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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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May, 1987

HEALTH EFFECTS ASSESSMENT FOR BIS(2-CHLOROETHYL)ETHER

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DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with bis(2-chloroethyl)ether. All estimates of acceptable intake and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Chloroalkyl Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-030. NTIS PB 81-117418.

U.S. EPA. 1980b. Hazard Profile for Bis(2-chloroethyl)ether. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Bis(2-chloroethyl)ether was carcinogenic in orally exposed mice, associated with an increased incidence of hepatomas. The EPA weight of evidence classification for carcinogenicity is Group B2 because of strong response in mice and supporting mutagenicity findings. The U.S. EPA (1980a) derived a q_1^* of 1.1 $(mg/kg/day)^{-1}$ from the study in mice. This q_1^* is adopted for the purposes of this document. Because the chemical is a carcinogen in animals, it is inappropriate to derive RfD_S and RfD values.

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LIST OF ABBREVIATIONS

CS	Composite score
ppm	Parts per million
STEL	Short-term exposed level
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

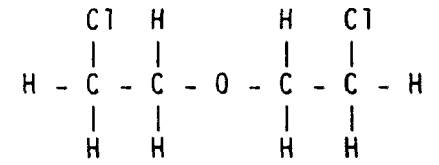
The relevant physical and chemical properties and environmental fate of bis(2-chloroethyl)ether are presented in Table 1-1. Synonyms for bis-(2-chloroethyl)ether are: sym-dichloroethyl ether; 1,1'-oxybis(2-chloro-ethane); ß,ß'-dichloroethyl ether; DCEE and Chlorex.

In the atmosphere, bis(2-chloroethyl)ether is expected to exist primarily in the vapor phase. The atmospheric half-life listed in Table 1-1 is the half-life for the reaction of gaseous bis(2-chloroethyl)ether with photochemically generated hydroxyl radicals. Based on a rate constant of 1.79×10^{-11} cm^3/molecule-sec at 25°C and an ambient hydroxyl radical concentration of 8.0×10^5 molecules/cm^3, a half-life of 13.44 hours has been calculated (U.S. EPA, 1986a). Considering its relatively high water solubility (1.74×10^4 mg/ℓ at 20°C), bis(2-chloroethyl) ether also is likely to be removed by wet deposition from the atmosphere.

The half-life of bis(2-chloroethyl)ether in aqueous and soil systems could not be located in the available literature. In aqueous systems, volatilization and hydrolysis may be important removal mechanisms, although the former process is expected to be much faster than the latter (Callahan et al., 1979). Based on the bioconcentration factor and soil adsorption coefficient, bioaccumulation in aquatic organisms and adsorption to sus-pended solids and sediments should not be significant. In soils with low sorption constant, bis(2-chloroethyl)ether should be mobile and groundwater contamination may occur below solid waste landfills (Wilson et al., 1981; DeWalle and Chian, 1981). Based on its vapor pressure (0.75 mm Hg at 20°C), bis(2-chloroethyl)ether should volatilize relatively rapidly from dry soil surfaces.

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Bis(2-Chloroethyl)Ether

Property	Value	Reference
CAS number:	111-44-4	
Chemical class:	aliphatic haloether	
Molecular weight:	143.01	
Chemical Structure:		
Freezing point:	-50°C	ACGIH, 1986
Boiling point:	178.5°C	ACGIH, 1986
Vapor pressure:	0.75 mm Hg (20°C)	Weber et al., 1981
Water solubility:	1.74×10^4 mg/ℓ (20°C) 1.02×10^4 mg/ℓ (temperature unspecified)	Veith et al., 1980 Callahan et al., 1979
Log octanol/water partition coefficient:	1.29	Hansch and Leo, 1985
Bioconcentration factor:	11, bluegill sunfish (Lepomis macrochirus)	Veith et al., 1980
Soil adsorption: coefficient	80, fine sand	Wilson et al., 1981
Half-lives:		
Air	~13 hours	U.S. EPA, 1986a
Water	NA	
Soil	NA	

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Bis(2-chloroethyl)ether appears to be nearly completely absorbed from the gastrointestinal tract of rats. Lingg et al. (1982) administered a 40 mg/kg dose of ^{14}C-bis(2-chloroethyl)ether in corn oil by gavage to adult male Sprague-Dawley rats and measured the radioactivity in expired air excreta, carcass and cage wash at 48 hours posttreatment. Only 2.4% of the administered dose of radioactivity was located in the feces. Total recovery accounted for 80.9% of the administered dose. These data suggest that gastrointestinal absorption was nearly complete.

2.2. INHALATION

Limited data concerning the inhalation absorption of bis(2-chloroethyl) ether were available. Schrenk et al. (1933) reported that exposure to bis (2-chloroethyl)ether in guinea pigs was assoicated with brain, liver and kidney congestion as well as lung congestion. These results suggest some absorption by the respiratory tract.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the oral subchronic toxicity of bis(2-chloroethyl)ether could not be located in the available literature.

3.1.2. Inhalation. Pertinent data regarding the inhalation subchronic toxicity of bis(2-chloroethyl)ether could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Weisburger et al. (1981) gave groups of 26 male and 26 female Charles River CD rats 25 or 50 mg/kg bis(2-chlorethyl)ether by gavage, twice weekly for 18 months, followed by a 6-month observation period. Negative and vehicle controls were also maintained. High-dose females had a higher mortality rate than negative or pooled vehicle controls and survival was unaffected in males. Mean body weights were lower in treated females and high-dose males than in the corresponding controls.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of bis(2-chlorethyl)ether could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenic and reproductive effects after oral administration of bis(2-chlorethyl)ether could not be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding the teratogenic and reproductive effects after inhalation exposure to bis(2-chlorethyl)ether could not be located in the available literatue.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding the toxicant interactions of bis(2-chloroethyl)ether with other chemicals could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity to humans of bis(2-chloroethyl)ether from oral exposure could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity to humans of bis(2-chloroethyl)ether from inhalation could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Innes et al. (1969) gave groups of 18 male and 18 female mice of two different cross strains 100 mg/kg of bis(2-chloroethyl)ether by stomach tube from age 7-28 days and thereafter in the diet at 300 ppm until week 80. The incidence of hepatomas in males of both strains and females of one strain were statistically higher than controls. Details are presented in Table 4-1.

Weisburger et al. (1981) obtained negative results in an oral carcinogenicity assay in which Charles Liver CD rats of both sexes were given 25 and 50 mg/kg/day of bis(2-chloroethyl)ether twice weekly for 18 months, followed by a 6-month observation period. Although the authors suggested that the doses for males were not sufficient to elicit a carcinogenic response, they nonetheless concluded that bis(2-chloroethyl)ether was not carcinogenic in rats.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity to animals of bis(2-chloroethyl)ether from inhalation could not be located in the available literature.

TABLE 4-1

Incidence of Hepatomas in Two Strains of Mice Given Oral Doses of Bis(2-chloroethyl)ether for ~18 months[a]

Strain	Sex	Dose[b] (mg/kg/day)	Tumor Incidence (p value)
Controls[c]		0	8/79
C57Bl/6xC3H/Anf	M	39	14/16 (p<0.01)
Controls[c]		0	0/87
C57Bl/6xC3H/Anf	F	39	4/18 (p<0.01)
Controls[c]		0	5/90
C57Bl/6xAKR	M	39	9/17 (p<0.01)

[a]Source: Innes et al., 1969

[b]Dose as calculated by U.S. EPA (1980a) based on dietary consumption of 300 ppm and assuming a mouse consumes 13% of its body weight as food/day.

[c]Pooled control data were used because statistical tests revealed little heterogeneity among groups.

4.3. OTHER RELEVANT INFORMATION

Bis(2-chloroethyl)ether was negative in qualitative tests. Van Duuren et al. (1972) observed no initiating activity in the 2-stage mouse skin assay using phorbol myristate acetate as a promoter. Weekly subcutaneous injections of 1 mg bis(2-chloroethyl)ether showed a borderline increase ($p>0.05$) in the incidence of injection site sarcomas in exposed female ICR/Ha Swiss mice (Van Duuren et al., 1972). No tumors were detected at sites distant from the injection site. Male mice injected intraperitoneally with bis(2-chloroethyl)ether did not exhibit a pulmonary tumor response significantly different from that of controls (Thiess et al., 1973).

Bis(2-chloroethyl)ether was positive in microbial mutagenicity tests and negative in mammalian test systems. Using different tester strains of Escherichia coli, Salmonella typhimurium and Bacillus subtilis, Shirasu et al. (1975) found bis(2-chloroethyl)ether to be a direct-acting mutagen. Positive results were obtained in S. typhimurium strain TA100 with bis(2-chloroethyl)ether vapors (Simmon et al., 1977). Jorgenson et al. (1977) obtained negative results in mice using the heritable translocation test.

4.4. WEIGHT OF EVIDENCE

The degree of evidence on carcinogenicity of bis(2-chloroethyl)ether in humans is considered inadequate because of the lack of human case reports or epidemiological studies. The degree of evidence in animals is considered sufficient; although bis(2-chloroethyl)ether was not carcinogenic in rats by the oral route (Weisburger et al., 1981), it elicited hepatomas in mice after oral exposure (Innes et al., 1969). Two limitations of the Innes et al. (1969) study are noted. First, an increased tumor incidence was observed in a tumor type (hepatoma) that often occurs spontaneously in

mice. Second, hepatomas in mice are difficult to classify. In the rat study it is difficult to evaluate carcinogenic potential of bis(2-chloroethyl)ether because the exposure was less than a lifetime.

These limitations and negative results obtained in qualitative tests (Van Duuren et al., 1972; Thiess et al., 1973) suggested that the quality of evidence for bis(2-chloroethyl)ether was more appropriately viewed as limited; however, assigning this chemical to Group B2, probable human carcinogen, is appropriate because the incidences observed in the Innes et al. (1969) study were very high (53-88%) and were statistically significantly greater than controls. The supporting details of this study together with the positive mutagenicity findings do not warrant a downgrading of the mouse liver tumor response. Therefore, bis(2-chloroethyl)ether is assigned to EPA Group B2: probable human carcinogen (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1980a) derived the criteria of 0.003, 0.030 and 0.30 µg/ℓ at risk levels of 10^{-7}, 10^{-6} and 10^{-5}, respectively, based on the incidence of hepatomas in strain (C57Bl/6xC3H/Anf)F_1 male mice orally exposed for 80 weeks. In deriving these criteria, a bioconcentration factor of 6.9 was applied and daily consumption of 2 ℓ water and 6.5 g of fish was assumed. NAS (1980) estimated that at a concentration of 1 µg/ℓ, the risk of cancer for both sexes was 8.1×10^{-7}. The upper 95% confidence estimate was 1.2×10^{-6}.

ACGIH (1986) recommended a TLV-TWA of 5 ppm (~30 mg/m³) and a TLV-STEL of 10 ppm (~60 mg/m³) and noted that skin exposure may contribute to overall exposure. OSHA (1985) adopted a ceiling of 15 ppm (90 mg/m³) and also noted that bis(2-chloroethyl)ether may be absorbed through the skin.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). It is inappropriate to derive an RfD_{SO} because bis(2-chloroethyl)ether is a carcinogen.

6.1.2. Inhalation (RfD_{SI}). It is inappropriate to derive an RfD_{SI} because bis(2-chloroethyl)ether is a carcinogen.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). It is inappropriate to derive an RfD_O because bis(2-chloroethyl)ether is a carcinogen.

6.2.2. Inhalation (RfD_I). It is inappropriate to derive an RfD_I because bis(2-chloroethyl)ether is a carcinogen.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. U.S. EPA (1980a) used the linearized multistage model to derive a q_1^* of 1.1 $(mg/kg/day)^{-1}$. The q_1^* was based on a hepatoma incidence of 14/16 ($p<0.01$) in male mice (strain C57Bl/6xC3H/Anf) given 39 mg/kg/day bis(2-chloroethyl)ether for 80 weeks, compared with an incidence of 8/79 in controls. The data used in the derivation of this q_1^* are presented in Table 6-1. Although some of the assumptions and calculations applied in this derivation vary slightly from current methodology (U.S. EPA, 1980c), the q_1^* of 1.1 $(mg/kg/day)^{-1}$ is adopted as the q_1^* for orally exposed humans for the purposes of this document.

6.3.2. Inhalation. Data were insufficient for deriving an inhalation q_1^*.

TABLE 6-1

Cancer Data Sheet for Derivation of a q_1^*

Compound: bis(2-chloroethyl)ether

Reference: Innes et al., 1969

Species/strain/sex: C57Bl/6xC3H/Anf male mice

Route/vehicle: oral: gavage followed by diet

Length of exposure (le) = 560 days

Length of experiment (Le) = 560 days

Lifespan of animal (L) = 560 days

Body weight = 0.03 kg (assumed)

Tumor site and type: hepatomas

Exposure (ppm)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	8/79
300	39	14/16

Unadjusted $q_1^* = 8.6 \times 10^{-2}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 1.1$ $(mg/kg/day)^{-1}$

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