.1.5 Chronic Exposure

No data on chronic exposure were located.

8.2 Reproductive and Teratological Effects

No data on reproductive or teratological effects were located.

8.3 Carcinogenicity

No data on carcinogenicity were found. The EPA classified bis(2-chloroethoxy)methane as D which means that it is not classifiable as to human carcinogenicity because of the lack of human and animal carcinogenicity data (IRIS, 1998).

8.4 Genetic Toxicity

No genetic toxicity data were found.

8.5 Immunotoxicity

No immunotoxicity data were located.

9.0 STRUCTURE-ACTIVITY RELATIONSHIPS

The reactivity of chlorinated alkyl ethers, such as bis(2-chloroethoxy)methane, bis 2chloroethyl ether (BCEE), 2-chloroethyl vinyl ether (CEVE), and bis chlororisopropyl ether (BCIE), was observed to be essentially the same as their non-chlorinated analogs in a study by Musafija-Jeknic and Hyman (1997). Bis(2-chloroethoxy)methane, BCEE, and CEVE inhibited nitrite production from ammonia, while BCIE had no effect on this activity. Their equivalent non-chlorinated ethers showed the same inhibition pattern.

10.0 ONLINE DATABASES AND SECONDARY REFERENCES

10.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System) TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Kirk-Othmer Encyclopedia of Chemical Technology

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS	EMBASE	Registry
CANCERLIT	HSDB	RTECS
CAPLUS	MEDLINE	TOXLINE
CHEMLIST		

TOXLINE includes the following subfiles:

T ''' D'11' 1	TOVDID
Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989	ETIC
by DART)	
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet

Integrated Risk Information System (IRIS) [http://www.epa.gov/ngispgm3/iris].

In-House Databases

CPI Electronic Publishing Federal Databases on CD, 1998 Current Contents on Diskette 7 The Merck Index, 1996, on CD-ROM

10.2 Secondary References

Anon. 1986. Hazardous materials: Bis(beta-chloroethyl)formal. Dangerous Properties of Industrial Materials Report 6(3):44-46.

Grayson, M. (ed). 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed. Volume 18. New York: John Wiley and Sons., p. 815.

Lewis R. J. 1993. Hawley s Condensed Chemical Dictionary. New York: Van Nostrand

Reinhold Co., p. 380.

Radian Corporation. 1991. Bis(2-chloroethoxy)methane. NTP Chemical Repository. Internet address: http://ntp-db.niehs.nih.gov/NTP_Re_H&S/NTP_Chem1/Radian111-91-1.txt.

Sax, N. I. 1984. Dangerous Properties of Industrial Materials. 6th ed. New York: Van Nostrand Reinhold, p. 459.

11.0 REFERENCES

Bio/dynamics, Inc. 1990. An oral range-finding study in rats with formal [bis(2-chloroethoxy)methane]. Project No. 88-3386. East Millstone, NJ, p. 22.

Bio/dynamics, Inc. 1989. A subchronic (3 month) oral toxicity study in the rat with formal [bis(2-chloroethoxy)methane]. Project No. 88-3429. East Millstone, NJ, p. 22.

Camanzo, J., C. P. Rice, D. J. Jude, and R. Rossmann. 1987. Organic priority pollutants in nearshore fish from 14 Lake Michigan tributaries and embayments, 1983. J. Great Lakes Res. 13:296-309.

Carpenter, C. P., H. F. Smyth, and U. C. Pozzani. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Tox. 31(6):343-346.

Carpenter, C. P., and H. F. Smyth. 1946. Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29:1363-1372.

Chemical Sources International (CSI). 1998. Chem Sources USA. 1998. Pendelton, SC: Chemical Sources International, Inc., p.178.

Duarte-Davidson, R., and K.C. Jones. 1996. Screening the environmental fate of organic contaminants in sewage sludge applied to agricultural soils. II. The potential for transfers to plants and grazing animals. Sci. Total Environ. 185:59-70.

Gersich, F. M., and M. A. Mayes. 1986. Acute toxicity tests with *Daphnia magna* Straus and *Pimephales promelas* Rafinesque in support of national pollutant discharge elimination permit requirements. Water Res. 20(7):939-941.

Haag, W. R., and T. Mill. 1989. Hydrolysis kinetics of bis(2-chloroethoxy)methane. SRI Project No. 6877-1. Menlo Park, CA, p. 20.

Huang, S. D., C. Y. Ting, and C. S. Lin. 1997. Determination of haloethers in water by solid-phase microextraction. J. Chromatogr. A 769:239-246.

McFall, J. A., S. R. Antoine, and I. R. DeLeon. 1985. Base-neutral extractable organic pollutants in biota and sediments from Lake Pontchartrain. Chemosphere 14(10):1561-1569.

Musafija-Jeknic, T., and M. Hyman. 1997. Co-metabolic degradation of chlorinated ethers by *Nitrosamonas europea*. 97th General Meeting of the General Society for Microbiology, Miami Beach Florida, USA, May 4-8, 1997. Abstracts of the General Meeting of the Society of Microbiology 97:473.

National Institute of Standards and Technology (NIST). 1998. Methane, bis(2-chloroethoxy)-. NIST Standard Reference Data Program On-line database. [http://webbook.nist.gov/cgi/].

Patterson, J. W., and P. S. Kodukala. 1981. Emissison and effluent control: biodegradation of hazardous organic pollutants. Chem. Eng. Prog. 77:48-55.

Saxton, W. L. 1987. Emergence temperature indices and relative retention times of pesticides and industrial chemicals determined by linear programmed temperature gas chromatography. J. Chromatogr. 393(2):175-194.

Shear, N. M., C. W. Schmidt, S. L. Huntley, D. W. Crawford, and B. L. Finley. 1996. Evaluation of the factors relating combined sewer overflows with sediment contamination of the lower Passaic River. Marine Pollut. Bull. 32(3):288-304.

Smyth, H. F., and C. P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30(1):63-64.

Van Steenderen, R. A., S. J. Theron, and A. J. Hassett. 1987. The occurrence of organic micropollutants in the Vaal River between Grootraai Dam and Parys. Water S A (Pretoria). 13(4):209-214.

Vietti, D., and M. Scherrer. 1992. Polysulfides. In: J. I. Kroschwitz (ed). Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed. Volume 19. New York: John Wiley and Sons, p. 933-944.

Webb, R. G., A. W. Garrison, L. H. Keith, and J. M. McGuire. 1973. Current Practice in GC/MS Analysis of Organics in Water. Project No. 16020GHP. EPA Report No. EPA-R2-73-77. U.S. Environmental Protection Agency, Washington, D.C., p. 65

Webber, M. D., R. I. Pietz, T. C. Granato, and M. L. Svoboda. 1994. Plant uptake of PCBs and other organic contaminants from sludge-treated coal refuse. J. Environ. Qual. 23(5):1019-1026.

12.0 REFERENCES CONSIDERED BUT NOT CITED

Bennett, G. F. 1989. Impact of toxic chemicals on local wastewater treatment plant and the environment. Environ. Geol. Water. Sci. 13(3):201-212.

DeVault, D. S. 1985. Contaminants in fish from Great Lakes harbors and tributary mouths. Arch. Environ. Contam. Toxicol. 14(5):587-594.

Donnelly, J. R., M. S. Abdel-Hamid, and J. L. Jeter. 1993. Application of gas chromatographic retention properties to the identification of environmental contaminants. J. Chromatogr. 642(1-2):409-415.

Drinkwater, L. A., J. Zoltek, and J. J. Delfino. 1986. Bench scale treatability of leachate from an abandoned phenolic waste site. J. Water Pollut. Control Fed. 58(11):1057-1065.

Eichelberger, J. W., T. A. Bellar, J. P. Donnelly, and W. L. Budde. 1990. Determination of volatile organics in drinking water with USEPA method 524.2 and the ion trap detector. J. Chromatogr. Sci. 28(9):460-467.

Garman, J. R., T. Freund, E. W. Lawless. 1987. Testing for groundwater contamination at hazardous waste sites. J. Chromatogr. Sci. 25(8):328-337.

Gersich, F. M., and P. G. Murphy. 1984. The static acute toxicity of bis(2chloroethoxy)methane, Dinoset, aniline, p-chloro-m-cresol, and Silvex to the water flea, *Daphnia magna* Straus. Report ES-721. Midland, MI: Dow Chemical U.S.A.

Glidden Coatings and Resins. 1980. Priority pollutant investigation report. Report HK-239. Charlotte, NC: Glidden Coatings and Resins.

Gurka, D. F., and S. M. Pyle. 1988. Qualitative and quantitative environmental analysis by capillary column gas chromatography/lightpipe fourier transform infrared spectrometry. Environ. Sci. Technol. 22(8):963-967.

Hall, L. W., A. E. Pinkney, L. O. Horseman, and S. E. Finger. 1985. Mortality of striped bass larvae in relation to contaminants and water quality in a Chesapeake Bay tributary. Trans. Am. Fish. Soc. 114:861-868.

Hess, G. G. 1986. Selective preconcentration of polynuclear aromatic hydrocarbons and polychlorinated biphenyls by *in situ* metal hydroxide precipitation. J. Chromatogr. 366:197-204.

Kiang, P. H., and R. L. Grob. 1986. Development of a screening method for the determination of 49 priority pollutants in soil. J. Environ. Sci. Health A21(1):15-53.

Lega, R., G. Ladwig, O. Meresz, R. E. Clement, G. Crawford, R. Salemi, and Y. Jones. 1997. Quantitative determination of organic priority pollutants in sewage sludge by GC/MS. Chemosphere 34(8):1705-1712.

Lopez-Avila, V., R. Young, and N. Teplitsky. 1996. Microwave-assisted extraction as an alternative to soxhlet, sonication, and supercritical fluid extraction. J. AOAC Int. 79(1):142-156.

Lopez-Avila, V., W. F. Beckert, and S. Billets. 1991. Supercritical fluid extraction and its application to environmental analysis. In: Friedman, D. (ed). 1991. Waste Testing and Quality Assurance: Vol. 3. ASTM STP 1075. Philadelphia, PA: American Society for Testing and Materials.

Lopez-Avila, V., N. Heath, and A. Hu. 1987. Determination of purgeable halocarbons and aromatics by photoionization and hall electrolytic conductivity detectors connected in series. J. Chromatogr. Sci. 25(8):356-363.

Louter, A. J. H., C. A. van Beekvelt, P. Cid Montanes, J. Slobodnik, J. J. Vreuls, and U. A. T. Brinkman. 1996. Analysis of microcontaminants in aqueous samples by fully automated on-line solid-phase extraction-gas chromatography-mass selective detection. J. Chromatogr. A. 725(1):67-83.

Mayes, M. A., and E. A. Bartlett. 1984. The static acute toxicity of bis(2chloroethoxy)methane and 2-sec-butyl-4,6-dinitrophenol (Dinoseb) to the fathead minnow, *Pimephales promelas* Rafinesque. Midland, MI: Dow Chemical USA, p.12.

McCabe, A. 1990. Microorganisms in nuclear waste disposal part I: The potential significance of microbial activity in radioactive waste disposal. Experientia 46(8):779-787.

Paola, V., B. Antonella, N. Giancarlo, and L. A. Gino. 1993. Detection of mutagenic pollutants of inland and coastal waters by means of the *Salmonella*/microsome assay. Environ. Technol. 14(6):543-553.

Pax us, N., P. Robinson, and P. Balm r. 1992. Study of organic pollutants in municipal wastewater in G teborg, Sweden. Water Sci. Tech. 25(11):249-256.

Plumb, R. H. 1991. The occurrence of Appendix IX organic constituents in disposal site ground water. Ground Water Monit. Rev. 11(2):157-164.

Popisil, P. A., M. F. Marcus, and M. A. Kobus. 1991. The application of supercritical fluid capillary chromatography to the analysis of Appendix VIII and IX compounds. In: Friedman, D. (ed). 1991. Waste Testing and Quality Assurance: Vol 3. ASTM STP 1075. Philadelphia, PA: American Society for Testing and Materials.

Rosenfeld, J. K., and R. H. Plumb. 1991. Ground water contamination at wood treatment facilities. Ground Water Monit. Rev. 11(1):133-140.

Sauter, A. D., and L. D. Betowski. 1983. Comparison of priority pollutant response factors for triple and single quadrupole mass spectrometers. Anal. Chem. 55(1):116-119.

Schwartz, B. S., D. P. Ford, K. I. Bolla, J. Agnew, N. Rothman, and M. L. Bleecker. 1990. Solvent-associated decrements in olfactory function in paint manufacturing workers. Am. J. Ind. Med. 18(6):697-706.

Sorini, S. S., and L. P. Jackson. 1988. Evaluation of the toxicity characteristic leaching procedure (TCLP) on utility wastes. Nucl. Chem. Waste Manage. 8:217-223.

Telliard, W. A. 1990. Broad-range methods for determination of pollutants in wastewater. J. Chromatogr. Sci. 28(9):453-459.

Theobald, N., W. Lange, W. G hlert, and F. Renner. 1995. Mass spectrometric investigations of water extracts of the river Elbe for the determination of potential inputs of pollutants into the North Sea. Fresenius J. Anal. Chem. 353(1):50-56.

ACKNOWLEDGEMENTS

Support to the National Toxicology Program for the preparation of Bis(2-

chloroethoxy)methane Review of Toxicological Literature was provided by Integrated

Laboratory Systems, Inc., through NIEHS Contract Number N01-ES-65402. Contributors

included: Raymond R. Tice, Ph.D. (Principal Investigator); Brigette D. Brevard, M.A. (Co-

Principal Investigator); Esther Morris, M.S., and John Winters, B.S.

APPENDIX A. UNITS AND ABBREVIATIONS

°C = degrees Celsius

 $\mu g/L = micrograms per liter$

 $\mu g/m^3 =$ micrograms per cubic meter

 $\mu g/mL = micrograms per milliliter$

 $\mu M = micromolar$

BCEE = bis 2-chloroethyl ether

BCIE = bis chloroisopropyl ether

CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act

CEVE = 2-chloroethyl vinyl ether

CWA = Clean Water Act

d = day(s)

DOE = U. S. Department of Energy

EPA = U.S. Environmental Protection Agency

F = female

g = grams

g/mL = grams per milliliter

GC/MS = gas chromatography/mass spectrometry

h = hour(s)

Hg = mercury

kg = kilograms

 LC_{50} = lethal concentration for 50% of test animals

 LD_{50} = lethal dose for 50% of test animals

M = male

mg/kg = milligrams per kilogram

 $mg/m^3 = milligrams$ per cubic meter

mg/mL = milligrams per milliliter

mL/kg = milliliters per kilogram

mm = millimeters

mM = millimolar

mmol = millimoles

- mmol/kg = millimoles per kilogram
- mo = month(s)
- N/A = not applicable
- n.p. = not provided
- ng/g = nanograms/gram
- ppb = parts per billion
- ppm = parts per million
- PTGC = programmed temperature gas chromatography
- RCRA = Resource Conservation and Recovery Act
- SPME = solid phase micro-extraction
- TSCA = Toxic Substances Control Act