Toxicological Profile for Bis(2-Chloroethyl)Ether (BCEE)

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
December 1989	Final toxicological profile released
July 2009	Addendum to the toxicological profile released
October 2017	Update of data in Chapters 2, 3, and 7

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Bis(2-Chloroethyl)Ether (BCEE)* was released in 1989. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

Bis(2-chloroethyl)ether (BCEE; CAS Number 111-44-4) is a colorless non-flammable liquid. BCEE is manufactured for use in the production of pesticides and other chemicals. BCEE is soluble in water and will slowly evaporate from water and soil. The most likely source of exposure for the general population is from contaminated drinking water. Populations living near facilities manufacturing or using BCEE may also be exposed via contaminated air.

1.2 SUMMARY OF HEALTH EFFECTS

A small number of studies (<10) have evaluated the toxicity of BCEE following inhalation, oral, or dermal exposure. All but one of these studies were conducted in laboratory animals. Most studies examined a limited number of potential endpoints; one intermediate-duration inhalation study examined a wide range of potential targets.

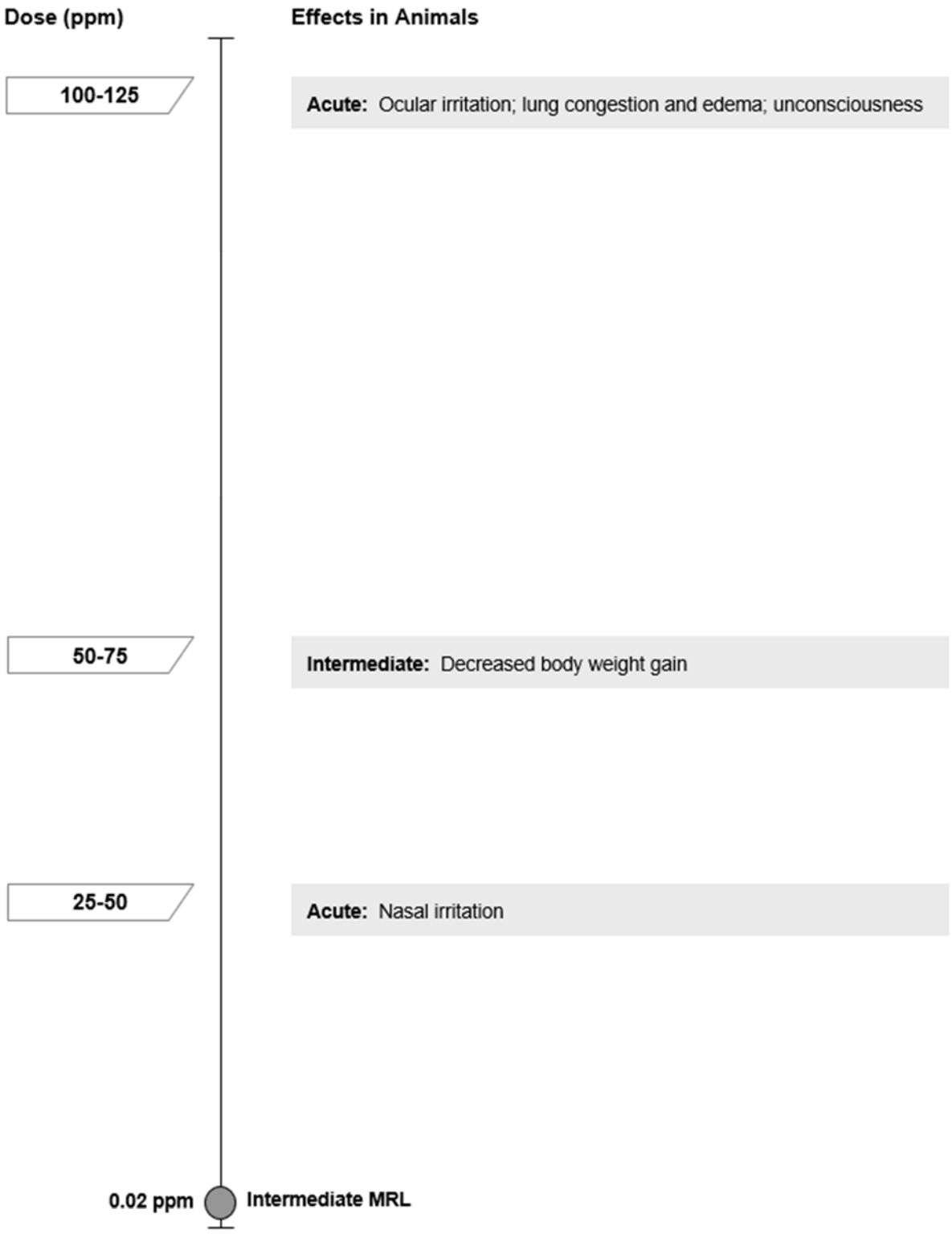
As illustrated in Figure 1-1, the most sensitive effects following inhalation exposure are respiratory and ocular irritation and damage, unconsciousness, and body weight alterations. Alterations in body weight have also been observed following chronic oral exposure. The oral exposure studies were limited in scope and were not considered sufficient for identifying critical targets of toxicity.

Respiratory Effects. Nasal irritation was reported in humans briefly exposed to BCEE in air (Schrenk et al. 1933). In guinea pigs exposed to airborne BCEE, nasal irritation was the most sensitive effect (Schrenk et al. 1933). At higher concentrations (≥105 ppm), lung congestion, edema, and hemorrhage were noted. A repeated exposure study in rats and guinea pigs did not report histological alterations in the respiratory tract (Dow Chemical 1958).

Ocular Effects. Humans briefly exposed to airborne BCEE reported eye irritation (Schrenk et al. 1933). Squinting and lacrimation were reported in guinea pigs exposed to airborne BCEE at 105 and 260 ppm, respectively (Schrenk et al. 1933).

Nervous System Effects. Loss of consciousness was observed in guinea pigs exposed to lethal concentrations of BCEE (≥105 ppm) for 13 hours (Schrenk et al. 1933). In guinea pigs exposed to airborne BCEE, nasal irritation was the most sensitive effect.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Bis(2-Chloroethyl)Ether



Body Weight Effects. An intermediate-duration inhalation study (Dow Chemical 1958) and a chronic-duration oral study (Weisburger et al.1981) suggest that decreases in body weight gain may be a sensitive endpoint of BCEE toxicity.

Cancer Effects. The carcinogenic potential of BCEE has not been evaluated following inhalation exposure. In a chronic oral mouse study, BCEE exposure resulted in increases in the incidence of liver tumors (Innes et al. 1969). A second study (Weisburger et al. 1981) did not find increases in tumors in rats.

The U.S. Department of Health and Human Services (NTP 2016) and the International Agency for Research on Cancer (IARC 2017) have not categorized the carcinogenicity of BCEE. EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002).

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-2, the limited available inhalation data for BCEE suggest that the respiratory tract, body weight, and nervous system are sensitive targets of toxicity. The oral database was not considered adequate for deriving MRLs. Available studies have only examined lethality, body weight, and carcinogenicity endpoints. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of Bis(2-Chloroethyl)Ether -- Inhalation

The respiratory tract is the most sensitive target of bis(2-chloroethyl)ether.
Numbers in circles are the lowest LOAELs (ppm) for all health effects in animals; no reliable human data were identified.

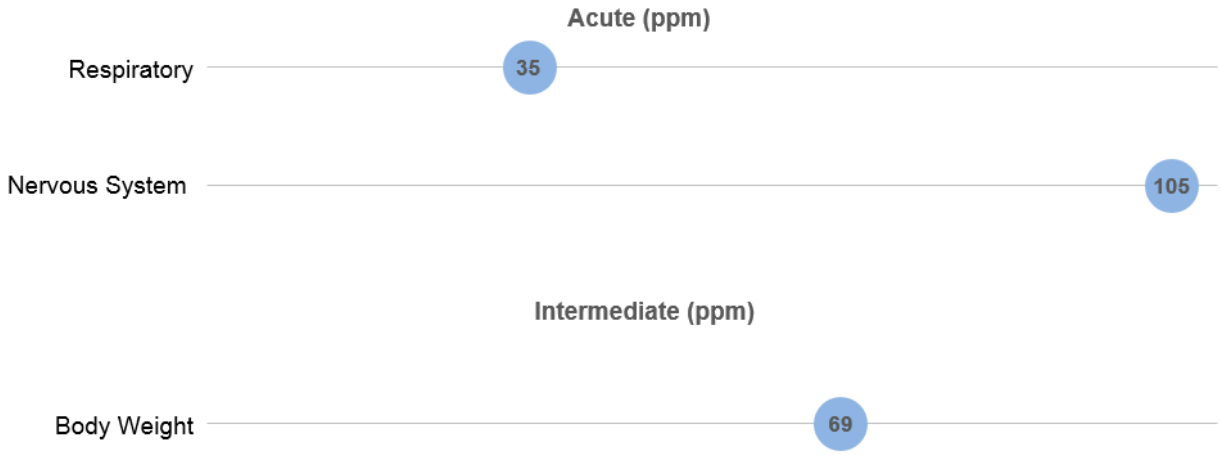


Table 1-1. Minimal Risk Levels (MRLs) for Bis(2-Chloroethyl)Ether[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.02	Decreased body weight gain	69 (LOAEL)	1,000	Dow Chemical 1958
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of BCEE. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to BCEE, but may not be inclusive of the entire body of literature.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal studies are presented in Table 2-3.

The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient

data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of BCEE are indicated in Table 2-2 and Figure 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of BCEE have been evaluated in a human experimental study and in animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation studies in animals. In addition to the studies summarized in Figure 2-1, seven studies have examined the acute lethality of BCEE following inhalation, oral, or dermal exposure. Animal data are available for most health effect category, but these data are mostly derived from a single intermediate-duration inhalation study that identified NOAEL values for most effects. It is noted that no studies examined reproductive function, immune function, or developmental toxicity.

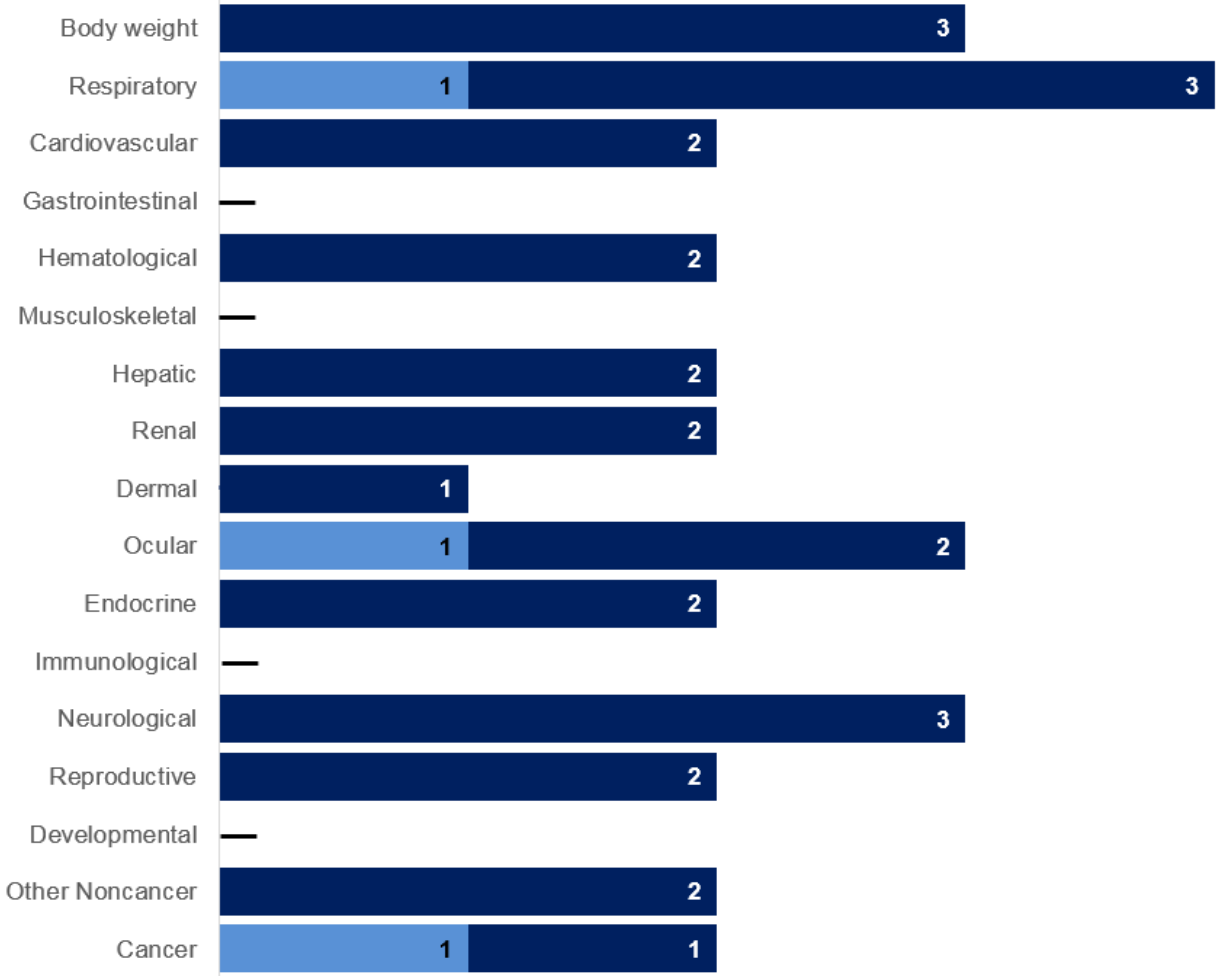
The available human and animal studies suggest the following sensitive targets of toxicity:

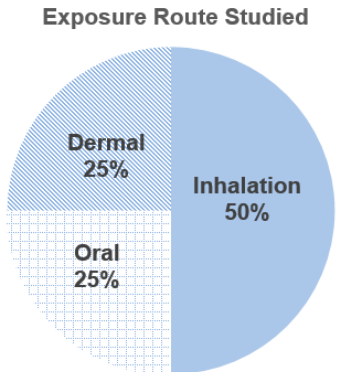
- **Respiratory Endpoint:** Nasal irritation has been reported by humans briefly exposed to BCEE and has been noted in laboratory animals. At higher, lethal concentrations of airborne BCEE, lung congestion and edema have been observed.
- **Ocular Endpoint:** Ocular irritation has been observed in laboratory animals exposed to airborne BCEE and following direct instillation.
- **Nervous System Endpoint:** At lethal concentrations, loss of consciousness and decreased motility have been observed in laboratory animals.
- **Body Weight Endpoint:** Decreases in body weight gain have been observed following intermediate-duration inhalation exposure and chronic-duration oral exposure.

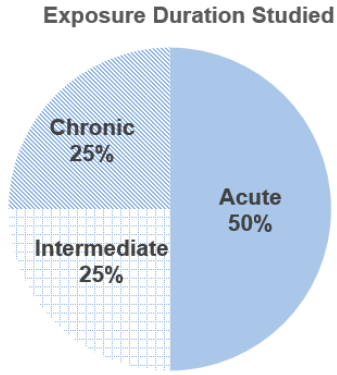
Figure 2-1. Overview of the Number of Studies Examining Bis(2-Chloroethyl)Ether Health Effects

Most studies examined the potential body weight, respiratory, and nervous system effects of bis(2-chloroethyl)ether

More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 7 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat 6 M,F	4 hours	175–340	LE	Death			250	Death in 2, 3, or 4 of 6 rats
Carpenter et al. 1949									
2	Guinea pigs 6	1–15 hours	0, 35, 105, 260, 550, 1,000	CS, GN, HP	Death			105	Deaths occurred with 5–7 hours at 1,000 ppm, 8–12 hours at 260 ppm, and after 13 hours at 105 ppm
					Respiratory		35	105	Slight nasal irritation at 35 ppm, lung congestion, edema, and hemorrhage at ≥105 ppm
					Ocular	35	105		Squinting at ≥105 ppm, lacrimation at ≥260 ppm
					Neurological	35		105	Unconsciousness, decreased motility
Schrenk et al. 1933									
3	Rat 6	45 minutes	1,000	LE	Death			1,000	3/6 animals died
Smyth and Carpenter 1948									
INTERMEDIATE EXPOSURE									
4	Rat 15 M,F	7 hours/day 5 days/week 130 days	0, 69	BW, OW, GN, HP, BC, CS, UR	Death				No deaths occurred
					Bd wt		69[b]		Decreased body weight gain
					Respiratory	69			
					Cardio	69			
					Hemato	69			
					Hepatic	69			
					Renal	69			
					Neuro	69			No effect on “behavior”
					Repro	69			No histological alterations in testes
Dow Chemical 1958									

Table 2-1. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
5	Guinea pig 8 M,F	7 hours/day 5 days/week 130 days	0, 69	BW, OW, GN, HP, BC, CS, UR	Death				No deaths occurred
					Bd wt		69[b]		Decreased body weight gain
					Respiratory	69			
					Cardio	69			
					Hemato	69			
					Hepatic	69			
					Renal	69			
					Neuro	69			No effect on “behavior”
					Repro	69			No histological alterations in testes

Dow Chemical 1958

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate-duration MRL of 0.02 ppm. Concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

BC = biochemistry; BW or Bd wt = body weight; Cardio = cardiovascular; CS = clinical signs; F = female(s); GN = gross necropsy; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Neuro = neurological; OW = organ weight; Repro = reproductive; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to BCEE – Inhalation
Acute (≤ 14 days)

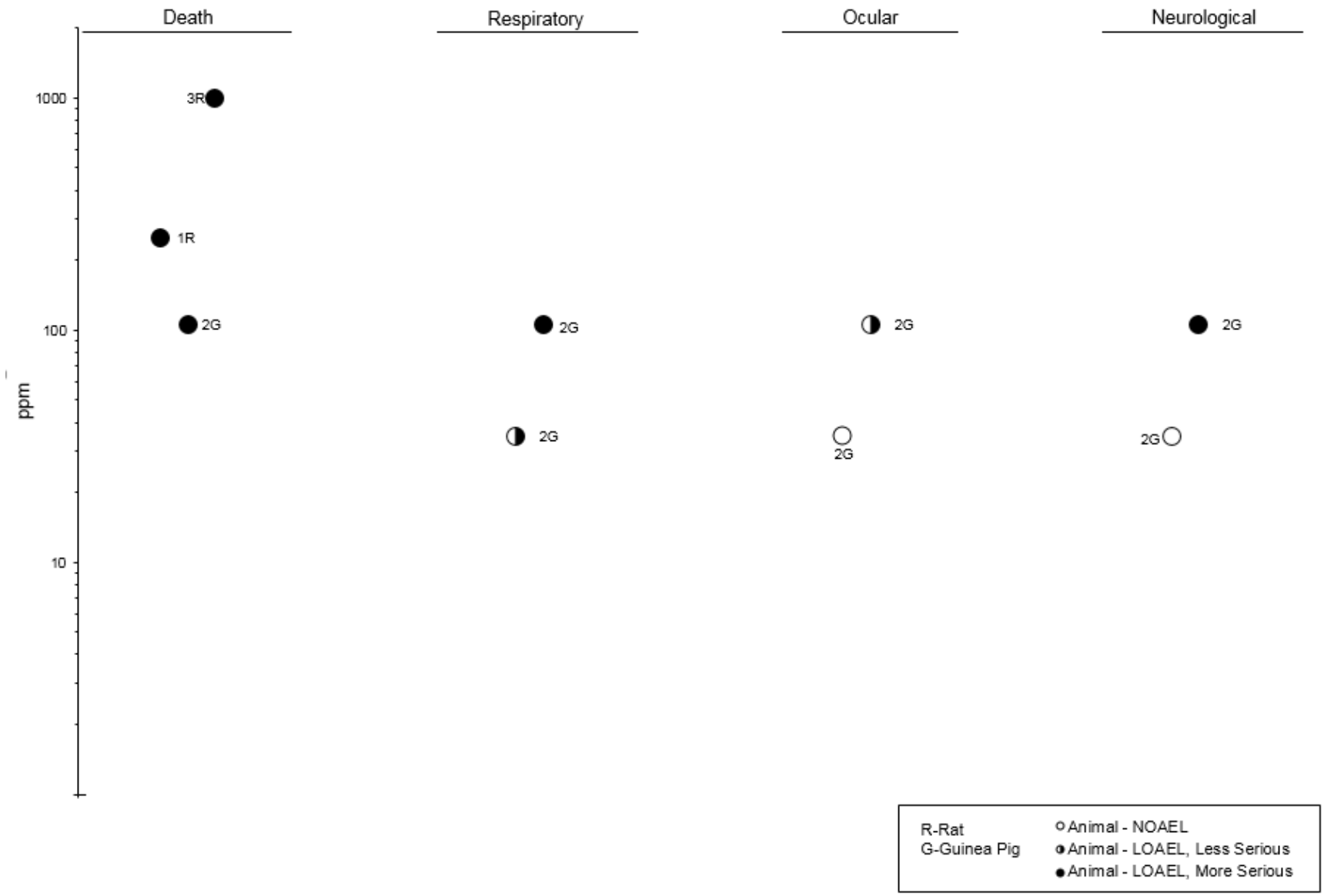


Figure 2-2. Levels of Significant Exposure to BCEE – Inhalation
Intermediate (15-364 days)

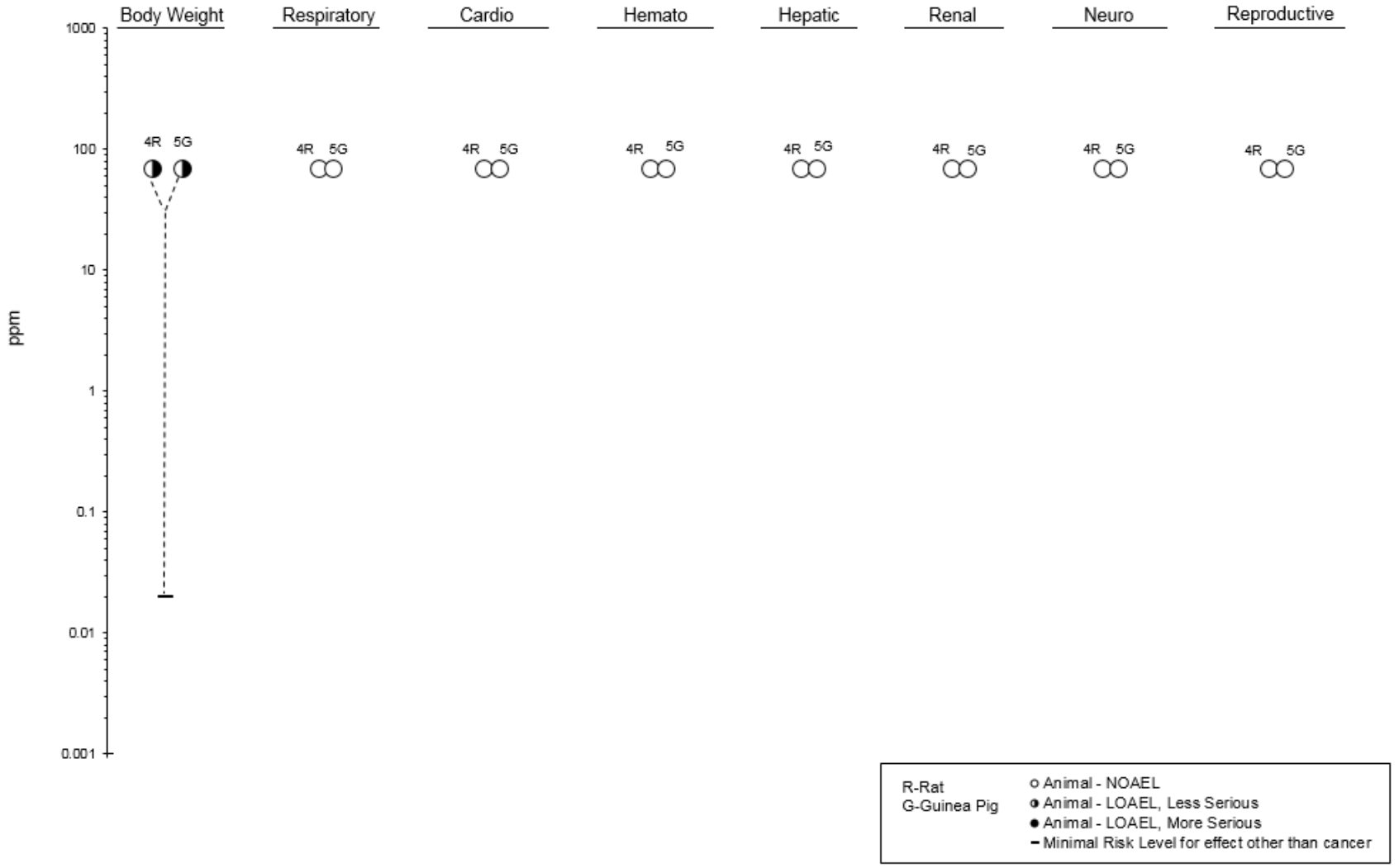


Table 2-2. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/d)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M,F	Once (GO)	70, 100, 150, 210	LE, CS	Death			144	Combined LD_{50}; LD_{50} females = 122 mg/kg; LD_{50} in males= 215 mg/kg
Drake and Myer 1992									
2	Mouse (CD-1) 5 M,F	Once (GO)	140, 200, 240 290	LE, CS	Death			211	Combined LD_{50}; LD_{50} females = 209 mg/kg; LD_{50} in males= 175 mg/kg
Drake and Myer 1992									
3	Rat 6	Once (G)	NR	LE	Death			75	LD_{50}
Smyth and Carpenter 1948									
CHRONIC EXPOSURE									
4	Rat 26 M,F	2 times/week 18 months with 6-month recovery (G)	0, 25, 50	BW, GN, HP	Death			5 0F	Increased mortality at 52 weeks in females only
					Bd wt		25		Decreased body weight in females at ≥25 mg/kg and in males at 50 mg/kg
					Cancer				No increases in neoplastic lesions
Weisburger et al. 1981									
5	Mouse 18 M,F	18 months (F)	0, 41	GN, HP	Cancer			41	Increased incidence of hepatomas
Innes et al. 1969									

[a]The number corresponds to entries in Figure 2-3.

BW or Bd wt = body weight; F = female(s); (F) = exposure in feed; (G) = gavage; GN = gross necropsy; (GO) = gavage in oil vehicle; HP = histopathology; LD_{50} = lethal dose, 50% mortality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported

Figure 2-3. Levels of Significant Exposure to BCEE - Oral
Acute (≤ 14 days)

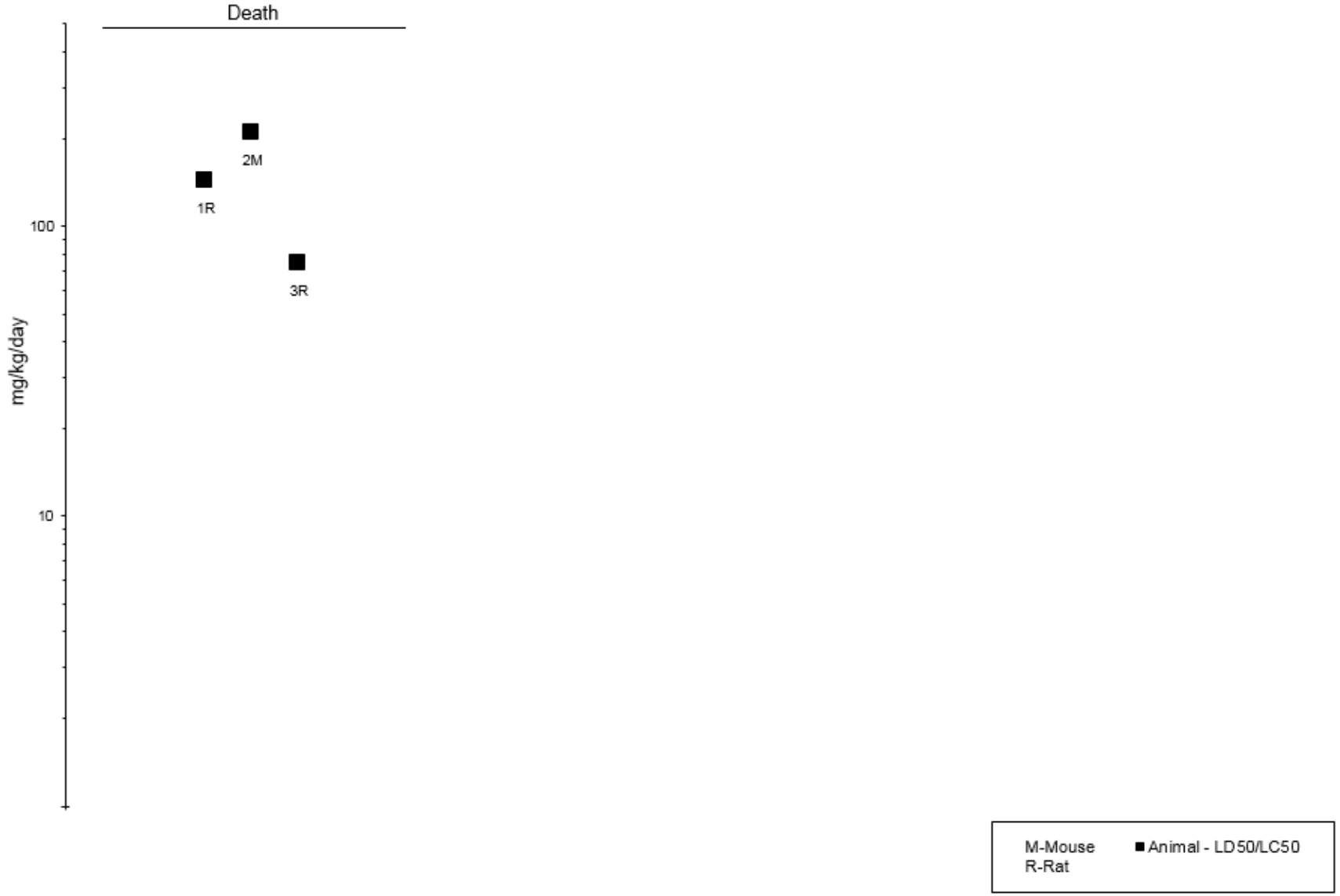


Figure 2-3. Levels of Significant Exposure to BCEE – Oral
Chronic (≥ 365 days)

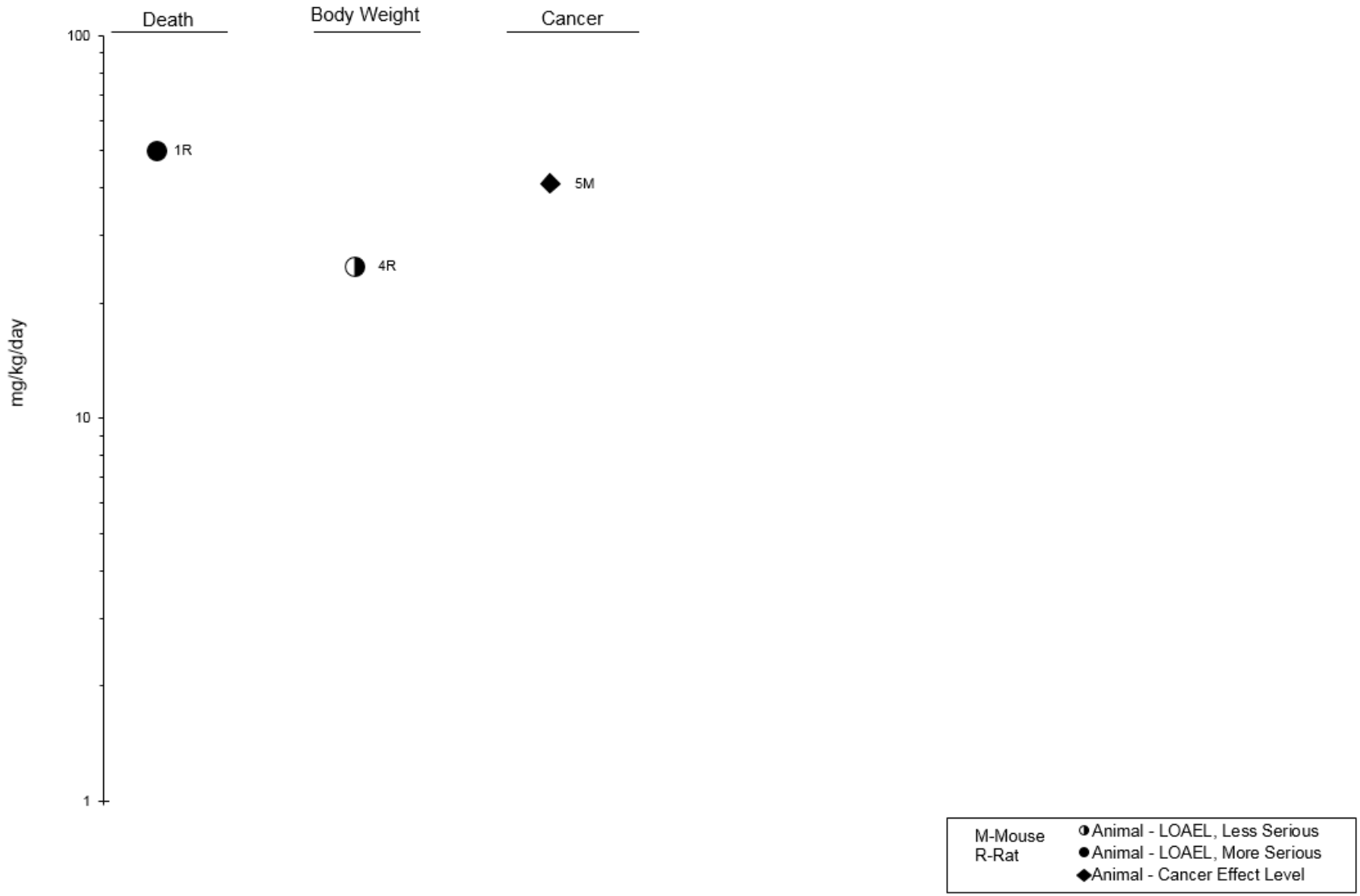


Table 2-3. Levels of Significant Exposure to Bis(2-Chloroethyl)Ether – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Rabbit NR	Once	25 mg		Ocular		25 mg		Eye irritation; grade of 4 (on a scale of 1 to 10)
Carpenter and Smyth 1946								
Rabbit NR	Once	10 mg		Dermal		10 mg		Skin irritation
Smyth and Carpenter 1948								
Guinea pig 6	24 hours	366 mg/cm^2		Death			366 mg/cm^2	LD_{50}
Smyth and Carpenter 1948								
Rabbit NR	NR	NR		Death			870 mg/kg	LD_{50}
Union Carbide 1948								

LD_{50} = lethal dose, 50% mortality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NR = not reported

2.2 DEATH

There are limited data on the lethality of BCEE in humans. Elkins (1959) reported a case of death occurring in an individual exposure to BCEE vapors at a fulling mill.

In animals, acute inhalation lethality depends on the level and duration of exposure to BCEE. Exposure of animals (rats, mice guinea pigs, rabbits) to concentrations of 500–1,000 ppm caused death within 1–2 hours (Schrenk et al. 1933; Smyth and Carpenter 1948; Union Carbide 1948). Exposure of rats to 250 ppm for 4 hours caused death in about half the animals (Carpenter et al. 1949), while exposure of mice, rats, and rabbits to 200 ppm for 1 hour did not cause any deaths (Union Carbide 1948). Four of six guinea pigs exposed to 105 ppm for 13 hours died within 4 hours after the exposure, while no deaths occurred in animals exposed to 35 ppm for 13.5 hours (Schrenk et al. 1933). Animals exposed to BCEE vapors displayed marked signs of respiratory distress, and acute lung injury appeared to be the principal cause of death (Carpenter et al. 1949).

The acute oral LD_{50} for BCEE in rats is 75 mg/kg (Smyth and Carpenter 1948). Similar acute oral LD_{50} values (105–136 mg/kg) were reported for mice, rabbits, and rats by Union Carbide (1948). Slightly higher LD_{50} values were reported by Drake and Myer (1992) for rats (144 mg/kg) and mice (211 mg/kg). Little information exists regarding lethality following chronic oral exposure. Decreased survival was reported in female rats dosed twice a week with 50 mg/kg for 18 months (Weisburger et al. 1981). The cause of the increased mortality was not determined.

BCEE has moderate dermal toxicity, with an estimated LD_{50} in rabbits of 870 mg/kg (Union Carbide 1948). Smyth and Carpenter (1948) and Union Carbide (1948) estimated that the amount absorbed through the skin of guinea pigs leading to death in 50% of the animals was about 370–390 mg/kg.

2.3 BODY WEIGHT

A significant decrease in body weight gain was observed in both rats and guinea pigs exposed to 69 ppm BCEE via inhalation for 130 days (Dow Chemical 1958).

Weisburger et al. (1981) reported that oral exposure to doses of 25 or 50 mg/kg (twice a week for 78 weeks) resulted in decreased body weights in rats, but the magnitude of this effect was not described.

2.4 RESPIRATORY

The principal acute effect of inhalation exposure to BCEE vapor is irritation and injury to the cells of the respiratory epithelium. In humans, brief exposure to concentrations ≥550 ppm was reported to be very irritating to the nasal passages (Schrenk et al. 1933). Exposure to 260 ppm was less irritating, and irritation was considered mild at 100 ppm and minimal at 35 ppm (Schrenk et al. 1933).

Studies in guinea pigs provide similar findings, with 35 ppm producing slight nasal irritation within 10 minutes, and higher concentrations producing proportionately greater and more rapid signs of nasal irritation (Schrenk et al. 1933). Exposure to concentrations ≥105 ppm resulted in lung congestion, edema, and hemorrhage. The severity of the pulmonary lesions increased with exposure duration and concentration. Exposure of rats or guinea pigs to 69 ppm BCEE for 130 days did not result in significant changes in lung/body weight ratios, and did not lead to histological changes in lung (Dow Chemical 1958).

2.5 CARDIOVASCULAR

No histological alterations were observed in the hearts of rats and guinea pigs exposed to 69 ppm for 130 days (Dow Chemical 1958).

2.6 GASTROINTESTINAL

No human or animal studies examining gastrointestinal effects were located.

2.7 HEMATOLOGICAL

Intermediate-duration inhalation exposure of rats and guinea pigs to 69 ppm of BCEE did not result in hematological effects or histological damage to the spleen (Dow Chemical 1958).

2.8 MUSCULOSKELETAL

No human or animal studies examining musculoskeletal effects were located.

2.9 HEPATIC

No gross or histological signs of hepatic injury were observed in rats or guinea pigs exposed to 69 ppm for 130 days (Dow Chemical 1958).

2.10 RENAL

No gross or histological alterations were observed in the kidney of rats or guinea pigs exposed to 69 ppm BCEE for 130 days (Dow Chemical 1958).

2.11 DERMAL

Smyth and Carpenter (1948) reported irritation in rabbits following application of 10 mg BCEE to skin.

2.12 OCULAR

Schrenk et al. (1933) reported that a brief exposure to 550 and 1,000 ppm BCEE resulted in profuse lacrimation and was very irritating to the eyes. The severity of the irritation decreased at lower concentrations and minimal irritation was observed at 35 ppm.

In guinea pigs, exposure to BCEE in air resulted in lacrimation within 3 minutes of exposure to ≥260 ppm, but not at 105 ppm (Schrenk et al. 1933). Squinting (which is likely suggestive of eye irritation) was observed after a 20-minute exposure to 105 ppm and 1-minute exposure to 260 ppm, but was not observed at 35 ppm. Carpenter and Smyth (1946) reported that 25 mg BCEE (0.02 mL of undiluted liquid) instilled in the eye of rabbits caused moderate irritation (a grade of 4 out of 10 was assigned).

2.13 ENDOCRINE

Intermediate-duration inhalation exposure to 69 ppm did not result in histological alterations in the adrenal or pancreas of rats and guinea pigs (Dow Chemical 1958).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to BCEE. In an *in vitro* assay, dose-dependent inhalation of BALB/c mouse splenic

T-cell lymphocyte mitogenesis in response to concanavalin A was observed (Sakazaki et al. 2001). No response to lipopolysaccharide was found in C3H/He mouse splenic B-cell lymphocytes.

2.15 NEUROLOGICAL

Data from animal studies indicate that BCEE is a central nervous system depressant following inhalation exposure. Schrenk et al. (1933) observed that guinea pigs exposed to concentrations ≥105 ppm began to become lethargic and uncoordinated within several hours, and that unconsciousness and death could follow. No neurological symptoms were observed at 35 ppm. No effects on behavior were noted in guinea pigs or rats exposed to 69 ppm for 130 days (Dow Chemical 1958), but no details were provided on how behavior was evaluated.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following inhalation exposure to BCEE. In animals, no gross or histological effects were observed in reproductive tissues of rats and guinea pigs exposed to 69 ppm of BCEE for 18 weeks (Dow Chemical 1958), but no tests of reproductive function or success were performed.

2.17 DEVELOPMENTAL

No studies were located regarding the developmental effects in humans or animals following exposure to BCEE.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals following exposure to BCEE.

2.19 CANCER

Innes et al. (1969) reported an increased incidence of hepatomas in two strains of mice exposed to an average oral dose of 41 mg/kg/day for 80 weeks. The effect was most marked in the males, with liver tumors occurring in 53 and 88% of the exposed males of the two strains, compared with 10 and 6% in unexposed controls, respectively. A smaller effect (22 versus 0%) was observed in females from one strain, but no effect was seen in females of the other strain. The authors of the study emphasized that

although the tumors were described as hepatomas, the majority of tumors might have had malignant potential. No increased incidence of tumors was observed in male or female rats exposed twice a week to doses of 25 or 50 mg/kg (Weisburger et al. 1981).

Van Duuren et al. (1972) performed a two-stage initiation-promotion test for tumor production in mouse skin using a single dermal dose of BCEE (as the initiator) followed by repeated doses of phorbol myristate acetate (as promotor) for 2 years. The frequency of skin papillomas in the BCEE-treated mice (3/20) was not significantly different from the control group (2/20). Tests were not performed to investigate whether BCEE had any promotor activity, or if it was carcinogenic if applied repeatedly itself.

Based on positive carcinogenicity data in the Innes et al. (1969) study and positive genotoxicity evidence, EPA (IRIS 2002) has classified BCEE in Group B2, probable human carcinogen.

2.20 GENOTOXICITY

The *in vivo* genotoxicity of BCEE, summarized in Table 2-4, has been investigated in mice and *Drosophila*. No evidence of heritable reciprocal translocation of chromosomes was observed in mice following 8-week gavage administration of BCEE (Jorgenson et al. 1978; only available as an abstract). Similarly, no increases in reciprocal translocations were observed in *Drosophila* (Foureman et al. 1994). Positive evidence of sex-linked recessive lethality was observed in *Drosophila* when BCEE was injected but not when it was administered in feed (Foureman et al. 1994). Weak positive results were found in an assay of somatic cell recombination (Ballering et al. 1996).

Table 2-4. Genotoxicity of Bis(2-Chloroethyl)Ether *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mice (8-week gavage)	Heritable reciprocal translocation	–	Jorgenson et al. 1978
Drosophila melanogaster (inhalation)	White/white$^+$ eye mosaic recombination	(+)	Ballering et al. 1996
D. melanogaster (feed)	Sex-linked recessive lethality	–	Foureman et al. 1994
D. melanogaster (injection)	Sex-linked recessive lethality	+	Foureman et al. 1994
D. melanogaster (injection)	Heritable reciprocal translocation	–	Foureman et al. 1994

– = negative result; + = positive result; (+) = weakly positive results

In *in vitro* genotoxicity studies (Table 2-5), a positive result for mutations in *Salmonella* was found for BCEE without metabolic activation (Simmon 1977); with activation, no alterations in mutation frequency were found (Norpoth et al. 1986). In three genotoxicity assays in *Escherichia coli*, BCEE did not induce forward mutations, recombination, or SOS induction (Quinto and Radman 1987).

Table 2-5. Genotoxicity of Bis(2-Chloroethyl)Ether *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (TA100)	Mutation	–	ND	Norpoth et al. 1986
S. typhimurium (TA100)	Mutation	ND	+	Simmon 1977
Escherichia coli (MT103)	Forward mutation	ND	–	Quinto and Radman 1987
E. coli (MT119)	Recombination	ND	–	Quinto and Radman 1987
E. coli (MT126)	SOS induction	ND	–	Quinto and Radman 1987

– = negative results; + = positive results; ND = not determined

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

No studies were located regarding BCEE toxicokinetics in humans, but there are limited data from animal studies. These data are summarized below.

- Greater than 95% of BCEE is absorbed following inhalation or oral exposure. BCEE appears to be absorbed through the skin, but there are no data on the rate or extent of absorption.
- BCEE appears to be widely distributed throughout the body, with the highest levels found in the liver, kidney, and small intestine following oral exposure.
- The predominant pathway for BCEE metabolism is hydroxylation to ultimately form thiodiglycolic acid. BCEE is also metabolized via direct substitution and oxidative dehalogenation.
- BCEE is primarily excreted in the urine as the metabolite thiodiglycolic acid. Within 48 hours of oral administration, 80% of the dose is excreted.

3.1.1 Absorption

There are limited quantitative data on BCEE absorption. Gwinner et al. (1983) reported that rats placed in a chamber containing BCEE vapor absorbed >95% of the compound within 18 hours. Lingg et al. (1982) reported that only 2% of a single oral dose of BCEE administered to rats was excreted in the feces, indicating that absorption across the gastrointestinal tract was essentially complete. No studies were located regarding the rate or the extent of absorption by the dermal route. However, acute dermal toxicity studies (Smyth and Carpenter 1948) suggest that BCEE is absorbed across the skin.

3.1.2 Distribution

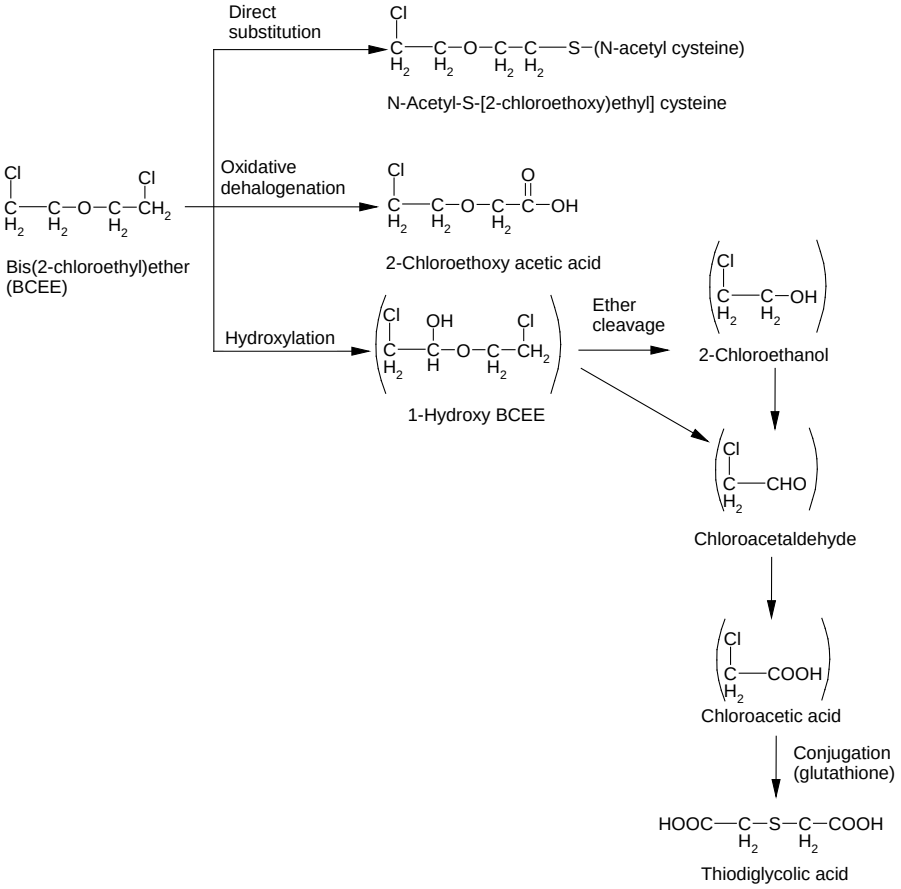
Lingg et al. (1982) administered a single oral dose of ^{14}C-labelled BCEE to rats, and measured the radioactive content of tissues 48 hours later. Only a small fraction of the dose (2.3%) was found in organs and tissues, with 0.96% in muscle, 0.56% in kidney, 0.49% in blood, 0.19% in liver, and 0.1% in other tissues. No distribution data were identified for inhalation or dermal exposure.

3.1.3 Metabolism

Studies in animals indicate that BCEE is extensively metabolized, with thiodiglycolic acid (TDGA) being the principal endproduct (Lingg et al. 1979; Norpoth et al. 1986). The pathway leading to TDGA

formation is not certain, but probably involves oxidative cleavage of the ether bond to yield chloroacetaldehyde and 2-chloroethanol, as shown in Figure 3-1 (Bolt 1984; Gwinner et al. 1983; Lingg et al. 1979, 1982; Muller and Norpoth 1979; Norpoth et al. 1986). TDGA recovered in urine usually accounts for 50% to 80% of a dose of BCEE (Lingg et al. 1979, 1982). Smaller amounts of BCEE (3–5%) are metabolized by oxidation or substitution at a chlorine without ether cleavage (see Figure 2-3), and about 12% is degraded to CO_2 (Lingg et al. 1982). Only about 2% of the dose is excreted via the lungs as unchanged BCEE (Lingg et al. 1979). Gwinner et al. (1983) exposed rats to ^{14}C-labelled BCEE vapor, and measured the amount of radioactivity irreversibly bound to tissue proteins 24 hours later. Distribution of unbound parent or metabolites was not measured. Highest levels were found in liver, kidney, and small intestine, with much lower levels in lung, spleen, and muscle. The presence of protein-bound label in these tissues suggested to the authors that reactive intermediates were formed that led to covalent adducts, but incorporation of label into protein might also have occurred through normal synthetic pathways involving nontoxic breakdown products from BCEE. No label was detectable in liver deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

Figure 3-1. Summary of Bis(2-Chloroethyl)Ether Metabolism in Rats



3.1.4 Excretion

Lingg et al. (1979, 1982) found that approximately 80% of an oral dose of BCEE administered to rats was excreted within 48 hours. Most of the dose (65%) was excreted as urinary metabolites (mostly thiodiglycolic acid), with smaller amounts excreted in feces (3%) or expired air (11% as CO_2 and <2% as parent BCEE). Only 2% of the dose remained in the body. This indicates that BCEE is effectively excreted, and that it has a low tendency to accumulate in tissues.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models were identified for BCEE.

3.1.6 Animal-to-Human Extrapolations

There are insufficient data to evaluate possible species differences in the toxicokinetic properties of BCEE because the available studies only tested rats. Toxicity studies in rats, mice, rabbits, and guinea pigs suggest similarities in the lethality and toxicity of BCEE across species. Schrenk et al. (1933) reported nasal and eye irritation in humans briefly exposed to BCEE, irritation was also reported in guinea pigs exposed to similar concentrations.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal

exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to BCEE are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available on the toxicity of BCEE in children and it is assumed to be similar to adults. No developmental toxicity studies have been identified for BCEE. No information was located to indicate that any human population might be especially susceptible to the toxic effects of BCEE. Based on the observation that BCEE is a powerful irritant of the respiratory tract, it may be expected that individuals with lung disease or other forms of respiratory distress might be particularly vulnerable to the effects of BCEE vapors.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to BCEE are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for BCEE from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by BCEE are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The use of BCEE or its principal metabolite, TDGA, as biomarkers of exposure has not been investigated.

3.3.2 Biomarkers of Effect

There are no specific biomarkers to characterize the effects caused by BCEE.

3.4 INTERACTIONS WITH OTHER CHEMICALS

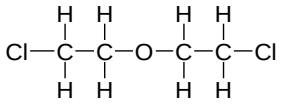
No information was located on the interaction of BCEE with other chemicals.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names and other pertinent identification information for BCEE.

Table 4-1. Chemical Identity of Bis(2-Chloroethyl)Ether

Characteristic	Information	Reference
Chemical name	Bis(2-chloroethyl) ether	IARC 1975
Synonym(s) and registered trade name(s)	1,1'-Oxybis(2-chloro) ethane; bis(chloroethyl) ether; bis(β-chloroethyl)ether; sym-dichloroethylether; 2,2'-dichloro-diethyl ether; 2-dichloroethyl ether; dichloroethyl ether; dichloroethyl oxide; DCEE; Chlorex	IARC 1975
Chemical formula	$C_4H_8Cl_2O$	Weast 1985
Chemical structure		
Identification numbers:		
CAS Registry	111-44-4	NLM 1988

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of BCEE.

Table 4-2. Physical and Chemical Properties of Bis(2-Chloroethyl)Ether

Property	Information	Reference
Molecular weight	143.04	Weast 1985
Color	colorless, clear	Windholz 1983
Physical state	Liquid	Windholz 1983
Melting point	-24.5	Weast 1985
Boiling point	178	Weast 1985
Density at 20°C	1.2199	Weast 1985
Odor	pungent	Windholz 1983
Odor threshold:		
Air	0.049	Amoore and Hautala 1983

Table 4-2. Physical and Chemical Properties of Bis(2-Chloroethyl)Ether

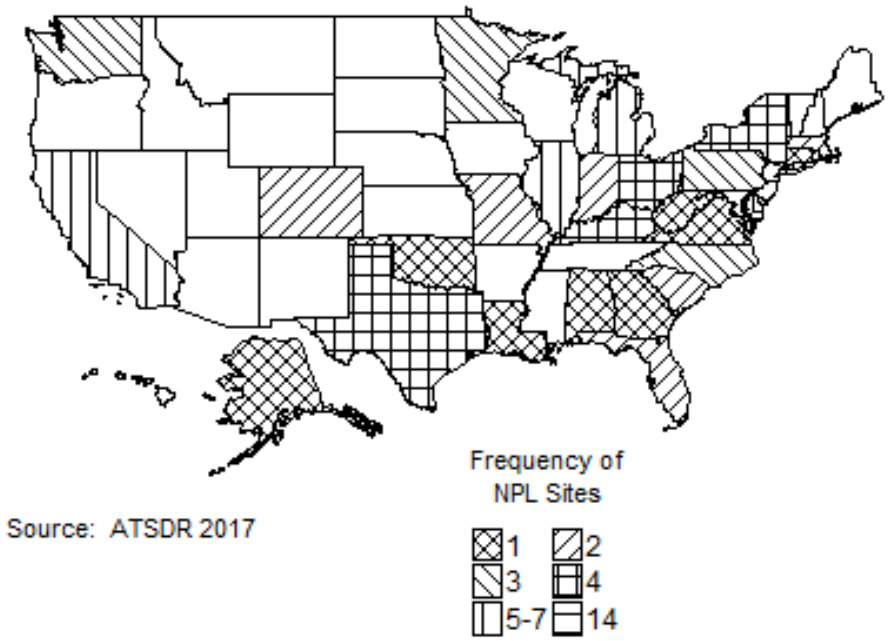
Solubility:		
Water at 20°C	10,700 10,200 17,200	Hake and Rowe 1963 Verschueren 1977 Veith et al. 1980
Organic solvents	soluble	Weast 1985
Partition coefficients:		
Log K_{ow}	1.58 1.5 1.1	Callahan et al. 1979 Mabey et al. 1982 Veith et al. 1980
Log K_{oc}	1.1	Mabey et al. 1982
Vapor pressure at 20°C	0.71	Verschueren 1977
Henry's law constant at 25°C	1.31E-05	Mabey et al. 1982
Autoignition temperature	369	
Flashpoint	55	
Flammability limits	No data	
Conversion factors:		
ppm (v/v) to mg/m^3 in air (25°C)	1 ppm • 5.85 mg/m	Verschueren 1977
mg/m^3 to ppm (v/v) in air (25°C)	1 mg/m^3 • 0.17 ppm	Verschueren 1977

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Bis(2-chloroethyl)ether has been identified in at least 89 of the1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which bis(2-chloroethyl)ether has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Bis(2-Chloroethyl)Ether Contamination



- The most likely route of exposure to BCEE for the general population is via ingestion of BCEE in drinking water.
- A daily intake of BCEE from drinking water is estimated at 0.003 µg/kg/day.
- BCEE is primarily used as a chemical intermediate in pesticide manufacturing.
- BCEE will slowly volatilize from water and soil. Biodegradation is likely an important fate process for BCEE in water.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of bromodichloromethane in 2016 (TRI16 2017). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Bis(2-Chloroethyl)Ether

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
GA	1	100,000	999,999	2, 3, 6
KY	1	10,000	99,999	1, 3, 6
LA	7	0	9,999	1, 5, 12, 13
MO	1	100,000	999,999	1, 3, 4, 6, 9
OH	2	1,000	9,999	12
OK	1	10,000	99,999	7
TX	10	1,000	999,999	1, 5, 6, 12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

All BCEE produced in the United States is made by direct chlorination of ethylene glycol (Buckman Laboratories 1988). BCEE can also be produced by the treatment of ethylene chlorohydrin or 2-chloroethanol with sulfuric acid, or by chlorination of ethylene chlorohydrin at 80°C. Production of BCEE in the United States in 1986 was estimated to be 1,200 kkg (Buckman Laboratories 1988).

5.2.2 Import/Export

Imports of BCEE in 1977 were estimated to be about 590 kkg (HSDB 1988). Imports of BCEE in 1986 were estimated to be about 60 kkg (Buckman Laboratories 1988).

5.2.3 Use

In the past, BCEE has been used as a solvent for fats, waxes, greases, and esters (Schrenk et al. 1933). It has also been used as a constituent of paints and varnishes, as a cleaning fluid for textiles, in the purification of oils and gasoline, in the manufacture of medicines and pharmaceuticals, as an intermediate in the synthesis of other chemicals, and as an insecticide and a soil fumigant (Browning 1965; Hake and Rowe 1963; HSDB 1988; Verschueren 1977; Windholz 1983).

BCEE is currently used primarily as a chemical intermediate for the manufacture of pesticides. The two major pesticide products made from BCEE are WSCP, an isoprene polymer used primarily as an algicide, and CDQ, a diquaternary ammonium compound used as a microbicide and corrosion inhibitor in the petroleum industry. A small amount of BCEE (about 1%) is still used as a solvent.

5.2.4 Disposal

No information was located on the amounts of BCEE disposed of to the environment or to waste sites. Because BCEE is classified as a hazardous waste under the Resource Conservation and Recovery Act (RCRA), all BCEE waste must be disposed of in an authorized RCRA facility. Permitted disposal methods include incineration and land disposal, although EPA is currently considering possible restrictions on land disposal methods (40 CFR 268.11).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data, presented in Table 5-2, should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and

if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Bis(2-Choroethyl) Ether[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
GA	1	1	0	0	0	0	1	0	1
KY	1	0	0	0	0	0	0	0	0
LA	7	13	3	0	0	0	16	0	16
MO	1	34	1	0	0	0	35	0	35
OH	2	0	0	0	0	0	0	0	0
OK	1	0	0	0	0	0	0	0	0
TX	10	48	0	0	0	0	48	0	48
Total	23	97	4	0	0	0	101	0	101

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

5.3.1 Air

Estimated releases of 97 pounds (~0.044 metric tons) of BCEE to the atmosphere from 23 domestic manufacturing and processing facilities in 2016, accounted for about 96% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

5.3.2 Water

Estimated releases of 4 pounds (~0.0018 metric tons) of BCEE to surface water from 23 domestic manufacturing and processing facilities in 2016, accounted for about 4% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

5.3.3 Soil

No BCEE was released to soil from 23 domestic manufacturing and processing facilities in 2016 (TRI16 2017). These releases are summarized in Table 5-2.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Little information was located on the transport or partitioning of BCEE in the environment. The vapor pressure of BCEE at 20°C is 0.7 mm Hg (Verschueren 1977), suggesting that volatilization from soil or water, while probably very slow, could be significant (Callahan et al. 1979). EPA (1987a) calculated a half-time for volatilization of BCEE from a river to be 3.4 days. Because BCEE is quite soluble in water (10,200 mg/L) (Verschueren 1977), it is expected that BCEE in air would tend to be removed by wet deposition, resulting in a cycle between water, soil, and air (Callahan et al. 1979). The relative distribution between these phases, however, is not known.

Because BCEE has good solubility in water and a relatively low log octanol-water partition coefficient (measured to be 1.1 by Veith et al. 1980), BCEE in aqueous media is not expected to adsorb strongly to sediments, nor is it likely to be bioaccumulated by aquatic organisms (Callahan et al. 1979). Consistent with this, a bioconcentration factor of 11 has been measured in sunfish by Veith et al. (1980).

For the same reasons, BCEE is not expected to adsorb strongly to soils, and would be expected to migrate in soil water. Consistent with this, Wilson et al. (1981) reported a soil retardation factor of <1.5 for sandy soil with low organic content, while other contaminants (e.g., di- and trichlorobenzene) had retardation factors of 3.4–9.4.

5.4.2 Transformation and Degradation

Air. Callahan et al. (1979) reviewed the potential fate of BCEE in the environment and suggested that BCEE in a smog-like atmosphere would probably undergo photooxidative destruction with a half-life of approximately 4 hours. The rate of atmospheric photooxidation under other conditions was not estimated. Direct photolysis was judged to be an unimportant process, since BCEE does not absorb visible or near ultraviolet light (Callahan et al. 1979).

Water. Most ethers are very resistant to hydrolysis, and the rate of cleavage of the carbon-oxygen bond by abiotic processes is expected to be insignificant (Callahan et al. 1979). The carbon-chlorine bond is also quite stable to abiotic cleavage. Based on a measured hydrolysis rate constant of $1.5x10^{-5}$ minutes at 100°C, Mabey et al. (1982) estimated the half-life of the carbon-chlorine bond to be about 22 years at 20°C. This rate is somewhat slower than observed for simple alkyl halides (Callahan et al. 1979; Mabey et al. 1982), an effect that Mabey et al. (1982) attributed to the effect of the chloro-ethoxy group on the adjacent carbon.

Biodegradation may be an important fate process for BCEE in water. In laboratory studies, Tabak et al. (1981) found that in aqueous media inoculated with sewage, BCEE underwent 100% transformation within 7 days, and there was a rapid adaptation of the degradative microorganisms. Similar results were reported by Ludzack and Ettinger (1963), although in this case, there was a 25-day lag before adaption occurred, and 30 more days were required to convert 80% of the BCEE to CO_2. A second dose of BCEE added to the adapted medium was 80% oxidized in 15 days. Monsen (1986) reported that BCEE also underwent significant biodegradation (68%) in an anaerobic laboratory test pond designed to simulate an industrial primary lagoon. Losses via evaporation and sorption were minimal. In contrast to these findings, Dojlido (1979) did not observe significant biodegradation of BCEE in several laboratory test systems. The reason for this discrepancy is not certain, but may be due to insufficient incubation time (2 weeks) for the adaptation to occur. Biodegradation in surface waters would likely be slower than observed in the laboratory, but could lead to significant destruction of BCEE.

Sediment and Soil. Wilson et al. (1981) observed no significant transformation of BCEE percolated through soil for 45 days, but Kincannon and Lin (1986) found that BCEE was significantly degraded in a 97-day laboratory soil column study. The initial rate constant for degradation was reported to be 0.042 day^{-1} (half-time of 16.7 days). After 48 days, the rate increased to 0.086 day^{-1} (half-time of 8.0 days), suggesting that there was an acclimation of soil microbes occurring.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to BCEE depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of BCEE in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on BCEE levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	1 µg/m^3	Berck 1965
Water	0.005 µg/L	Dressman et al. 1977
Soil/sediment	1 mg/kg	EPA 1986a
Whole blood	No method identified	

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-4. Summary of Environmental Levels of Bis(2-Chloroethyl)Ether

Media	Low	High	For more information
Outdoor air (ppbv)	No monitoring data were identified		
Indoor air (ppbv)	No monitoring data were identified		
Surface water (ppb)	Trace quantities measured		Section 5.5.2
Ground water (ppb)	840 µg/L (geometric mean)		Section 5.5.2
Drinking water (ppb)	0.01 µg/L	0.36 µg/L	Section 5.5.2
Food (ppb)	No monitoring data were identified		
Soil	No monitoring data were identified		

Detections of BCEE in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. Bis(2-Chloroethyl)Ether Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of concentrations	NPL sites
Water (ppb)	300	237	43,900	25	21
Soil (ppb)	6,950	1,060	12,800	14	10
Air (ppbv)	No data	No data	No data	No data	No data

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No studies were located with regard to concentrations of BCEE in ambient air. Based on the physical-chemical properties of BCEE, some release of BCEE into air from contaminated chemical waste sites or industrial settings is expected, but no quantitative data were located.

5.5.2 Water

In 1977, the EPA carried out an extensive study (the National Organics Monitoring Survey) of organic contaminants in finished drinking water supplies across the United States. BCEE was not detected in any samples in Phase I of the study, but the detection limit was only 5 µg/L. In phase II, the detection limit was lowered to 0.005 µg/L, and BCEE was detected in water from 13 of 113 cities sampled. The values ranged from 0.01 to 0.36 µg/L, with a mean concentration (for the 13 positive samples) of 0.1 µg/L (Dressman et al. 1977). In phase III of the Survey, BCEE was detected in drinking water from 8 of 110 cities, with a mean concentration of 0.024 µg/L. Trace quantities of BCEE have been reported in several rivers, including the Mississippi, the Delaware, and the Kanawha (EPA 1987a; Staples et al. 1985). BCEE was detected in groundwater at about 2% of waste disposal sites being investigated under Superfund, at a geometric mean concentration of around 840 µg/L (CLPSD 1988).

5.5.3 Sediment and Soil

BCEE was detected in soil at only 0.4% of waste sites monitored under Superfund, at geometric mean concentration of 140 ppb (CLPSD 1988).

5.5.4 Other Media

No studies were located regarding the occurrence of BCEE in food or other media.

5.6 GENERAL POPULATION EXPOSURE

The primary known source of exposure for the general population is via the water supply. The reports of quantities in several drinking water supplies provided a mean value of approximately 0.1 ppb. Ingestion of approximately 2 L of water per day by an adult would provide a daily intake of 0.003 µg/kg/day of BCEE.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Even though there are no exposure data, those at greatest risk of exposure to BCEE are probably workers who are exposed to BCEE while on the job. Residents who live near waste sites or industrial facilities that permit escape of BCEE may also experience higher than average exposure to BCEE. Exposure would be most likely by ingestion of contaminated water, but inhalation exposure might also occur. The level and significance of such exposures can only be evaluated on a site-by-site basis.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of BCEE is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of BCEE.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

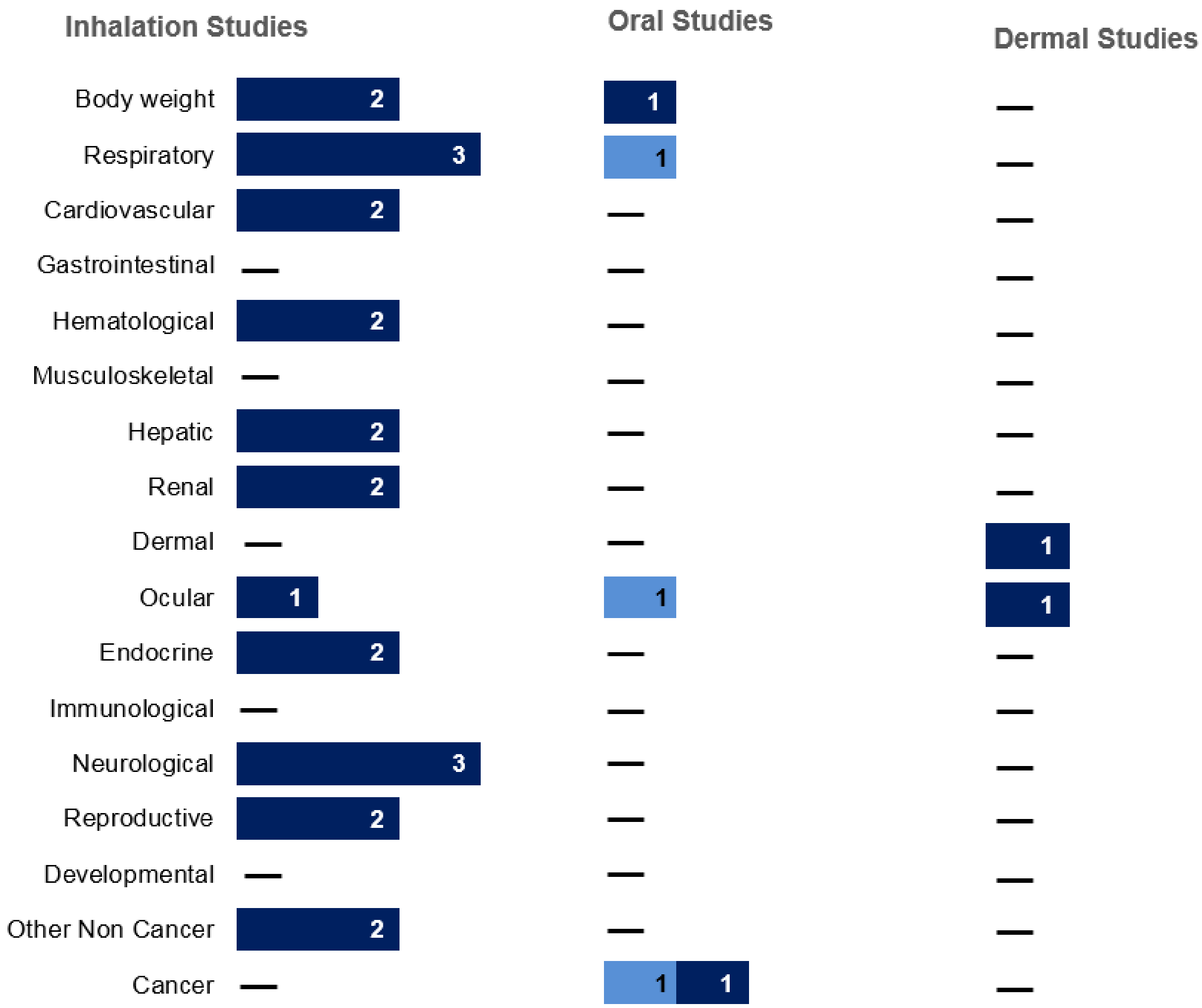
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to BCEE that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of BCEE. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, a small number of studies have evaluated the toxicity of BCEE. Half of these studies involved inhalation exposure in laboratory animals. The most commonly examined endpoints were body weight, respiratory, and neurological. In addition, six studies examined the acute lethality of BCEE following inhalation, oral, or dermal exposure. An inhalation study in rats and guinea pigs was the only study examined a wide range of potential endpoints (Dow Chemical 1958).

Figure 6-1. Summary of Existing Health Effects Studies on Bis(2-Chloroethyl)Ether By Route and Endpoint*

The majority of the studies examined inhalation exposure in animals (versus **humans**)
Potential body weight, respiratory, and neurological effects were the most studied endpoints



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The available acute inhalation database was not considered adequate for derivation of an MRL. Several limitations were identified in the only available study (Schrenk et al. 1933), including limited evaluation of the respiratory tract and other potential targets of toxicity, lack of reporting incidence data for the nasal lesions, and limited details on the study design. Additional inhalation toxicity studies are needed; these studies should include examination of a wide range of potential targets including the nose and lungs. Acute-duration oral studies are needed to identify sensitive targets of toxicity and establish dose-response relationships.

Intermediate-Duration MRLs. Although limited data are available on the effects of intermediate-duration inhalation exposure to BCEE, the database was considered adequate for derivation of an MRL. Further studies using modern histological and biochemical tests would be useful to support this MRL. No intermediate-duration oral studies were identified and are necessary for derivation of an MRL. These studies should evaluate a wide variety of potential endpoints and test a range of dose levels.

Chronic-Duration MRLs. The lack of chronic-duration inhalation studies precluded derivation of a chronic MRL. The only available chronic-duration oral study (Weisburger et al. 1981) was limited to an examination of body weight and carcinogenic endpoints and was not considered suitable for derivation of an MRL. Chronic toxicity studies utilizing inhalation and oral exposure and examining a wide range of endpoints are needed to identify the most sensitive target and establish dose-response relationships.

Health Effects. A small number of studies have evaluated the toxicity of BCEE. The available studies suggest that the most sensitive effect of BCEE is mucosal irritation; however, the data are not sufficient for establishing concentration-response relationships. Acute-, intermediate-, and chronic-duration inhalation and oral studies examining a wide range of potential targets of toxicity are needed to identify the critical targets and effect levels. Inhalation studies should also include examination of the nasal cavity

since the results of an acute study (Schrenk et al. 1933) suggest that this may be the most sensitive target. Dermal studies are also needed to examine the toxicity of repeated exposure to BCEE.

No studies were located on reproductive or developmental effects of BCEE. Single-generation tests of reproductive toxicity and developmental toxicity studies would be valuable in determining whether these may be effects of concern for humans. The results of an *in vitro* study (Sakazaki et al. 2001) provide suggestive evidence that the immune system may be a target of BCEE toxicity; inhalation and/or oral studies examining immune function would be useful for determining whether it is target of concern for humans. Inhalation exposure to high doses of BCEE appears to cause central nervous system depression and sedation (Schrenk et al. 1933), but the concentration-response curve for this effect is not well defined. Further studies to identify the threshold for central nervous system depression and other effects on behavior following both oral and inhalation exposure would be helpful.

Epidemiology and Human Dosimetry Studies. No epidemiological studies were located in humans exposed to BCEE. Performance of such studies could be helpful in evaluating the chronic human health risk from BCEE exposure, especially cancer.

Biomarkers of Exposure and Effect. No biomarkers of exposure to BCEE were located. Studies evaluating whether levels of BCEE or one of its metabolites in biological fluids are reflective of exposure levels would be useful. Using radioactively labeled BCEE, Gwinner et al. (1983) reported incorporation of label into cellular proteins of animals exposed to BCEE. Studies to determine if this is due to protein adduct formation would be valuable.

Absorption, Distribution, Metabolism, and Excretion. Although there are limited toxicokinetic data on BCEE from studies of animals, there are several areas where additional information would be valuable. Since available information is derived from studies employing single exposures, studies of uptake, distribution, and excretion patterns following repeated exposures would be useful. Quantitative studies of absorption rates across the lungs and the skin would be helpful is estimating absorbed doses and resultant health effects following inhalation and dermal exposure. Additional metabolism studies would be valuable in identifying intermediate metabolites that might be involved in the genotoxic or carcinogenic effects of BCEE. Finally, further studies of the kinetics of BCEE metabolism and clearance would be valuable in evaluating the potential for cumulative toxicity.

Comparative Toxicokinetics. Toxicokinetic studies of BCEE metabolism and excretion have been performed in rats (Gwinner et al. 1983; Lingg et al. 1979; Muller and Norpoth 1979; Norpoth et al. 1986). Consequently, studies of metabolism in other species would be valuable, especially in mice (since a carcinogenic response has been observed in mice but not in rats). In addition, studies of the pattern of BCEE degradation products in human urine would be helpful in evaluating whether BCEE is metabolized in humans as it is in rats.

Children's Susceptibility. No studies have evaluated the toxicity of BCEE in children or young animals. Studies in young animals and/or children would be useful to address potential concerns of that children may be more susceptible to the toxicity of BCEE than adults.

Physical and Chemical Properties. The physical and chemical properties of BCEE have been determined (Table 4-1), and further research on these properties does not appear to be essential.

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to BCEE.

Environmental Fate. Although there is information that provides general prediction of the likely fate and transport of BCEE in the environment, quantitative data are not available for most fate processes. Reliable quantitative data on rates of volatilization from water and soil, atmospheric oxidation, hydrolysis in water, and biodegradation in soil and water would be useful in estimating likely concentrations of BCEE in air, soil, and water around waste sites and other possible sources of BCEE emissions.

Bioavailability from Environmental Media. No studies were located on the relative bioavailability of BCEE in different environmental media. Based on the physical properties of BCEE, it would not be expected that bioavailability would vary widely between media, but studies to investigate this would be helpful in risk assessments involving exposure to BCEE in soil or food.

Available data suggest that contamination of water may occur around chemical waste sites or industrial facilities where BCEE is present. For this reason, additional monitoring data on BCEE concentrations in water (both surface water and groundwater) around such sites would be valuable. Monitoring of BCEE levels in air, soil, fish, and possibly other foods would be helpful in estimating the significance of exposures through these media.

Food Chain Bioaccumulation. No studies were located on food chain bioaccumulation of BCEE; studies designed to evaluate potential BCEE accumulation in fish and plants would also be valuable.

Exposure Levels in Environmental Media. Available data suggest that contamination of water may occur around chemical waste sites or industrial facilities where BCEE is present. For this reason, additional monitoring data on BCEE concentrations in water (both surface water and groundwater) around such sites would be valuable. Monitoring of BCEE levels in air, soil, fish, and possibly other foods would be helpful in estimating the significance of exposures through these media.

Exposure Levels in Humans. Information on exposure of the general population to BCEE is limited. The compound has been reported in drinking water in some locations, but many water supplies have not been tested. It would appear that an increased monitoring of drinking water supplies for this compound would be beneficial. Similarly, data on typical occupational exposure levels and durations would be valuable in estimating doses to workers, and data on exposure levels around chemical waste sites would be valuable in determining whether nearby residents are likely to be subject to significant health risk.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

Analytical Methods. Since there are no standard methods for analysis of BCEE in biological materials, development of such methods would be useful. The properties of this compound suggest that it should be amenable to determination in biological samples. It is a relatively high-boiling liquid (178°C) with a low log octanol/water partition coefficient, extractable from water into dichloromethane, relatively stable to hydrolysis, and easily measured by gas chromatography. The high boiling temperature suggests that purge-and-trap and headspace techniques may not be readily applicable to the determination of BCEE in biological samples, but techniques based upon solvent extraction should work well. Norpoth et al. (1986) reported a method for measuring TDGA in urine. Although this is the principal animal metabolite of BCEE, it occurs naturally in the urine of control animals and is also formed by metabolism of other chemicals. For these reasons, it would be helpful to develop methods for the detection and quantification of urinary metabolites that are unique to BCEE, such as N-acetyl-S-[2-(chloroethoxy)ethyl] cysteine or 2-chloroethoxyacetic acid. Although methods exist for the determination of BCEE in environmental samples, detection limits are not adequate to measure BCEE in water or air at low concentrations.

Consequently, improvements in sensitivity would be helpful. The problem of high humidity interfering with the collection of BCEE from air (lowered breakthrough volume) should also be addressed.

6.3 Ongoing Studies

No ongoing studies were identified for BCEE.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding BCEE in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs which are substance specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for BCEE.

Table 7-1. Regulations and Guidelines Applicable to Bis(2-chloroethyl)Ether

Agency	Description	Information	Reference
		Air	
EPA	RfC	No data	IRIS 2002
WHO	Air quality guidelines	No data	WHO 2010
		Water & Food	
EPA	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water regulations	No data	EPA 2009
	RfD	No data	IRIS 2002
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	No data[a]	FDA 2013
		Cancer	
ACGIH	Carcinogenicity classification	A4[b]	ACGIH 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	B2[c,d]	IRIS 2002
IARC	Carcinogenicity classification	Group 3[e,f]	IARC 1999, 2017
		Occupational	
ACGIH	TLV	5 ppm[g]	ACGIH 2016
	STEL	10 ppm[g]	
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	15 ppm (90 mg/m^3)[g,h]	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	5 ppm (30 mg/m^3)[g,i]	NIOSH 2016
	STEL	10 ppm (60 mg/m^3)[g,i]	
	IDLH	100 ppm[i]	

Table 7-1. Regulations and Guidelines Applicable to Bis(2-chloroethyl)Ether

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air		DOE 2016a
	PAC-1[j]	10 ppm	
	PAC-2[j]	25 ppm	
	PAC-3[j]	250 ppm	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]A4: not classifiable as a human carcinogen.
Group 2B: possibly carcinogenic to humans.
[c]Group B2: probable human carcinogen.
[d]Based on positive carcinogenicity results in two strains of mice and evidence of mutagenicity.
[e]Group 3: not classifiable as to its carcinogenicity to humans.
[f]Based on inadequate evidence of carcinogenicity in humans and limited evidence in experimental animals.
[g]Skin notation.
[h]Ceiling concentration; exposure concentration should not be exceeded at any time during an 8-hour shift.
[i]Potential occupational carcinogen
[j]Definitions of PAC terminology are available from DOE (2016b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: The acute-duration inhalation database was not considered suitable for derivation of an MRL because the study design and results of the only available study were poorly reported, had a lack of incidence data, and only examined a limited number of potential endpoints.

Schrenk et al. (1933) reported slight nasal irritation in guinea pigs exposed to 35 ppm BCEE for up to 15 hours. At higher concentrations (≥105 ppm), lung congestion, edema, and hemorrhage; loss of consciousness and decreased motility; and death were observed. Eye irritation as evidenced as squinting at ≥105 ppm and lacrimation at ≥260 ppm were also noted. The investigators did not report whether other potential endpoints were examined or whether a histological examination of the respiratory tract was conducted.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.02 ppm
Critical Effect: Decreased body weight gain
Reference: Dow Chemical 1958
Point of Departure: LOAEL of 69 ppm
Uncertainty Factor: 1,000
LSE Graph Key: 4
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.02 ppm was derived for BCEE. The MRL is based on a LOAEL of 69 ppm for increases in body weight gain in rats exposed to BCEE for 130 days (Dow Chemical 1958). The LOAEL was adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: The Dow Chemical (1958) study examined a wide range of potential endpoints, including the lungs; the only adverse finding was a decrease in body weight gain. This effect was also observed in guinea pigs similarly exposed (Dow Chemical 1958).

Selection of the Principal Study: The Dow Chemical (1958) study is the only available intermediate-duration inhalation study.

Summary of the Principal Study:

Dow Chemical. 1958. Results of repeated exposures of laboratory animals to the vapor of dichlorodiethyl ether at a concentration of 69 mm. Midland, MI: The Dow Chemical Company.

Groups of 15 male and 15 female rats were exposed to 0 or 69 ppm BCEE 7 hours/day, 5 days/week for 130 days. The following parameters were used to assess toxicity: clinical signs, body weight, organ weight, gross necropsy, histopathology, and hematological parameters. A decrease in body weight gain was observed in male rats; a decrease was also observed in females, but the was less marked. No alterations in red blood cell, white blood cell, hemoglobin, neutrophil, lymphocyte, or blood urea nitrogen levels were observed. No alterations in organ weight or histopathology were observed in the lungs, heart, liver, or kidneys were observed.

Selection of the Point of Departure for the MRL: The LOAEL of 69 ppm for decreased body weight gain was selected as the basis of the MRL.

Adjustment for Intermittent Exposure: The LOAEL was adjusted for intermittent exposure (7 hours/day, 5 days/week)

Human Equivalent Concentration: The LOAEL was converted to a human equivalent concentration.

Uncertainty Factor: The human equivalent LOAEL was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: A decrease in body weight gain was also observed in rats receiving gavage administration of 25 mg/kg BCEE for 78 weeks.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for BCEE.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Available data on the acute-duration oral toxicity of BCEE is limited to LD_{50} studies in rats and mice (Drake and Myer 1992; Smyth and Carpenter 1948).

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies were identified for BCEE.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(2-chloroethyl)ether (BCEE)
CAS Numbers: 111-44-4
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: Two studies have evaluated the chronic toxicity of BCEE (Innes et al. 1969; Weisburger et al. 1981); however, the primary focus of both studies was carcinogenicity. The only noncancer endpoint reported was a decrease in body weight gain observed in rats administered 25 (females only) or 50 mg/kg BCEE twice per week for 18 months (Weisburger et al. 1981).

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BIS(2-CHLOROETHYL)ETHER

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to bis(2-chloroethyl)ether.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for bis(2-chloroethyl)ether. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of bis(2-chloroethyl)ether have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of bis(2-chloroethyl)ether are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for bis(2-chloroethyl)ether (ATSDR 1989), thus, the literature search was restricted to studies published between January 1987 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for bis(2-chloroethyl)ether. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to bis(2-chloro-ethyl)ether were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((6K7D1G5M5N[rn] OR 111-44-4[rn] OR "bis(2-chloroethyl)ether"[supplementary concept] OR "bis(2-chloroethyl)ether"[nm]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[mhda])) OR (("1,1'-Oxybis(2-chloro)ethane"[tw] OR "1,5-Dichloro-3-oxapentane"[tw] OR "1-Chloro-2-(beta-chloroethoxy)ethane"[tw] OR "2,2'-Dichloorethylether"[tw] OR "2,2'-Dichlor-diaethylaether"[tw] OR "2,2'-Dichlorethyl ether"[tw] OR "2,2'-Dichlorodiethyl ether"[tw] OR "2,2'-Dichloroethyl ether"[tw] OR "2,2'-Dicloroetiletere"[tw] OR "2-Chloroethyl ether"[tw] OR "BCEE"[tw] OR "beta,beta-Dichlorodiethyl ether"[tw] OR "Bis(2-chloroethyl) ether"[tw] OR "Bis(2-chloroethyl)ether"[tw] OR "Bis(beta-chloroethyl) ether"[tw] OR "Bis(chloro-2-ethyl) oxide"[tw] OR "Chlorex"[tw] OR "Chloroethyl ether"[tw] OR "Clorex"[tw] OR "DCEE"[tw] OR "Di(2-chloroethyl) ether"[tw] OR "Di(beta-chloroethyl)ether"[tw] OR "Dichloroether"[tw] OR "Dichloroethyl ether"[tw] OR "Dichloroethyl oxide"[tw] OR "Dwuchlorodwuetylowy eter"[tw] OR "Ether dichlore"[tw] OR "Khloreks"[tw] OR "Oxyde de chlorethyle"[tw] OR "sym-Dichloroethyl ether"[tw]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[crdat] OR 1987/01/01 : 3000[edat]))
Toxline	
03/2017	("1 1'-oxybis (2-chloro) ethane" OR "1 5-dichloro-3-oxapentane" OR "1-chloro-2- (beta-chloroethoxy) ethane" OR "2 2'-dichloorethylether" OR "2 2'-dichlor-diaethylaether" OR "2 2'-dichlorethyl ether" OR "2 2'-dichlorodiethyl ether" OR "2 2'-dichloroethyl ether" OR "2 2'-dicloroetiletere" OR "2-chloroethyl ether" OR "bcee" OR "beta beta-dichlorodiethyl ether" OR "bis (2-chloroethyl) ether" OR "bis (2-chloroethyl) ether" OR "bis (beta-chloroethyl) ether" OR "bis (chloro-2-ethyl) oxide" OR "chlorex" OR "chloroethyl ether" OR "clorex" OR "dcee" OR "di (2-chloroethyl) ether" OR "di (beta-chloroethyl) ether" OR "dichloroether" OR "dichloroethyl ether" OR "dichloroethyl oxide" OR "dwuchlorodwuetylowy eter" OR "ether dichlore" OR "khloreks" OR "oxyde de chlorethyle" OR "sym-dichloroethyl ether" OR 111-44-4 [rn]) AND 1987:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 15:05:12 ON 16 MAR 2017 CHARGED TO COST=EH011.13.01.01.ODC L1 835 SEA 111-44-4 L2 809 SEA L1 NOT TSCATS/FS L3 624 SEA L2 NOT PATENT/DT L4 398 SEA L3 AND PY>=1987 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)

Table B-2. Database Query Strings

Database search date	Query string
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 198 SEA L4 AND L37 L39 4 SEA L38 AND MEDLINE/FS L40 3 SEA L38 AND BIOSIS/FS L41 177 SEA L38 AND CAPLUS/FS L42 14 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 191 DUP REM L39 L40 L42 L41 (7 DUPLICATES REMOVED) L*** DEL 4 S L38 AND MEDLINE/FS L*** DEL 4 S L38 AND MEDLINE/FS L44 4 SEA L43 L*** DEL 3 S L38 AND BIOSIS/FS L*** DEL 3 S L38 AND BIOSIS/FS L45 3 SEA L43 L*** DEL 177 S L38 AND CAPLUS/FS L*** DEL 177 S L38 AND CAPLUS/FS L46 172 SEA L43 L*** DEL 14 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 14 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 12 SEA L43 L48 187 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS SAVE TEMP L48 BIS2/A D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 111-44-4
NTP	
03/2017	"111-44-4" OR "bis(2-Chloroethyl)ether" OR "Bis(2-chloroethyl) ether" OR "2,2'-Dichloorethylether" OR "2,2'-Dichlorethyl ether" OR "2,2'-Dichlorodiethyl ether" OR "2,2'-Dichloroethyl ether" OR "2-Chloroethyl ether" OR "Chloroethyl ether" OR "Dichloroethyl ether" OR "Dichloroethyl oxide" OR "sym-Dichloroethyl ether"
NIH RePORTER	
05/2017	Active projects "1,1'-Oxybis(2-chloro)ethane" OR "1,5-Dichloro-3-oxapentane" OR "1-Chloro-2-(beta-chloroethoxy)ethane" OR "2,2'-Dichloorethylether" OR "2,2'-Dichlor-diaethylaether" OR "2,2'-Dichlorethyl ether" OR "2,2'-Dichlorodiethyl ether" OR "2,2'-Dichloroethyl ether" OR "2,2'-Dicloroetiletere" OR "2-Chloroethyl ether" OR "BCEE" OR "beta,beta-Dichlorodiethyl ether" OR "Bis(2-chloroethyl) ether" OR "Bis(2-chloroethyl)ether" OR "Bis(beta-chloroethyl) ether" OR "Bis(chloro-2-ethyl) oxide" OR "Chlorex" OR "Chloroethyl ether" OR "Clorex" OR "DCEE" OR "Di(2-chloroethyl) ether" OR "Di(beta-chloroethyl)ether" OR "Dichloroether" OR "Dichloroethyl ether" OR "Dichloroethyl

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	oxide" OR "Dwuchlorodwuetylowy eter" OR "Ether dichlore" OR "Khloreks" OR "Oxyde de chlorethyle" OR "sym-Dichloroethyl ether"
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 317
- Number of records identified from other strategies: 26
- Total number of records to undergo literature screening: 343

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on bis(2-chloro-ethyl)ether:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

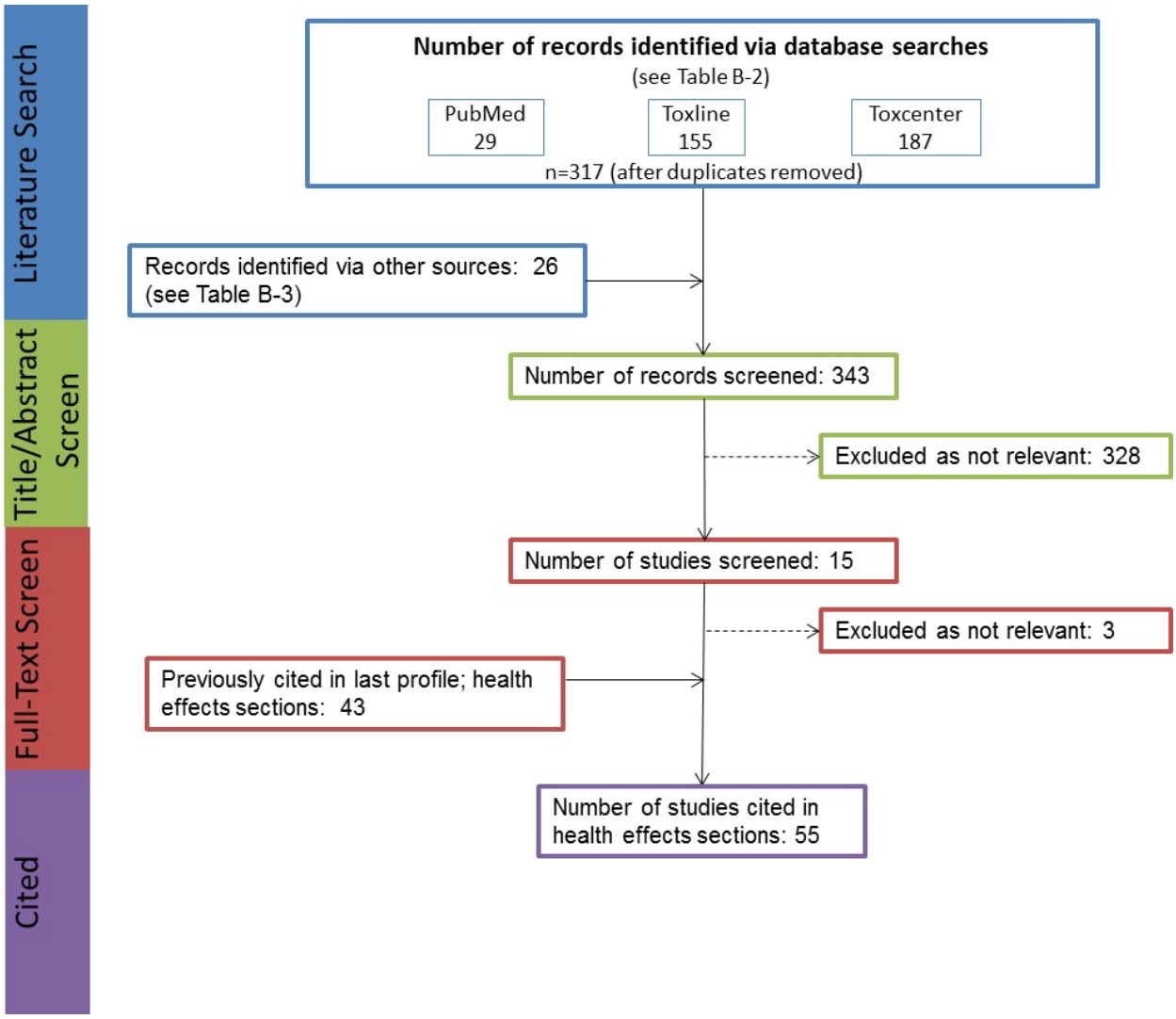
- Number of titles and abstracts screened: 343
- Number of studies considered relevant and moved to the next step: 15

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 15
- Number of studies cited in the health effects sections of the existing toxicological profile (December, 1989): 43
- Total number of studies cited in the health effects sections of the updated profile: 55

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. March 2017 Literature Search Results and Screen for Bis(2-chloroethyl)ether



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

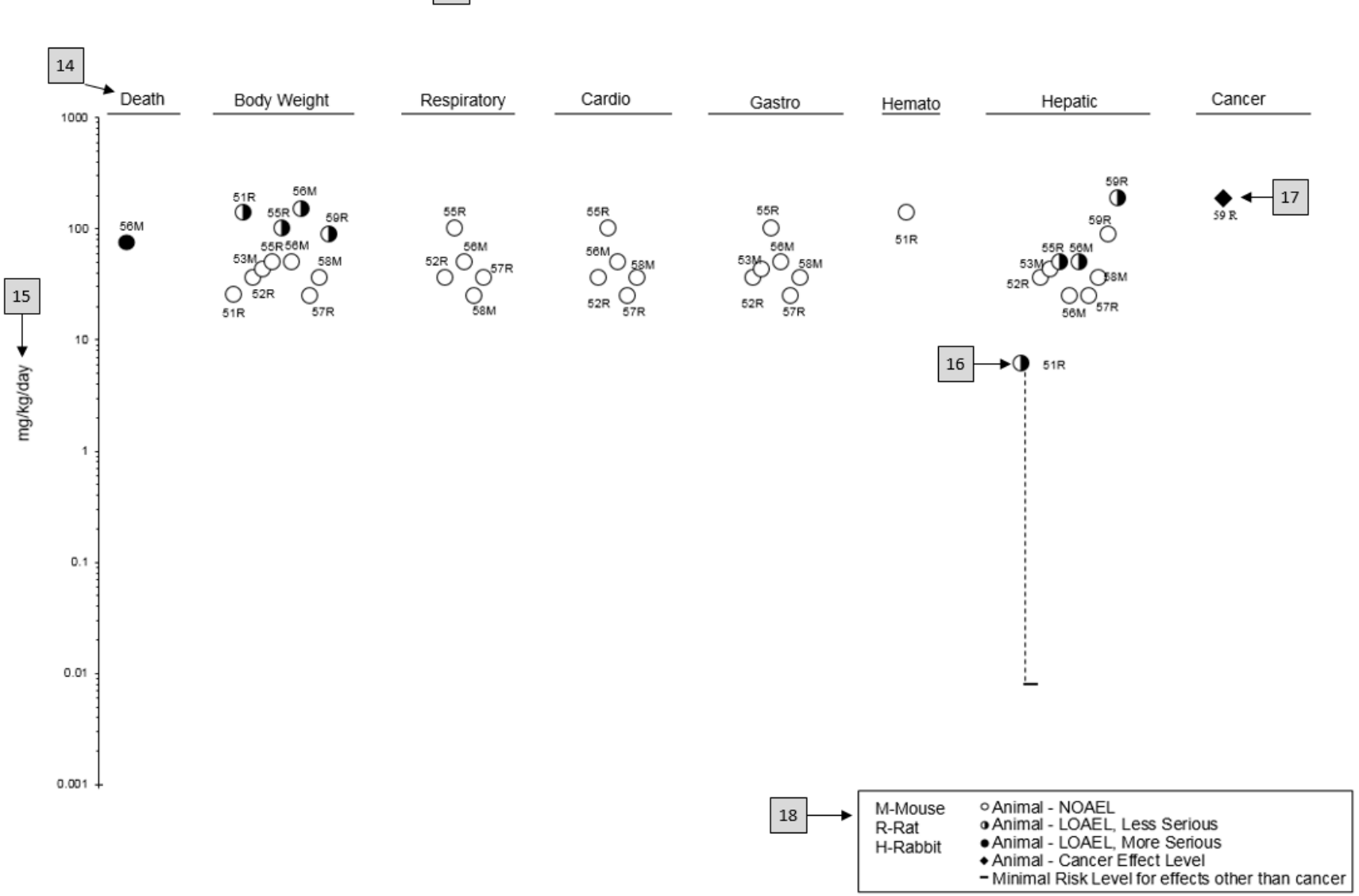
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) $\geq$1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result