Toxicological Profile for Bis(Chloromethyl)Ether (BCME)

November 2017

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
November 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-Chloromethyl)Ether* 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(chloromethyl)ether (BCME; CAS No. 542-88-1) is a colorless liquid that readily evaporates into air. BCME was used in the production of several types of polymers, resins, and textiles. However, most of these uses have been stopped and BCME is now only used in small amounts in fully enclosed systems in manufacturing facilities. BCME has a relatively short half-life in air and water, and exposure to the general population is minimal.

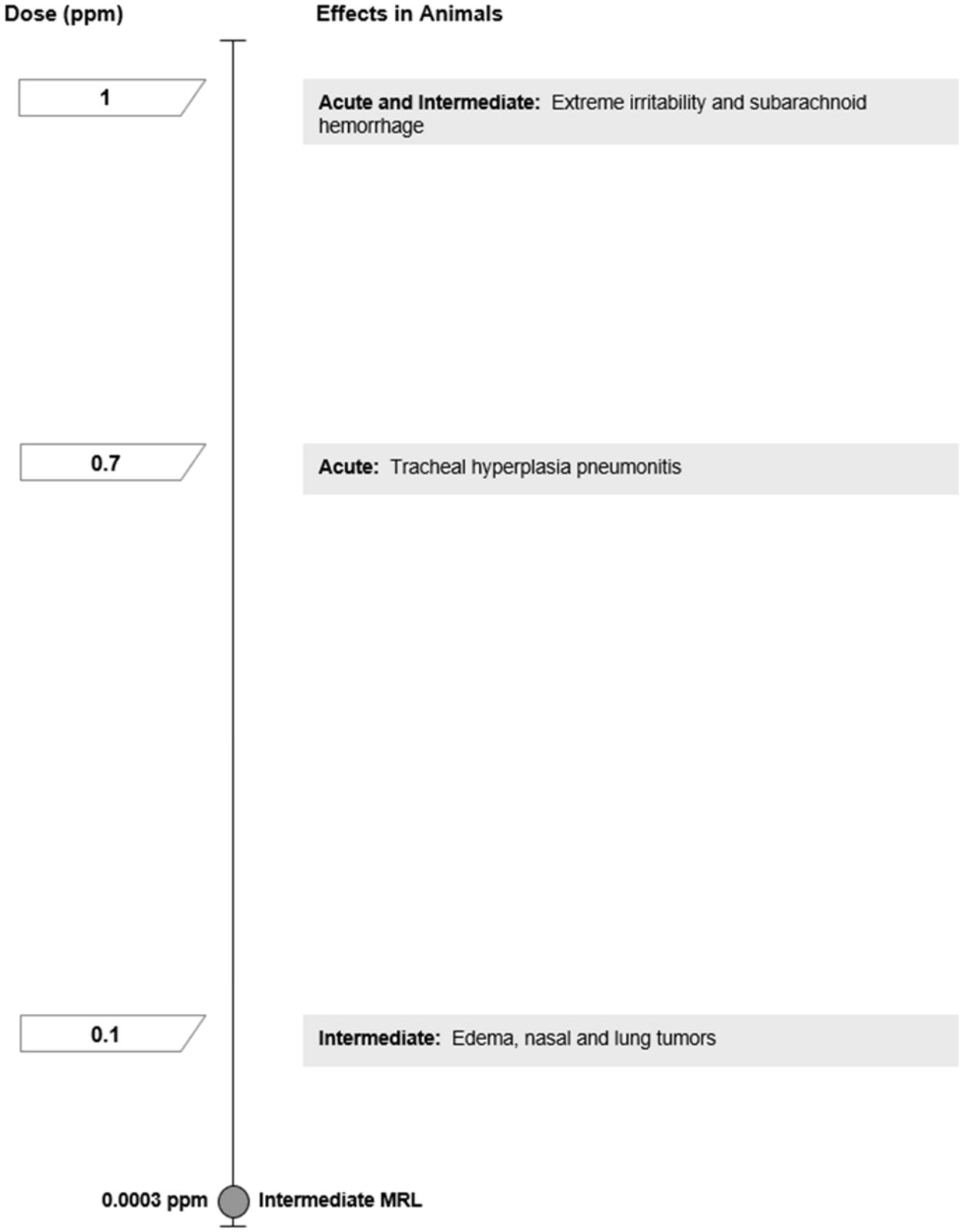
1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of BCME comes primarily from shorter duration inhalation studies in laboratory animals, many of which examined a limited number of potential endpoints. A number of occupational exposure studies have focused on the carcinogenicity of BCME. As illustrated in Figure 1-1, the most sensitive effects appear to be non-neoplastic respiratory effects, neurological effects, and cancer. The most sensitive target is epithelial tissues at the point of contact with BCME, which is consistent with the short half-life of BCME in aqueous media.

Respiratory Effects. A single exposure to 0.7 ppm resulted in tracheal epithelial hyperplasia in rats and pneumonitis in hamsters (Drew et al. 1975). Repeated exposure to 1 ppm resulted in signs of respiratory distress in mice (Leong et al. 1971); this concentration also resulted in increases in mortality. Gross necropsy of rats exposed to 0.1 ppm for 6 months did not find alterations in the respiratory tract (Leong et al. 1981). At lethal concentrations, lung congestion, hemorrhage, and edema have been observed.

Neurological Effects. Extreme irritability was noted in rats and hamsters exposed to 1 ppm for at least 10 exposures (Drew et al. 1975). Subarachnoid hemorrhaging was also observed in the rats. This exposure also resulted in an extreme shortening of the lifespan of the exposed rats and hamsters.

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



Cancer Effects. Lung cancer has been observed in a number of occupational exposure studies of workers exposed to BCME or chloromethyl ether containing BCME (for example, Collingwood et al. 1987; Gowers et al. 1993; Weiss 1989; see Section 2.19 for complete citation list). Studies in laboratory animals have shown that chronic exposure is not required for BCME tumorigenesis. Nasal and/or lung tumors were reported in rats exposed to 0.1 ppm BCME for 4 weeks (Kuschner et al. 1975) or rats and mice exposed for 6 months (Leong et al. 1981).

The U.S. Department of Health and Human Services (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2002), and International Agency for Research on Cancer (IARC 2012, 2017) have concluded that BCME is a human carcinogen.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-2, the limited available inhalation data for BCME suggest that the respiratory tract, nervous system, and cancer are sensitive targets of toxicity. The oral database is limited to an acute lethality study and was not considered adequate for deriving MRLs. The acute-duration inhalation MRL value is summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Cancer, the respiratory tract, and nervous system are the most sensitive targets of bis(chloromethyl)ether.

Numbers in circles are the lowest LOAELs (ppm) for all health effects in animals; no human data were identified.

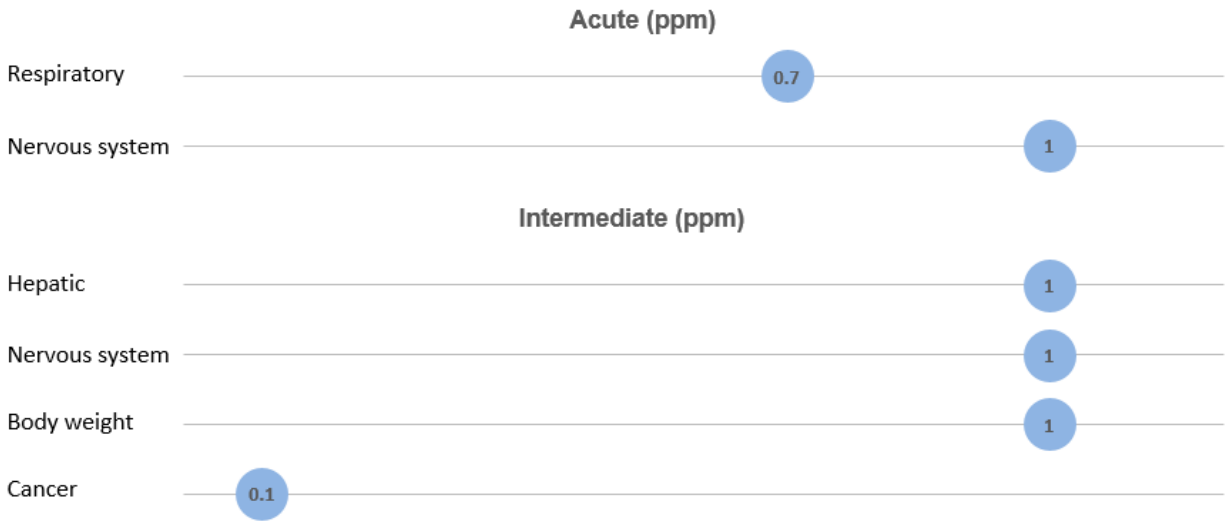


Table 1-1. Minimal Risk Levels (MRLs) for Bis(Chloromethyl)Ether[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.0003	Respiratory effects	0.1 (NOAEL)	100	Leong et al. 1971
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.

NOAEL = no-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 BCME. 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 BCME, 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; no oral or dermal data were identified for BCME.

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 BCME are indicated in Table 2-1 and Figure 2-2.

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.

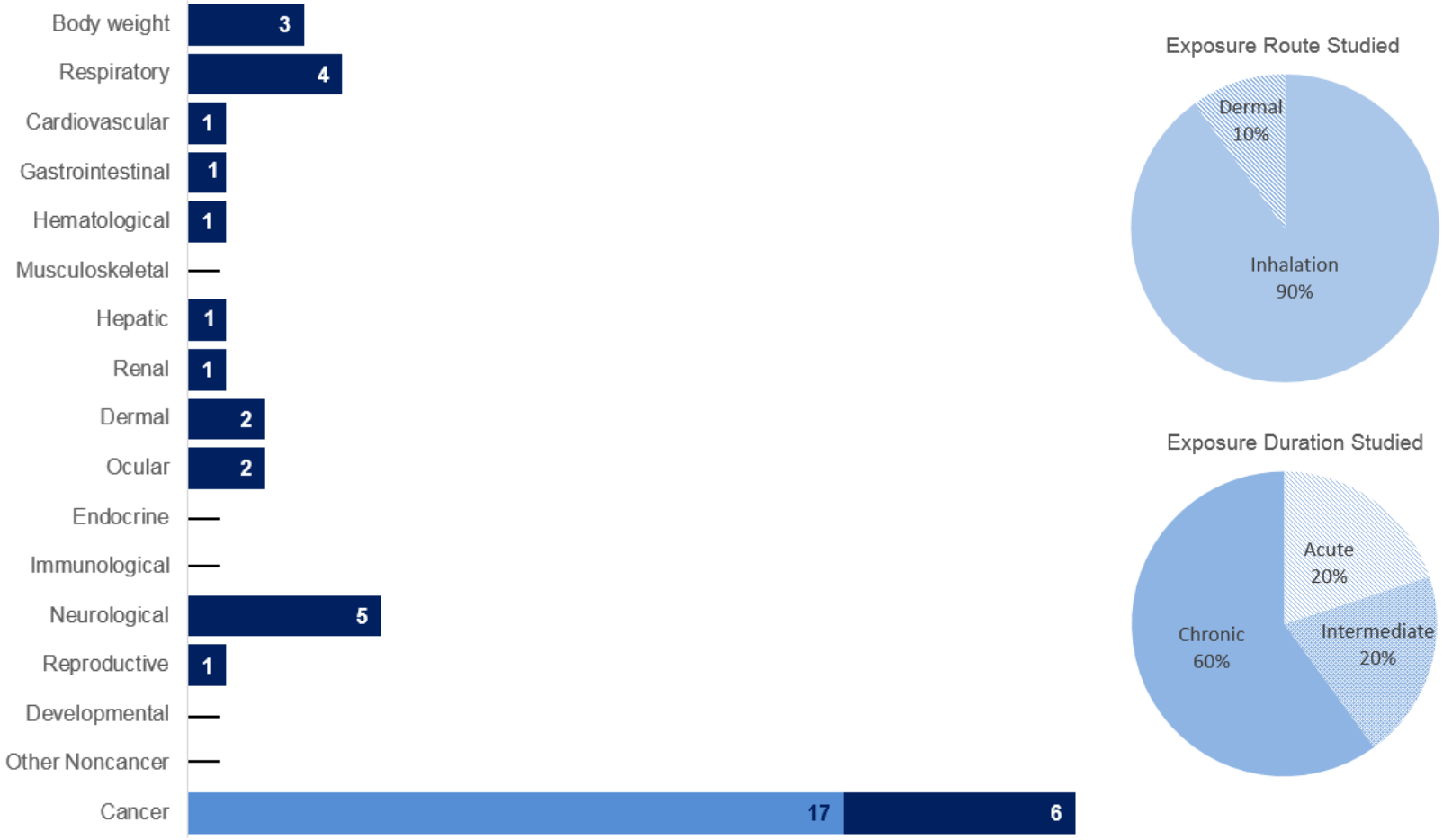
The health effects of BCME have been evaluated in occupational exposure studies and in animal studies. As illustrated in Figure 2-1, most of the health effects data come from animal studies mostly examining a limited number of health endpoints and from occupational cancer studies. In addition to the studies summarized in Figure 2-1, five studies have examined acute lethality following inhalation, oral, or dermal exposure. Animal data are available for most health effect categories, 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 Endpoints:** Respiratory distress, tracheal and bronchial hyperplasia and squamous metaplasia, and pneumonitis have been observed in laboratory animals.
- **Nervous System Endpoint:** At lethal concentrations, subarachnoid hemorrhage and extreme irritability have been observed in laboratory animals.
- **Cancer Endpoint:** Lung cancer has been reported in occupational exposure studies. Nasal and lung tumors have been reported in rats and mice following intermediate-duration inhalation exposure.

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

Most studies examined the potential cancer, nervous system, and respiratory effects of bis(chloromethyl)ether
More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 30 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Bis(Chloromethyl)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 (Sprague-Dawley) 25 M	7 hours (allowed to recover over lifetime)	0, 0.7, 2.1, 6.9, 9.5	HP, LE	Death			2.1	Decreased lifespan, 36 days compared to 462 days in controls
					Resp		0.7		Increased relative lung weight at ≥0.7 ppm; increased incidence of tracheal epithelial hyperplasia at 0.7 ppm; tracheal and bronchial hyperplasia and bronchial squamous metaplasia at 2.1 ppm
Drew et al. 1975									
2	Rat (Sprague-Dawley) 50 M	1, 3, or 10 days 6 hours/day	1	LE, CS	Death			1	Decreased lifespan in rats exposed for 3 or 10 days (168 and 21 days, respectively) compared to controls (462 days)
					Neuro			1	Subarachnoid hemorrhage and extreme irritability in rats exposed for 10 days
Drew et al. 1975									
3	Rat (Sprague-Dawley) M	7 hours	0.94, 4.6, 6.2, 7.3, 9, 19, 74	LE	Death			7.0	LC_{50}
Drew et al. 1975									
4	Hamster (Golden Syrian) M	7 hours	0.94, 4.6, 6.2, 7.3, 9, 19, 74	LE	Death			7.0	LC_{50}
Drew et al. 1975									

Table 2-1. Levels of Significant Exposure to Bis(Chloromethyl)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	Hamster (Golden Syrian) 25 M	7 hours (allowed to recover over lifetime)	0, 0.7, 2.1, 6.9, 9.5	HP, LE	Death			2.1	Decreased lifespan, 68 days compared to 675 days in controls
					Resp			0.7	Increased relative lung weight at ≥0.7 ppm; increased incidence of pneumonitis at 0.7 ppm; tracheal and bronchial hyperplasia and hyperplasia with atypia at 2.1 ppm
Drew et al. 1975									
6	Hamster (Golden Syrian) 50 M	1, 3, or 10 days 6 hours/day	1	LE, CS	Death			1	Decreased lifespan in hamsters exposed for 3 or 10 days (471 and 137 days, respectively) compared to controls (675 days)
					Neuro			1	Extreme irritability in hamsters exposed for 10 days
Drew et al. 1975									
7	Mouse (A/ Heston) M	6 hours	2.7–10.6	LE	Death			5.3	LC_{50}
Leong et al. 1971									
INTERMEDIATE EXPOSURE									
8	Rat (Sprague-Dawley) 50 M	30 days 6 hours/day	1	LE, CS	Death			1	Decreased lifespan (23 days) compared to controls (462 days)
					Neuro			1	Subarachnoid hemorrhage and extreme irritability
Drew et al. 1975									
9	Rat	4 weeks 5 days/week; 6 hours/day			Cancer			0.1	CEL: nasal and lung tumors
Kuschner et al. 1975									

Table 2-1. Levels of Significant Exposure to Bis(Chloromethyl)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
10	Rat (Sprague-Dawley) 120 M	6 months 6 hours/day; 5 days/week	0, 0.001, 0.01, 0.1	BC, HP, BW	Death			0.1	Increased mortality during the post-exposure period
					Bd wt	0.1			
					Resp	0.1[b]			
					Cardio	0.1			
					Gastro	0.1			
					Hemato	0.1			
					Hepatic	0.1			
					Renal	0.1			
					Endocr	0.1			
					Ocular	0.1			
					Neuro	0.1			
					Repro	0.1			
					Cancer			0.1	CEL: nasal esthesioneuroepithelioma tumors
Leong et al. 1981									
11	Mouse (A/Heston) 50 M	82 exposure days 6 hours/day, 5 days/week	0, 1	LE, BW, HP	Death			1	37/50 animals died compared to 6/50 in controls
					Bd Wt			1	Weight loss; magnitude not reported
					Resp			1	Respiratory distress
					Cancer				No increases in the incidence of lung tumors
Leong et al. 1971									
12	Mice (Ha/ICR) 120 M	6 months 6 hours/day; 5 days/week	0, 0.001, 0.01, 0.1	BC, HP	Bd Wt	0.1			
					Cancer			0.1	Increase in pulmonary adenomas in mice dying post-exposure
Leong et al. 1981									

Table 2-1. Levels of Significant Exposure to Bis(Chloromethyl)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
13	Hamster (Golden Syrian) 50 M	30 days 6 hours/day	1	LE	Death			1	Decreased lifespan (42 days) compared to controls (675 days)
					Neuro			1	Subarachnoid hemorrhage and extreme irritability

Drew et al. 1975

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive intermediate MRL; concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.0003 ppm.

BC = biochemistry; Bd Wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS – clinical signs; LC_{50} = lethal concentration, 50% mortality; Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; Neuro = neurological; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to Bis(Chloromethyl)Ether – Inhalation

Acute (≤ 14 days)

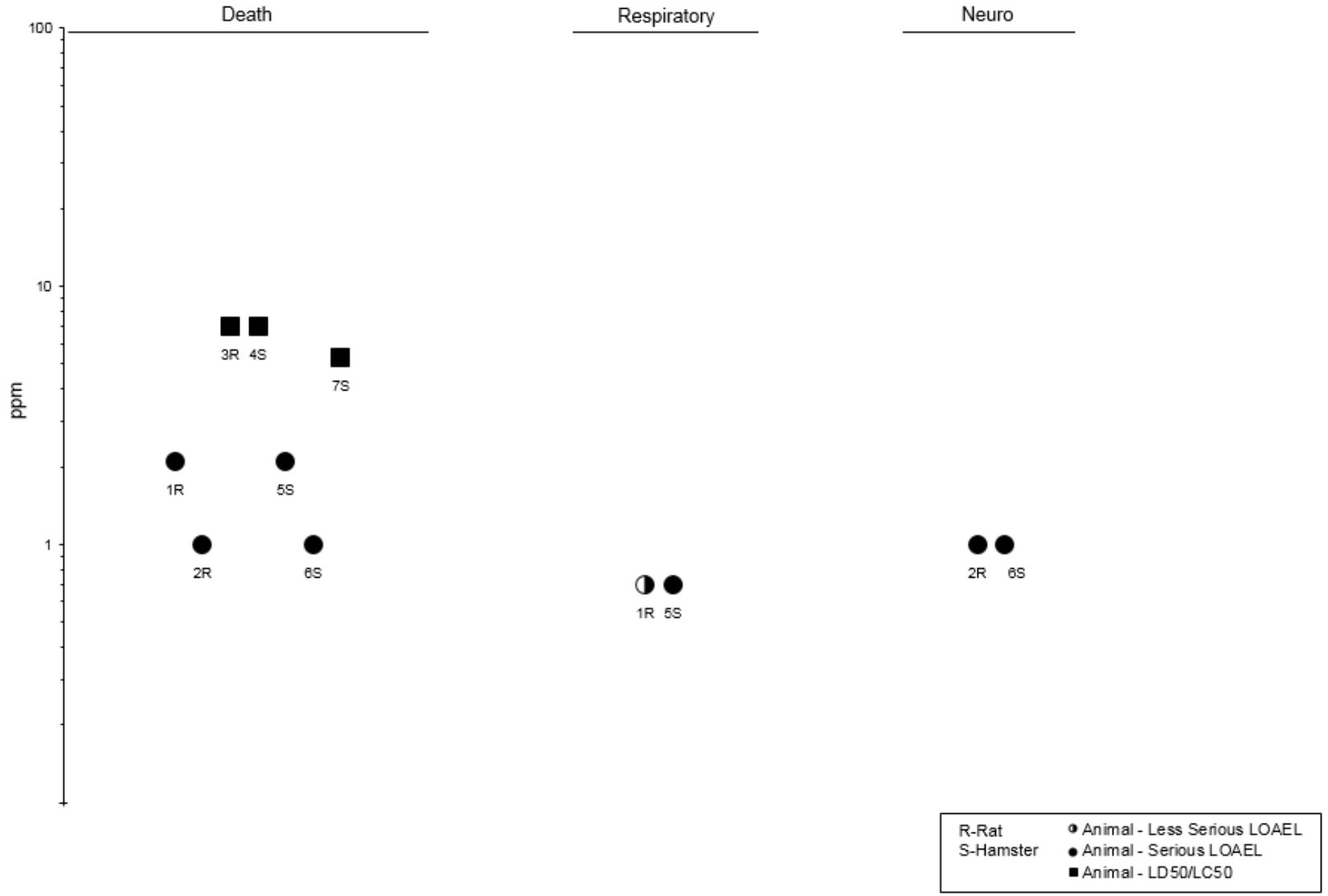
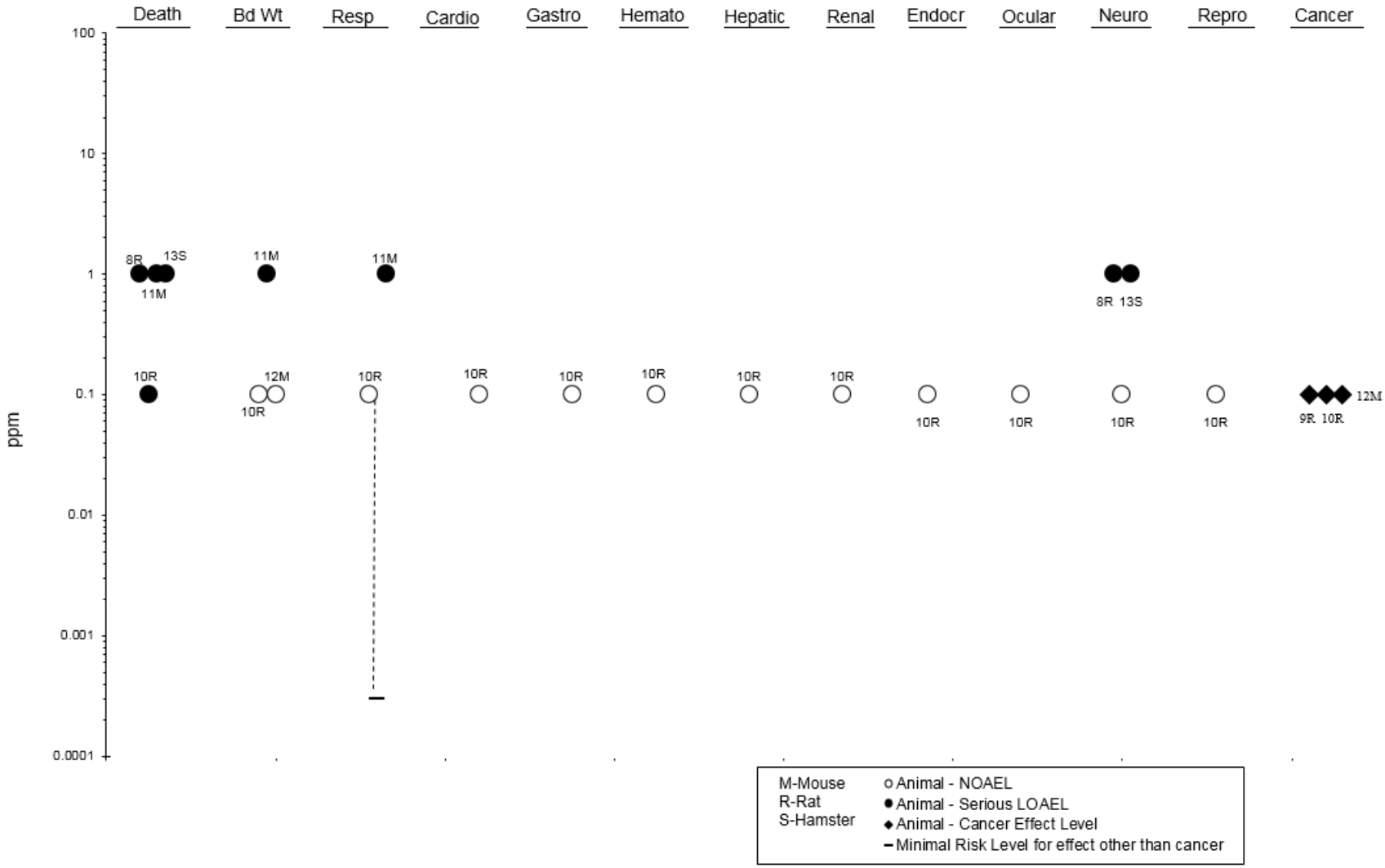


Figure 2-2. Levels of Significant Exposure to Bis(Chloromethyl)Ether – Inhalation

Intermediate (15-364 days)



2.2 DEATH

No reports of acute human lethality due to inhalation of BCME were located. Increased mortality from cancer has been observed in humans exposed to BCME in the workplace, as discussed in detail in Section 2.19.

In rats and hamsters, the acute inhalation LC_{50} for a 7-hour exposure has been estimated to be 7 ppm (Drew et al. 1975). The cause of death was acute lung irritation that resulted in congestion, edema, and hemorrhage. A similar LC_{50} of 5.3 ppm for a 6-hour exposure was estimated in mice (Leong et al. 1971). A single 7-hour exposure to 0.7 ppm did not cause acute or delayed mortality in rats or hamsters, but a single exposure to 2.1 ppm led to marked reduction in life span in both species (Drew et al. 1975). Repeated exposures to 1 ppm led to a duration-dependent increase in mortality. In rats, 3, 10, or 30 exposures to 1 ppm led to a median lifespans of 168, 21, or 23 days; lifespan in the controls was 462 days. Similar decreases in lifespan were also observed in hamsters (Drew et al. 1975). Exposure to concentrations as low as 0.1 ppm caused increased mortality in the post-exposure period in rats when exposure was extended to 6 months (Leong et al. 1981), primarily because of the occurrence of nasal tumors (see Section 2.19).

No studies were located regarding acute lethality in humans following oral exposure to BCME. The acute oral LD_{50} in rats for undiluted BCME is estimated to be 280 mg/kg (Union Carbide 1968).

The estimated LD_{50} for a single dermal application of undiluted BCME to rabbit skin is 370 mg/kg (Union Carbide 1968). No other estimates of lethal dermal doses were located.

2.3 BODY WEIGHT

There are limited data on body weight following inhalation exposure to BCME. No alterations in body weight gain were observed in rats or mice exposed to 0.1 ppm for 6 months (Leong et al. 1981). Weight loss (magnitude not reported) was observed in mice exposed to 1 ppm for 82 days (Leong et al. 1971).

2.4 RESPIRATORY

In humans, exposure to vapors of chloromethyl methyl ether (CME) containing BCME as a contaminant led to increased incidence of chronic bronchitis, manifest as chronic cough and impaired respiratory function (Weiss 1976; Weiss and Boucot 1975). Since CME is itself a lung irritant, it is not possible to determine the degree to which BCME may have contributed to the observed respiratory effects.

Studies in laboratory animals also demonstrate the respiratory toxicity of BCME. At lethal concentrations, lung congestion, edema, and hemorrhage in rats and hamsters have been observed (Drew et al. 1975). A single exposure to ≥0.7 ppm resulted in increases in lung weight, pneumonitis, and tracheal and bronchial hyperplasia (Drew et al. 1975). Exposure of mice to BCME at 1 ppm for 82 days caused marked respiratory distress (Leong et al. 1971), while exposure of rats to 0.1 ppm for 6 months did not result in non-neoplastic lesions in the respiratory tract (Leong et al. 1981).

2.5 CARDIOVASCULAR

Gross necropsy of the heart did not show evidence of lesions in rats exposed to 0.01 ppm BCME for 6 months (Leong et al. 1981).

2.6 GASTROINTESTINAL

No gross lesions were observed in the stomach, small intestine, or large intestine of rats exposed to 0.01 ppm BCME for 6 months (Leong et al. 1981).

2.7 HEMATOLOGICAL

No hematological alterations were observed rats exposed to 0.1 ppm BCME for 6 months (Leong et al. 1981).

2.8 MUSCULOSKELETAL

No studies examining musculoskeletal effects were identified.

2.9 HEPATIC

No gross lesions were observed in the liver of rats exposed to 0.1 ppm BCME for 6 months (Leong et al. 1981).

2.10 RENAL

No renal lesions were observed in the gross necropsy of rats exposed to 0.1 ppm BCME for 6 months (Leong et al. 1981).

2.11 DERMAL

Because BCME is highly reactive, it is directly irritating to skin and other epithelial tissues. Chronic (lifetime) application of BCME (1 mg/dose) to the skin of mice produced a strong corrosive response, including hair loss, hemorrhagic rash, and edema of subcutaneous tissue (Van Duuren et al. 1968). In rabbits, a single application of undiluted BCME led to moderate erythema and marked necrosis, and a primary dermal irritation score of 6 was assigned (Union Carbide 1968). No studies were located regarding dermal effects in humans or animals following inhalation or oral exposure to BCME.

2.12 OCULAR

A dose of 5 µL (7 mg) applied to the eye of rabbits produced severe cornea1 necrosis (Union Carbide 1968).

2.13 ENDOCRINE

Gross necropsy of the thyroid, parathyroid, and adrenal glands did not show evidence of damage in rats following a 6-month exposure to 0.1 ppm (Leong et al. 1981).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans or animals following inhalation, oral or dermal exposure to BCME.

2.15 NEUROLOGICAL

Leong et al. (1981) reported that exposure of male rats to 0.1 ppm for 6 months did not result in observable histopathology in the nervous system, but no tests of nervous system function were performed. Drew et al. (1975) noted extreme irritability in rats and hamsters exposed 10–30 times to 1 ppm of BCME, and concluded that this was evidence of central nervous system effects. However, these symptoms were possibly due to treatment-related stress associated with the discomfort of BCME exposure. An apparent dose-dependent increase in the frequency of subarachnoid hemorrhage was noted, but the cause of these lesions and the significance were not discussed.

No studies were located regarding neurological effects in humans or animals following oral or dermal exposure to BCME.

2.16 REPRODUCTIVE

No studies were located regarding effects on reproductive capacity in humans following inhalation, oral, or dermal exposure to BCME.

Leong et al. (1981) found no evidence testicular damage in rats exposed to 0.1 ppm of BCME in air for 6 months. However, no tests of reproductive function were performed, and no tests were performed on females.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans or animals following inhalation, oral, or dermal exposure to BCME.

2.18 OTHER NONCANCER

Other noncancer effects were not examined in inhalation, oral, or dermal exposure studies.

2.19 CANCER

A number of case studies and epidemiological studies of occupationally-exposed workers indicate that inhalation of BCME or CME containing BCME is associated with increased risk of lung cancer (Albert et al. 1975; Collingwood et al. 1987; DeFonso and Kelton 1976; Figueroa et al. 1973; Gowers et al. 1993;

Lemen et al. 1976; Maher and DeFonso 1987; Pasternack et al. 1977; Reznik et al. 1977; Roe 1985; Sakabe 1973; Thiess et al. 1973; Weiss 1976, 1982, 1989; Weiss and Boucot 1975; Weiss and Nash 1997). Table 2-2 summarizes the data from some of these studies. Although the study populations in these reports were often exposed not only to BCME, but also to CME and other chemicals, the consistent findings strongly support the conclusion that BCME is a lung carcinogen in humans. Although quantitative data on exposure levels were not available for most studies, increased risk as a function of exposure duration and/or qualitative estimates of exposure intensity was noted in some cases (DeFonso and Kelton 1976). Weiss and Nash (1997) reported that significant increases in lung cancer deaths were observed in workers with moderate (standardized mortality ratio [SMR] 7.49, 95% confidence interval [CI] 3.23–14.75) or high (SMR 15.21, 95% CI 7.87–26.6) exposure, but not in those with low exposure (SMR 1.38, 95% CI 0.17–4.98). A high proportion of the respiratory tumors were oat cell carcinomas, a particularly rapid-growing and highly lethal tumor (Figueroa et al. 1973; Gowers et al. 1993; Lemen et al. 1976; Weiss et al. 1979). Some tumors appeared after only 5–10 years of exposure (Weiss 1976; Weiss and Boucot 1975) and in young workers (Figueroa et al. 1973; Reznick et al. 1977). Weiss and Nash (1997) showed that the highest risks were found in workers with latencies of 10–19 years.

Table 2-2. Lung Cancer Mortality in Workers Exposed to Bis(Chloromethyl)Ether or Technical-Grade Chloromethyl Methyl Ether

Exposed population	Duration of exposure	Observed lung cancer deaths	Expected lung cancer deaths	Risk[a]	Reference
669 Chemical plant workers	<1 year (n=389)	3	2.1	1.2	DeFonso and Kelton 1976
	1–5 years (n=170)	5	1.3	3.8 (p<0.05)	
	≥5 years (n=101)	11	1.1	9.6 (p<0.01)	
	Total	19	5.2	3.8 (p<0.001)	
1,446 chemical plant workers (465 exposed)	≤12 years	39	18.1	2.15 (p<0.001)	Weiss et al. 1979
721 chemical plant workers	≤19 years	23	4.5	5.1 (p<0.05)	Pasternack et al. 1977
762 chemical plant workers	≤31 years	32	7.5	4.3 (p<0.01)	Collingwood et al. 1987
134 anion-exchange plant workers	≥5 years	5	0.54	9,24	Lemen et al. 1976

Table 2-2. Lung Cancer Mortality in Workers Exposed to Bis(Chloromethyl)Ether or Technical-Grade Chloromethyl Methyl Ether

Exposed population	Duration of exposure	Observed lung cancer deaths	Expected lung cancer deaths	Risk[a]	Reference
1,203 anion-exchange plant workers (258 exposed)	3,785 person-years at risk			5.0 (95% confidence interval 2.0–12.3)[b]	Gowers et al. 1993

[a]Observed/expected.
[b]Relative risk by internal comparison.

A number of studies in animals confirm that BCME is a potent carcinogen with a short latency period. Some of the key data from these studies are summarized in Table 2-3. As shown in the table, levels as low as 0.1 ppm of BCME produce a high incidence (60–86%) of respiratory tract tumors in exposed rats, and some tumors developed in animals that had been exposed for periods as short as 2 weeks (Kuschner et al. 1975; Laskin et al. 1971; Leong et al. 1981). Most of the tumors were nasal tumors, although some lung tumors also developed. Under similar conditions, mice exposed to 0.1–1.0 ppm did not develop nasal tumors, but they did have a slight increase in the incidence of mice with pulmonary adenomas (Leong et al. 1981) and in the number of tumors per tumor-bearing mouse (Leong et al. 1971). No increased incidence of nasal tumors or lung adenomas was noted in rats or mice exposed to 0.01 or 0.001 ppm (Leong et al. 1981). Hamsters appear to be more resistant to the carcinogenic effects of BCME than mice or rats. However, Drew et al. (1975) observed nasal tumors after 2 years in two hamsters that had been exposed only 1–3 times to 1.0 ppm BCME. Hamsters exposed for ≥10 times to 1.0 ppm had shortened lifespans, so tumors may not have had time to develop.

Table 2-3. Inhalation Carcinogenicity of Bis(Chloromethyl)Ether in Animals

Species (strain)	Exposure level (ppm)	Exposure duration[a]	Respiratory tumor type[b]	Incidence	Reference
Rat (Sprague-Dawley)	0.1	10 exposures	Nasal esthioneuroepithelioma, lung squamous cell carcinoma, and other respiratory tract tumors	1/41 (2%)	Kuschner et al. 1975
		20 exposures		3/46 (6%)	
		40 exposures		4/18 (22%)	
		60 exposures		4/18 (22%)	
		80 exposures		15/34 (44%)	
		100 exposures		12/20 (60%)	

Table 2-3. Inhalation Carcinogenicity of Bis(Chloromethyl)Ether in Animals

Species (strain)	Exposure level (ppm)	Exposure duration[a]	Respiratory tumor type[b]	Incidence	Reference
Rat (Sprague-Dawley)	0	6 months	Nasal esthioneuroepithelioma	0/112 (0%)	Leong et al. 1981
	0.001			0/113 (0%)	
	0.01			0/111 (0%)	
	0.1			96/111 (86%)	
Mouse (A/H)	0	21 weeks	Lung adenoma	20/49 (41%)	Leong et al. 1971
	1			26/47 (55%)	
Mouse (Ha/ICR)	0	6 months	Pulmonary adenoma	9/86 (10%)	Leong et al. 1981
	0.001			5/54 (9%)	
	0.01			3/37 (8%)	
	0.1			8/27 (30%)	
Hamster (Golden Syrian)	0.1	67 weeks	Lung carcinoma	1/100 (1%)	Kushner et al. 1975
Hamster (Golden Syrian)	0.7	6 hours	Nasal esthioneuroepithelioma	1/25 (4%)	Drew et al. 1975
		6 hours/day for 3 days		1/25 (4%)	
		6 hours/day for 10 days		0/25 (0%)	
		6 hours/day for 30 days		0/25 (0%)	

[a]Unless otherwise noted, exposures were for 6 hours/day, 5 days/week.
[b]Observation, after exposure, was for lifetime or until animals were moribund.

Following dermal exposure (skin painting), BCME was found to produce skin papillomas and carcinomas in >50% of mice tested after 325 days of treatment (Van Duuren et al. 1968). The carcinomas appeared early, with the first appearing after only 196 days of skin application. Subsequent reports confirmed these findings (Van Duuren et al. 1969, 1972; Zajdela et al. 1980). BCME has also been shown to be a skin tumor initiator. Thus, a single skin application of 1 mg of BCME followed by treatment with a known tumor promoter (phorbol myristate acetate) produced papillomas in a high percentage of treated mice (Van Duuren et al. 1968, 1969; Zajdela et al. 1980). No studies were located regarding carcinogenicity in humans or animals following oral exposure to BCME.

The Department of Health and Human Services has determined that BCME is a known human carcinogen (NTP 2016). EPA has concluded that BCME is a known human carcinogen (EPA Group A) (IRIS 2002) and IARC has concluded that BCME is carcinogenic to humans (Group 1) (IARC 2012, 2017).

2.20 GENOTOXICITY

No studies were located regarding genotoxic effects in humans following inhalation, oral, or dermal exposure to BCME. Leong et al. (1981) did not observe any effects on bone marrow chromosomes in rats exposed to 0.1 ppm for 6 months (6 hours/day, 5 days/week). However, the data as reported are not sufficient to conclude definitely that BCME is inactive in this system.

The genotoxicity of BCME has been investigated in several strains of bacteria (see Table 2-4) but such systems may not be optimal for investigating the effects of such a rapidly hydrolyzed material. Specifically, if BCME acts as an alkylating agent to damage DNA, then tests that favor hydrolysis before entry into the cell can occur may yield misleading results.

Table 2-4. Genotoxicity of Bis(Chloromethyl)Ether *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (strains TA1535, TA1538, TA98)	Gene mutation	+	NA	Anderson and Styles 1978
S. typhimurium (strain TA100)	Gene mutation	+	NA	Anderson and Styles 1978

+ = positive results; NA = not reported

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

3.1 TOXICOKINETICS

No information was located on the toxicokinetics of BCME in humans or animals. It is expected that BCME is rapidly degraded in the aqueous environment of tissues, forming formaldehyde and HCl.

3.1.1 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 located for BCME.

3.1.2 Animal-to-Human Extrapolations

The available suggest that BCME is a respiratory carcinogen in humans and laboratory animals. In the absence of data to the contrary, it is assumed that rodents, particularly rats, are appropriate models for humans.

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 BCME are discussed in Section 5.7, Populations with Potentially High Exposures.

No studies were identified that could be used to evaluate whether children would be more susceptible to the toxicity of BCME than adults; additionally, no developmental toxicity studies were located for humans or animals.

No evidence was located to suggest that any subpopulation is more susceptible to BCME than another. Since no data are available on pharmacokinetics or mechanisms of action, it is not possible to predict populations that might be unusually susceptible to BCME on the basis of genetic traits or health status.

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 BCME 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 BCME 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 BCME 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

No studies were located regarding the presence of BCME in human tissues and fluids. It is expected that BCME does not persist in tissues due to its rapid hydrolysis. Measurement of the hydrolysis products (formaldehyde and HCl) is unlikely to be a useful index of exposure, since levels of these products are highly variable due to formation from other sources, and the contribution from BCME would be extremely small and almost certainly would not be detectable against background levels.

3.3.2 Biomarkers of Effect

No biomarkers of effect were identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

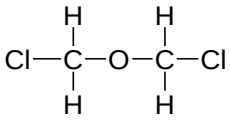
No information was located regarding interactive effects of BCME with other chemicals that would be relevant to its toxicity. Chemicals of special interest include chloromethyl methyl ether, formaldehyde, and HCl, since exposure to BCME frequently occurs along with exposure to CME, and formaldehyde and HCl are formed as BCME decomposes.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

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

Characteristic	Information	Reference
Chemical name	Bis(chloromethyl)ether	NLM 1988
Synonym(s) and registered trade name(s)	Oxybis (chloromethane); dichlorodimethyl ether; monochloromethyl ether	NLM 1988
Chemical formula	$C_2H_4Cl_2O$	Weast 1985
Chemical structure		
Identification numbers:		
CAS Registry	542-88-1	NLM 1988

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

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

Property	Information	Reference
Molecular weight	114.96	Weast 1985
Color	Colorless	Windholz 1983
Physical state	Liquid	Windholz 1983
Melting point	-41.5°C	Weast 1985
Boiling point	104°C	Weast 1985
Density at 20°C	1.328	Weast 1985
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	22,000[a]	Mabey et al. 1982
Organic solvents	Miscible	Weast 1985

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

Partition coefficients:		
Log K_{ow}	-0.38[a]	Mabey et al. 1982
Log K_{oc}	0.08	Mabey et al. 1982
Vapor pressure at 20°C	30	Mabey et al. 1982
Henry's law constant at 25°C	$2.1x10^{-4}$	Mabey et al. 1982
Autoignition temperature	No data	
Flashpoint	19°C	HSDB 1988
Flammability limits	No data	
Conversion factors ppm (v/v) to mg/m^3 in air (20°C)	 1 ppm=4.7 mg/m^3 1 mg/m^3=0.21 ppm	 ACGIH 1986

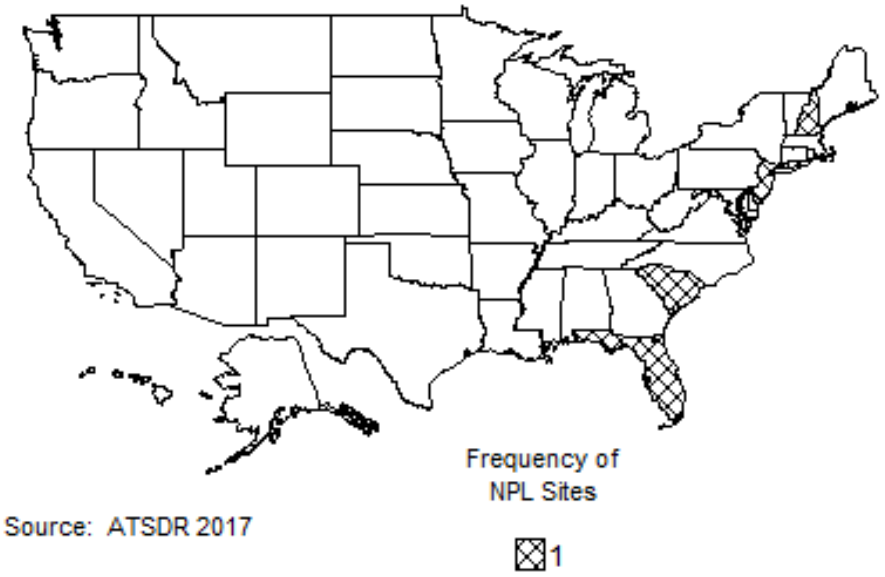
[a]Calculated values. Due to the rapid hydrolysis of BCME in water, significant concentrations in water would not be expected to occur.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

BCME has been identified in at least 4 of the 1,854 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 BCME 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(Chloromethyl)Ether Contamination



- Because BCME is not currently used as an isolated material in this country, and because it is rapidly degraded in the environment, the probability of human exposure to BCME is low. The most likely means of exposure is inhalation of BCME vapors in the workplace during the production and use of chemicals such as CME, in which BCME may occur as a contaminant or be formed inadvertently. Exposure through other media (water, food, soil) is unlikely to be significant.

- BCME in air is believed to be primarily degraded by reacting with photochemically-generated free hydroxyl radicals. BCME in the atmosphere can also undergo hydrolysis. In water, BCME is rapidly hydrolyzed.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Production of BCME in this country was curtailed in 1974 following stringent regulation by the Occupational Safety and Health Administration (EPA 1979; OSHA 1974). Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of BCME 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-(Chloromethyl)Ether

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
LA	1	10,000	99,999	1, 5
TX	1	1,000	9,999	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)

5.2.2 Import/Export

No data were located on imports of BCME.

5.2.3 Use

In the past, BCME was used for crosslinking of cellulose, preparation of styrene and other polymers, surface treatment of vulcanized rubber to increase adhesion, and in the manufacture of flame retardant fabrics (EPA 1980a). These applications have been discontinued, and no uses of BCME other than as a nonisolated intermediate were identified.

5.2.4 Disposal

Any products, residues, or container liners contaminated with BCME are considered acute hazardous waste under the Resource Conservation and Recovery Act (RCRA) (40 CFR 261.33 (c)), and must be disposed of by transport to a RCRA waste storage and disposal facility. The preferred method of disposal is incineration (OSHA 1974; Sittig 1985).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data for BCME, summarized 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(Chloromethyl)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
LA	1	No data	No data	No data	No data	No data	No data	No data	No data
TX	1	13	0	0	0	No data	13	No data	13
Total	2	13	0	0	0	0	13	0	13

[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 13 pounds (~0.006 metric tons) of BCME to the atmosphere from 2 domestic manufacturing and processing facilities in 2016, accounted for about 100% 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

No releases of BCME to surface water or publicly owned treatment works (POTWs) were reported from facilities required to report to the TRI (TRI16 2017), see Table 5-2.

5.3.3 Soil

No releases of BCME to soils were reported from facilities required to report to the TRI (TRI16 2017), see Table 5-2.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

No information was located on the transport and partitioning of BCME in the environment. Due to the relatively short half-life in both air and water, it is unlikely that significant transport or partitioning between media occurs.

5.4.2 Transformation and Degradation

Air. The primary process for BCME degradation in air is believed to be reaction with photochemically-generated hydroxyl radicals. Reaction products are believed to include chloromethyl formate, ClHCO, formaldehyde, and HCl (Cupitt 1980; EPA 1987a). The atmospheric half-life due to reaction with hydroxyl radicals is estimated to be 1.36 hours. Hydrolysis in the vapor phase is slower, with an estimated half-life of 25 hours in moist air (80% relative humidity at 25°C) (Tou and Kallos 1974). Reaction of BCME with molecular oxygen may also occur, but the rate of this reaction is not known. Other calculations suggest an atmospheric residence time of 0.2–2.9 days (Cupitt 1980).

Although hydrolysis of BCME to formaldehyde and HCl is highly favored thermodynamically, low levels of BCME may form by the reverse reaction when high concentrations of formaldehyde and HCl are mixed. Frankel et al. (1974) studied this reaction, and found that although BCME levels increased exponentially in proportion to reactant concentrations, yields were only 0.002–0.01 mol% at reactant concentrations ranging from 20 to 1,000 ppm. For example, the BCME concentration was 3 ppb in a mixture of 100 ppm formaldehyde and 100 ppm HCl. Based on the data of Frankel et al. (1974), Travenius (1982) proposed the empirical equation:

$$\log(\mathrm{BCME})_{ppb} = -2.25 + 0.67 \bullet \log(\mathrm{HCHO})_{ppm} + 0.77 \bullet \log(\mathrm{HCl})_{ppm}$$

Employing this equation, the concentration of BCME likely to form from any mixture of formaldehyde and HCl may be calculated. In the workplace, assuming that exposure occurred at the Threshold Limit

Values for each (1 ppm for formaldehyde and 5 ppm for HCl), the resulting BCME concentration would be 0.02 ppb. Concentrations in the home and the ambient environment are likely to be significantly lower for one or both reactants, and concentrations of BCME would be expected to be essentially negligible.

Water. BCME is rapidly hydrolyzed in water to yield formaldehyde and HCl, with a hydrolysis rate constant of 0.018 $second^{-1}$ at 20°C (Tou et al. 1974). This corresponds to a half-life of approximately 38 seconds. Under laboratory conditions (a sealed vessel from which formaldehyde and HCl cannot escape), an equilibrium is established in which about 80% of the BCME is rapidly hydrolyzed, with about 20% of the BCME remaining (Van Duuren et al. 1972). In the environment, formaldehyde and HCl formed by hydrolysis of BCME would be expected to dissipate by diffusion or volatilization, and BCME hydrolysis would rapidly proceed to completion.

Sediment and Soil. No information was located on the fate of BCME in soil. However, it is probable that BCME would rapidly hydrolyze upon contact with moisture in soil or would react with soil constituents. Consequently, it is not expected that BCME would persist for significant periods in soil.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to BCME depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of BCME 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 BCME 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.

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

Media	Detection limit	Reference
Air	0.1 ppb	Collier 1972
Drinking water	No data	
Surface water and groundwater	No data	
Soil	No data	
Sediment	No data	

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

No data are available on levels of BCME in air, water, and soil at NPL sites (ATSDR 2017).

5.5.1 Air

BCME has not been detected in ambient air. Some early reported industrial air concentrations ranged from 0.7 to 5.2 ppm, but increased care in the handling of this compound has reduced workplace levels to the sub-ppb range (NIOSH 1972a). No other quantitative data on BCME levels in air were located.

5.5.2 Water

BCME has not been detected in ambient waters, but has been reported to be present in groundwater at one chemical waste site being investigated under Superfund (CLPSD 1988). Because BCME hydrolyzes so quickly in water, this observation must be considered with skepticism.

5.5.3 Sediment and Soil

BCME was reported to be present at 0.5% of the waste sites being investigated under Superfund (CLPSD 1988), but quantitative data were not available. As with the data regarding occurrence in water, these data must be considered with caution, since BCME is unlikely to endure at measurable levels in soil.

5.5.4 Other Media

No studies were located regarding the occurrence of BCME in other media.

5.6 GENERAL POPULATION EXPOSURE

The most likely route of human exposure to BCME is by inhalation, but available data are not adequate to estimate typical dose levels. Doses are likely to be close to zero for the general population, but could be of concern inside or close by industrial sites where chloromethylation processes occur (Roe 1985).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

As discussed above, the individuals most likely to have potential exposure to BCME are industrial workers who manufacture or use chemicals such as CME that might contain BCME as a contaminant. The possibility exists that residents near a facility or a waste site that permits escape of BCME could also be exposed, but there are no data to establish whether or not this occurs or is of concern.

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 BCME 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 BCME.

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 BCME 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 BCME. 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.

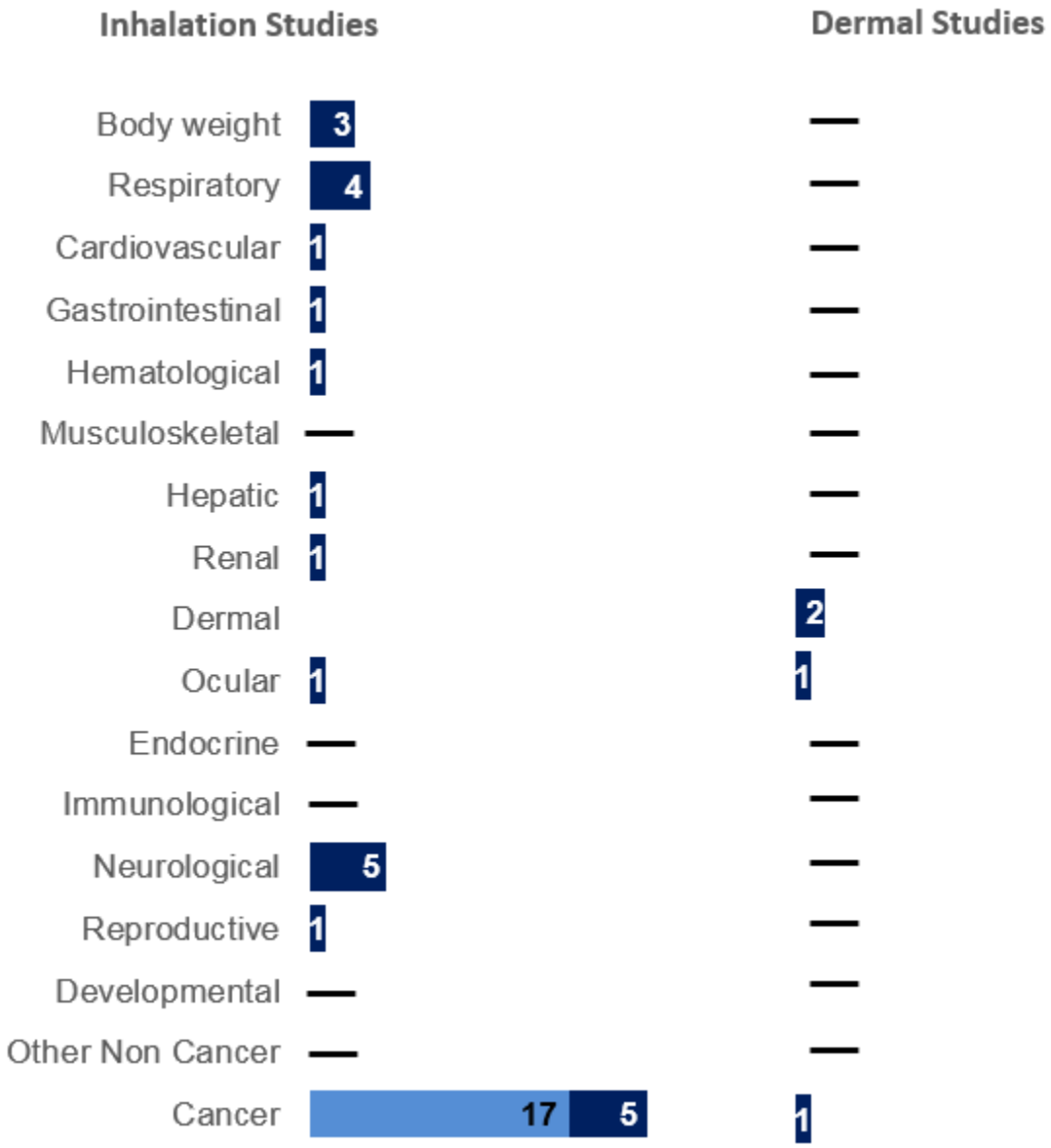
6.2 Identification of Data Needs

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. Several studies have been performed in animals on the effects of single inhalation exposures to BCME, and exposure conditions leading to acute lethality are reasonably well defined. However, the acute concentration-response curve for nonlethal effects on the respiratory has not been determined, and further studies to identify the acute NOAEL would be valuable for derivation of an

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

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



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No oral studies in humans or animals examining nonlethal endpoints were located.

MRL. The oral database is limited to a lethality study and repeated exposure studies are needed for MRL derivation.

Intermediate-Duration MRLs. Available studies on the effects of repeated inhalation exposure of animals to BCME (Leong et al. 1971, 1981) indicate that an exposure level of 0.1 ppm is a NOAEL for most systemic effects in rats. The data was considered adequate for derivation of an MRL; however, additional studies are needed to define the NOAEL/LOAEL boundary for noncancerous respiratory effects. No intermediate-duration oral studies were identified and are needed to identify sensitive targets of toxicity and for derivation of an MRL.

Chronic-Duration MRLs. No chronic-duration studies in laboratory animals were identified; epidemiology studies have focused on the carcinogenicity of BCME in workers. Given the lethality and carcinogenicity of BCME, studies examining low concentrations are needed to identify critical targets of toxicity and establish concentration-response relationships.

Health Effects. A small number of studies have evaluated the toxicity of BCME. The available studies suggest that the most sensitive effect of BCME is respiratory effects, neurotoxicity, and cancer; 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. Dermal studies are also needed to examine the toxicity of repeated exposure to BCME.

Cancer. A number of studies in animals indicate that inhalation of BCME is associated with risk of nasal or lung tumors. In order to assess the potential risks in the workplace, further studies in animals might be helpful in improving information on the dose- and time-dependency of BCME-induced tumorigenesis. In particular, studies would be valuable to investigate why BCME induces tumors with such a short latency, and why it results in nasal tumors in some species and lung tumors in others. Studies on the interaction of BCME with other chemicals such as CME (with which it is often associated in the workplace) would also be valuable.

Genotoxicity. The genotoxicity of BCME has been investigated in several strains of bacteria, but such systems may not be optimal for investigating the effects of such a rapidly hydrolyzed material. Specifically, if BCME acts as an alkylating agent to damage DNA, then tests that favor

hydrolysis before entry into the cell can occur may yield misleading results. Tests in prokaryotic and eukaryotic systems designed to minimize the degree of hydrolysis in the medium prior to cell penetration would be valuable in estimating the potential genotoxic effect of BCME on the respiratory epithelium.

Reproductive Toxicity. Only one study, Leong et al. (1981), was located that addressed the toxic effects of BCME on reproductive organs. This study examined the histological appearance of reproductive tissues in male rats only, and no test of reproductive function was performed. No studies were located on reproductive effects in females. On this basis, more extensive tests of BCME exposure on reproductive function in both male and female animals would be valuable in predicting the possible risk of reproductive effects in workers exposed to BCME.

Developmental Toxicity. No studies were located on the developmental toxicity of BCME. Although the rapid hydrolysis of BCME makes it unlikely that BCME could act on the fetus directly, effects might still occur as a consequence of maternal toxicity.

Immunotoxicity. No studies were located on the effects of BCME exposure on the immune system. Because the immune system is often observed to be especially sensitive to chemical toxicants, investigations in animals on the effects of BCME on the immune system would be valuable.

Neurotoxicity. Drew et al. (1975) reported that inhalation exposure of rats and hamsters led to subarachnoid hemorrhage, but the severity or significance of this finding was not discussed. These limited data suggest that a more thorough study of the effects of BCME on the nervous system would be useful, including tests both of functions (behavior, electrophysiological tests, etc.) and of structure (histopathology).

Epidemiology and Human Dosimetry Studies. A number of epidemiological studies have been performed on workers exposed to BCME in the past. While these studies are limited by the absence of reliable dosimetry data and the presence of other risk factors (smoking, other chemicals), the data nevertheless constitute strong evidence that BCME increases risk of lung cancer in humans. Although prospective epidemiological studies may not be feasible since exposure to BCME in the workplace is now so limited, continued follow-up of populations exposed in the past will be helpful in refining estimates of the latency and the incidence of cancer in these cohorts.

Biomarkers of Exposure and Effect. No biomarkers of exposure to BCME were located. Studies evaluating whether levels of BCME or one of its metabolites in biological fluids are reflective of exposure levels would be useful.

Absorption, Distribution, Metabolism, and Excretion. No studies were located on the toxicokinetics of BCME in animals or humans. Although acquisition of such data is made difficult by the rapid hydrolysis of BCME, studies focusing on the rate of entry of BCME into epithelial cells, the half-time for hydrolysis in the tissue environment, the fate of the degradation products, and interaction with DNA, if any, would be valuable in understanding the toxicity of this compound.

Comparative Toxicokinetics. No studies were located on the toxicokinetics of BCME in different species. Such studies might be helpful in understanding the differences that have been observed between species with respect to carcinogenic potency and tissue specificity.

Children's Susceptibility. No studies have evaluated the toxicity of BCME 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 BCME than adults.

Physical and Chemical Properties. The physical and chemical properties most important in evaluating the environmental fate of BCME have been determined (see Table 4-2). Although some of these values (e.g., solubility in water) are calculated, this is not a significant limitation, and additional studies on the physical or chemical properties of BCME do not appear essential.

Production, Import/Export, Use, Release, and Disposal. Although BCME is not produced as a commercial product in the United States, available information indicates that small quantities are produced and used in captive processes within at least one chemical factory. Determination of the amounts involved and whether BCME is used at other locations would be useful in evaluating whether risk of BCME exposure from current industrial practices remains of concern. In addition, compilation of data on typical contaminant levels of BCME currently found in other products such as CME would be helpful in determining whether or not this is a source of concern.

Environmental Fate. Available data make it clear that BCME is not likely to endure in the environment. No further studies appear to be required on fate in water or other moist media (food, soil),

since the principal fate is rapid hydrolysis. Additional studies on the kinetics of BCME destruction in air by oxidation and hydrolysis would be valuable in refining mathematical models used to calculate levels of BCME in air around a point source.

Bioavailability from Environmental Media. No studies were located on bioavailability of BCME in environmental media. However, this is not a significant limitation, since BCME is not expected to occur in significant quantities in any medium except air.

Food Chain Bioaccumulation. No studies were located on food chain bioaccumulation of BCME. This is not a significant limitation, however, since it is expected that BCME is rapidly hydrolyzed in living organisms and will not bioaccumulate.

Exposure Levels in Environmental Media. Information on the occurrence of BCME in environmental media is very limited. No information was located on levels in ambient air, water, or soil. BCME has been reported to occur in water or soil near a few waste sites, but these findings may not be reliable. Because of the instability of BCME in water and soil, further efforts to measure BCME in these media are unlikely to produce useful information. However, the volatility and atmospheric lifetime of BCME are such that monitoring air for BCME in the vicinity of waste sites, industrial facilities, or other possible sources could provide valuable information on the occurrence of this chemical in the environment.

Exposure Levels in Humans. No data exist on present-day exposure levels of humans to BCME. Exposure is likely to be close to zero for the general public. However, because BCME is such a potent carcinogen, even low levels of exposure are of potential concern, and additional data on exposure levels in the workplace and in the environment near waste sites would be valuable.

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. No methods were located for determining BCME in biological samples. It does not appear that this is a significant limitation, however, since BCME is not expected to endure in tissues or fluids. Although there are adequate methods for the detection of formaldehyde and chloride, these are not likely to be useful for assessing exposure to BCME, since any change in the levels of these compounds would be well within normal biological variability.

Air is the only environmental medium susceptible to significant contamination by BCME and methods for the determination of this compound in air are straightforward. The greatest need for improvement in the analysis of BCME is the development of methodologies that enable its efficient collection from large volumes of air without hydrolysis during collection or storage. Since health concern might extend to concentrations well below 1 ppb, improvement in sensitivity would also be valuable.

6.3 Ongoing Studies

No ongoing studies were identified for BCME.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding BCME 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 BCME.

Table 7-1. Regulations and Guidelines Applicable to Bis(Chloromethyl)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	A1[b,c]	ACGIH 2001, 2016
HHS	Carcinogenicity classification	Known to be a human carcinogen[d]	NTP 2016
EPA	Carcinogenicity classification	Group A[e,f]	IRIS 2002
IARC	Carcinogenicity classification	Group 1[g,h]	IARC 2012, 2017
		Occupational	
ACGIH	TLV	0.001 ppm (0.0047 mg/m^3)	ACGIH 2001, 2016
OSHA	Requirements for areas containing a carcinogen	Does not pertain to solid or liquid mixtures containing <0.1% by weight or volume	OSHA 2016
NIOSH	REL	Potential occupational carcinogen	NIOSH 2016

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

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2016
	AEGL 1	NR[i]	
	AEGL 2		
	10-minute	0.055 ppm	
	30-minute	0.055 ppm	
	60-minute	0.044 ppm	
	4-hour	0.028 ppm	
	8-hour	0.020 ppm	
	AEGL 3		
	10-minute	0.23 ppm	
	30-minute	0.23 ppm	
	60-minute	0.18 ppm	
	4-hour	0.11 ppm	
	8-hour	0.075 ppm	
DOE	PACs-air		DOE 2016a
	PAC-1[j]	0.004 ppm	
	PAC-2[j]	0.044 ppm	
	PAC-3[j]	0.18 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]A1: confirmed human carcinogen.
[c]Based on pulmonary cancer and nasal tumors in experimental animal studies and among exposed workers.
[d]Based on sufficient evidence of carcinogenicity from studies in humans.
[e]Group A: human carcinogen.
[f]Based on statistically significant increases in lung tumors (oat cell carcinomas) observed in six studies of exposed workers and bioassay data from rats and mice.
[g]Group 1: carcinogenic to humans.
[h]Based on sufficient evidence in humans for cancer of the lung and sufficient evidence of carcinogenicity in experimental animals.
[i]NR = not recommended due to insufficient data.
[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; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; 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; 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; TLV = threshold limit values; WHO = World Health Organization

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*ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH.

*ACGIH. 2001. Bis(chloromethyl)ether. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ACGIH. 2016. Bis(chloromethyl)ether. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, May 11, 2017.

*AIHA. 2015. Current ERPG Values (2015). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf. March 22, 2016.

*Albert RE, Sellakumar AR, Laskin S, et al. 1982. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J Nat Cancer Inst 68:597-603.

*Albert RE, Pasternack BS, Shore RE, et al. 1975. Mortality patterns among workers exposed to chloromethyl ethers- a preliminary report. Environ Health Perspect 2:109-214.

*Anderson D, Styles JA. 1978. The bacterial mutation test. Br J Cancer 37:924-930.

*ASTM. 1987. Bis(chloromethy1) ether (bis CME) in workplace atmospheres (gas chromatography - mass spectrometry - Method D 347679). 1987 Annual book of ASTM standards, Vol. 11.03, Atmospheric analysis; occupational health and safety. American Society for Testing and Materials, Philadelphia, PA: 259-264.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

*ATSDR. 2017. Bis(2-Chloroethyl)Ether. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. October 6, 2017.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Volume I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600886032a.

*Brothers RF. 1989. Written communication (May 5) to Director, Office of External Affairs, Agency for Toxic Substances and Disease Registry, regarding manufacture of BCME. Director, Issues Development, Eastman Kodak Company.

Bruner F, Bertonic G, Severni C. 1978. Gas chromatographic determination of bis(chloromethy1) ether emissions in the atmosphere of industrial plants. Anal Chem 50:53.

*Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. II. Halogenated aliphatic hydrocarbons, halogenated ethers, monocyclic aromatics, phthalate esters, polycyclic aromatic hydrocarbons, nitrosamines, and miscellaneous compounds. Washington, DC: U.S. Environmental Protection Agency. EPA 440479029b. PB80-2043816.

Chovil AC. 1979. Occupational lung cancer and smoking: A review in the light of current theories of carcinogenesis. Chem Manuf Assoc J 121:548-555.

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* Cited in text

8. REFERENCES

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*CLPSD. 1988. Contract laboratory program statistical database. Viar and Company, Alexandria VA: September 6, 1988.

*Cole P, Merletti F. 1980. Chemical agents and occupational cancer. J Environ Pathol 3:399-417.

*Collier L. 1972. Determination of bis-chloromethyl ether at the ppb level in air samples by high-resolution mass spectropy. Environ Sci Technol 6:930-932.

*Collingwood KW, Pasternack BS, Shore RE. 1987. Industry-wide study of respiratory cancer in chemical workers exposed to chloromethyl ether. J Nat Cancer Inst 78:1127-1135.

*Cupitt LT. 1980. Fate of toxic and hazardous materials in the air environment. Research Triangle Park, NC: U.S. Environmental Sciences Research Laboratory. PB8022194b.

*DOE. 2016a. Table 3: Protective Action Criteria (PAC) Rev. 29 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. May 2016. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/teel/Revision_29_Table3.pdf. February 28, 2017.

*DOE. 2016.b Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29 for Chemicals of Concern - May 2016. Oak Ridge, TN: U.S. Department of Energy. https://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-29-chemicals-concern-may-2016. February 28, 2017.

*DeFonso LR, Kelton SC. 1976. Lung cancer following exposure to chloromethyl methyl ether. Arch Environ Health 3l:125-130.

*Drew R, Laskin S, Kuschner M, et al. 1975. Inhalation carcinogenicity of alpha halo ethers. Arch Environ Health 30:61-69.

EPA. 1975. Investigation of selected potential environmental contaminants, haloethers. Washington, DC: U.S. Environmental Protection Agency. NTIS PB246356.

*EPA. 1979. Toxic Substances Control Act. Chemical substances inventory. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

*EPA. 1980a. An exposure and risk assessment for bis(chloromethy1) ether. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards (Interim Draft).

*EPA. 1980b. U.S. Environmental Protection Agency. Hazardous waste; identification and listing; final and interim rules. Fed Regist 45:3384-33133.

EPA. 1980c. Guidelines and methodology used in the preparation of health effect assessment chapters of the consent decree water criteria documents. U.S. Environmental Protection Agency. Fed Regist 45:79347-79357.

EPA. 1980d. Ambient water quality criteria document for haloethers. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440580050. NTIS PB81117616.

*EPA. 1985. U.S Environmental Protection Agency. Part II. Notification requirements; reportable quantity adjustments; final rule and proposed rule. Fed Regist 50:13456-13522.

*EPA. 1987a. Health and environmental effects document for haloethers. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. ECAOCING014.

*EPA 1987b. U.S. Environmental Protection Agency. Part II. Hazardous substances, reportable quantity adjustments; proposed rules. Fed Regist 52:8140-8171.

*EPA. 1987c. U.S. Environmental Protection Agency. Part II. Extremely hazardous substances list and threshold planning quantities; emergency planning and release notification requirements; final rule. Fed Regist 52:13378-13410.

*EPA. 1988. Integrated risk information system (IRIS). Printout for bis(chloromethy1) ether. Washington, DC: U.S. Environmental Protection Agency. November.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the

Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. EPA 816-F-09-0004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. February 28, 2017.

*EPA. 2012. Drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA 822-S-12-001. https://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf. May 11, 2017.

*EPA. 2016. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals. February 28, 2017.

Evans HJ. 1982. Cytogenetic studies on industrial populations exposed to mutagens. In: Bridges BA, Butterworth BE, Weinstein IB, eds. Indicators of genotoxic exposure. Banbury Report 13:325-336.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. February 28, 2017.

*Figueroa WC, Razkowski R, Weiss W. 1973. Lung cancer in chloromethyl methyl ether workers. N Engl J Med 288:1096-1097.

*Fishbein L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. III. Alkane halides, alkanols and ethers. Sci Total Environ 11:223-257.

*Frankel LS, McCallum KS, Collier L. 1974. Formation of bis(chloromethy1) ether from formaldehyde and hydrogen chloride. Environ Sci Technol 8:356-359.

Frost JK, Gupta PK, Erozan YS, et al. 1973. Pulmonary cytologic alterations in toxic environmental inhalation. Human Pathol 4:521-536.

*FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Federal-State Toxicology and Regulatory Alliance Committee. March, 1988.

*Gargus JL. Reese WH, Rutter HA. 1969. Induction of lung adenomas in newborn mice by bis(chloromethy1) ether. Toxicol Appl Pharmacol 15:9296.

Gilbert D, Eschenroeder A, Goyer M, et al. 1979. An exposure and risk assessment for bis(chloromethy1) ether. Interim draft. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

Gold LS, Backman GM, Hooper NK, et al. 1987. Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents. Environ Health Perspect 76:211-219.

Gosselin RE. 1984. Clinical toxicology of commercial products. 5th edition. Baltimore, MD: The Williams and Wilkins Co., 11-183.

*Gowers DS, DeFonso LR, Schaffer P, et al. 1993. Incidence of respiratory cancer among workers exposed to chloromethyl-ethers. Am J Epidemiol 137(1):31-42.

*HSDB. 1988. Hazardous Substances Data Base - computer printout for bis(chloromethy1) ether. Bethesda, MD: National Library of Medicine, National Toxicology Information Program.

*IARC. 1982. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, industrial processes and industries associated with cancer in humans. IARC Monographs, Volumes 1 to 29, Supplement 4. Lyon, France: International Agency for Research on Cancer.

*IARC. 2012. Bis(chloromethyl)ether and chloromethyl methyl ether. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 100F. Chemical agents and related occupations. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-25.pdf. May 10, 2017.

8. REFERENCES

*IARC. 2017. Agents classified by the IARC Monographs , Volumes 1–118. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf. May 10, 2017.

*IRIS. 2002. Bis(chloromethyl)ether (BCME); CASRN 542-88-1. Chemical assessment summary. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. May 11, 2017.

*Kallos GJ. 1981. Oxygen-induced response enhancement in determination of bis(chloromethy1) ether by gas chromatography with 63Ni electron capture detection. Anal Chem 53: 963-965.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Krost KJ, Pellizzari ED, Walburn SG, et al. 1982. Collection and analysis of hazardous organic emissions. Anal Chem 54: 810-817.

*Kuschner M, Laskin S, Drew RT, et al. 1975. Inhalation carcinogenicity of alpha halo ethers. Arch Environ Health 30:73-77.

*Laskin S, Kuschner M, Drew RT, et al. 1971. Tumors of the respiratory tract induced by inhalation of bis(chloromethy1) ether. Arch Environ Health 23:135-136.

Lemen RA. 1986. Occupationally induced lung cancer epidemiology. In: Merchant JA, ed. Occupational respiratory diseases. U.S. Department of Health and Human Services, 629-656.

*Lemen RA, Johnson WM, Wagoner JK, et al. 1976 A cytologic observations and cancer incidence following exposure to BCME. Ann NY Acad Sci 271:71-80.

*Leong BK, MacFarland HN, Reese WH. 1971. Induction of long adenomas by chronic inhalation of bis(chloromethy1) ether. Arch Environ Health 22:663-666.

*Leong BKJ, Kociba RI, Jersey GC. 1981. A lifetime study of rats and mice exposed to vapors of bis(chloromethy1) ether. Toxicol Appl Pharmacol 58:269-281.

*Mabey WR, Smith JH, Podoll RT, et al. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440481014. PB87169090.

*Maher KV, DeFonso IX. 1987. Respiratory cancer among chloromethyl ether workers. J Nat Cancer Inst 78:839-843.

Martin H, Worthing CR, eds. 1974. Pesticide manual. Basic information on the chemicals used as active components of pesticides. 4th ed. Worcester, England: British Crop Protection Council, 177.

McCallum RI, Woolley V, Petrie A. 1983. Lung cancer associated with chloromethyl methyl ether manufacture: an investigation at two factories in the United Kingdom. Brit J Ind Med 40:384-389.

*Mueller G, Norpoth K, Travenius SZM. 1981. Quantitative determination of bis(chloromethy1) ether (BCME) in the ppb range using portable air sample collectors. Int Arch Occup Environ Health 48:325-329.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

*NIOSH. 1972a. Field survey of Dow Chemical Company chloromethyl ether facilities, Midland, MI. Cincinnati, OH: National Institute for Occupational Safety and Health. PB82151598.

*NIOSH. 1972b. Field survey of Rohm and Haas Company Bridesburg Facilities Philadelphia, PA. Cincinnati, OH: National Institute for Occupational Safety and Health. PB82162561.

NIOSH. 1973. Hazard review of bis(chloromethy1) ether. Cincinnati, OH: National Institute for Occupational Safety and Health. PB87210779.

NIOSH. 1974. Survey of Burlington Industries, Inc. Burlington House Finishing Plant, Form Fabrics Plant, Durham Domestics Plant, Brookneal Finishing Plant. PB82151077.

*NIOSH. 1977. Manual of Analytical Methods. Vol. 1. Method 213. Cincinnati, OH: National Institute for Occupational Safety and Health.

8. REFERENCES

*NIOSH. 1986. NIOSH recommendations for occupational safety and health standards. Atlanta, GA: U.S. Department of Health and Human Services, National Institute for Occupation Safety and Health. September, 1986.

*NIOSH. 2016. bis-Chloromethyl ether. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgd0128.html. May 11, 2017.

*NLM. 1988. National Library of Medicine - chemline database printout for bis(chloromethy1) ether. August, 1988.

*Norpoth K, Mueller G, Zilius Z, et al. 1981. Sensitive spectrophotometric determination of carcinogenic alpha chloro ethers. Int Arch Occup Environ Health 49:151-155.

NTP. 1985. National Toxicology Program. Fourth annual report on carcinogens. Summary 1985. Washington, DC: U.S. Department of Health and Human Services.

*NTP. 2016. Bis(chloromethyl) ether and technical-grade chloromethyl methyl ether. Report on Carcinogens, Fourteenth Edition. CASRN Index in MS Excel. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/bis_chloromethyl_ether.pdf. May 11, 2017.

*OSHA. 1974. Occupational Safety and Health Administration, Department of Labor. Occupational Safety and Health Standards. Carcinogens. Fed Regist 39:3756-3796.

*OSHA. 2016. Subpart Z - Toxic and hazardous substances. Section 1910.1003 - 13 Carcinogens. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1910.1003 https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1003.pdf. May 10, 2017.

*Pasternack BBS, Shore R, Albert RE. 1977. Occupational exposure to chloromethyl ethers. J Occup Med 19:741-746.

Pepelko WE. 1984. Experimental respiratory carcinogenesis in small laboratory animals. Environ Res 33:144-188.

*Ress JF. 1977. Tight control prevents exposure to bis(chloromethy1) ether. Occupational Health and Safety. May/June 1977:40-43.

*Reznik G, Wagner HH, Atay Z. 1977. Lung cancer following exposure to bis(chloromethy1) ether: A case report. J Environ Pathol Toxicol 1:105-111.

*Roe FJC. 1985. Chloromethylation: Three lung cancer deaths in young men. The Lancet 2:268.

*Sakabe H. 1973. Lung cancer due to exposure to bis(chloromethy1) ether. Ind Health 11:145-148.

Sax NI, Lewis RJ, eds. 1987. Hawley's condensed chemical dictionary. 11th edition. New York, NY: Van Nostrand Reinhold Co., 149.

*Sellakumar AR, Snyder CA, Solomon JJ, et al. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol Appl Pharmacol 81:401-406.

*Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. Park Ridge, NJ: Noyes Publications, 133-135.

Sram RJ, Samkova I, Hola N. 1983. High-dose ascorbic prophylaxis in workers occupationally exposed to halogenated ethers. J Hyg Epidemiol Microbial Immunol 27:305-318.

*Thiess AM, Hey W, Zeller H. 1973. Zur Toxikologie von Dichlordimethylaether-Verdacht auf kanzerogene Wirkung such beim Menschen. Zentralbl Arbeitsmed 23:97-102.

Thomas DC, Whittemore AS. 1988, Methods for testing interactions, with applications to occupational exposures, smoking, and lung cancer. Am J Ind Med 13:131-147.

*Tou JC, Kallos GJ. 1974. Kinetic study of the stabilities of chloromethyl methyl ether and bis(chloromethy1) ether in humid air. Anal Chem 46:1866-1869.

*Tou JC, Westover LB, Sonnabend LF. 1974. Kinetic studies of bis(chloromethyl)ether hydrolysis by mass spectrometry. J Phys Chem 78:1096-1098.

*Travenius SZM. 1982. Formation and occurrence of bis(chloromethy1) ether and its prevention in the chemical industry. Scand J Work Environ Health 8 (Suppl. 3):1-86.

8. REFERENCES

*TRI16 2017. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. October 18, 2017.

*Union Carbide. 1968. Summary of acute toxicity and irritancy studies of bis(chloromethyl)ether. Danbury, CT: Union Carbide Corporation. Rpt 31-85; 1968.

*USITC. 1987. Synthetic organic chemicals. United States production and sales. 1986. Washington, DC: U.S. International Trade Commission. Pub. 2009.

Van Duuren BL. 1969. Carcinogenic epoxides, lactones, and halo-ethers and their mode of action. Ann NY Acad Sci 163:633-651.

Van Duuren BL. 1980. Prediction of carcinogenicity based on structure, chemical reactivity and possible metabolic pathways. J Environ Pathol Toxicol 3:11-34.

Van Duuren BL. 1989. Comparison of potency of human carcinogens: vinyl chloride, chloromethyl methyl ether and bis(chloromethyl)ether. Environ Res 49:143-151.

Van Duuren BL, Van Duuren SB. 1988. Chemistry, reactivity and carcinogenicity of chloro ethers. In: Politzer P, Martin FJ, eds. Chemical carcinogens. New York, NY: Elsevier, 114-176.

*Van Duuren BL, Goldschmidt BM, Katz C, et al. 1968. Alpha-haloethers: A new type of akylating carcinogen. Arch Environ Health 16:472-476.

*Van Duuren BL, Sivak A, Goldschmidt BM, et al. 1969. Carcinogenicity of halo-ethers. J Nat Cancer Inst 43:481-486.

*Van Duuren BL, Goldschmidt BM, Katz C, et al. 1972. Carcinogenicity of halo-ethers. 11. Structure-activity relationships of analogs of bis(chloromethy1) ether. J Nat Cancer Inst 48:1431-1439.

*Weast RC, ed. 1985. CRC handbook of chemistry and physics. 66th ed. Boca Raton, FL: CRC Press.

*Weiss W. 1976. Chloromethyl ethers, cigarettes, cough and cancer. J Occup Med 18:194-199.

Weiss W. 1980. The cigarette factor in lung cancer due to chloromethyl ethers. J Occup Med 22:527-529.

*Weiss W. 1982. Epidemic curve of respiratory cancer due to chloromethyl ethers. J Nat Cancer Inst 69:1265-1270.

*Weiss W, Boucot KR. 1975. The respiratory effects of chloromethyl methyl ether. J Am Med Assoc 234:1139-1142.

*Weiss W. 1989. Lung cancer due to chloromethyl ethers: Bias in cohort definition. J Occup Med 31:102-105.

*Weiss W, Moser RL, Auerbach 0. 1979. Lung cancer in chloromethyl ether workers. Am Rev Respir Disease 120:1031-1037.

*Weiss W, Nash D. 1997. An epidemic of lung cancer due to chloromethyl ethers. 30 Years of observation. J Occup Environ Med 39(10):1003-1009.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. January 08, 2014.

*WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

Wilbourn J. 1978. Evaluation of the carcinogenicity of chemicals: A review of the monograph program of the International Agency for Research on Cancer (1971-1977). Cancer Res 38:877-885.

Wilbourn J, Haroun L, Haseltine E, et al. 1986. Response of experimental animals to human carcinogens: An analysis based upon the IARC Monographs Programme. Carcinogenesis 7:1853-1863.

Windholz M, ed. 1983. The Merck index. Tenth edition. Rahway, NJ: Merck & Co., Inc.

8. REFERENCES

*Zajdela F, Croisy A, Barbin A, et al. 1980. Carcinogenicity of chloroethylene oxide, an ultimate reactive metabolite of vinyl chloride, and bis(chloromethy1) ether after subcutaneous administration and in initiation-promotion experiments in mice. Cancer Res 40:352-356.

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(chloromethyl)ether (BCME)
CAS Numbers: 542-88-1
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 only study reporting effects at nonlethal concentrations involved a single 7-hour exposure to BCME and only examined a limited number of potential endpoints.

Drew et al. (1975) exposed rats and hamsters to concentrations ≥0.7 ppm for 7 hours. The effects observed in the rats included increases in lung weight at 0.7 ppm, tracheal epithelial hyperplasia at 0.7 ppm, and tracheal and bronchial hyperplasia and squamous metaplasia at 2.1 ppm. In the hamsters, exposure to 0.7 ppm resulted in increases in lung weight and pneumonitis; tracheal and bronchial hyperplasia and hyperplasia with atypia were observed at 2.1 ppm. In both species, exposure to 0.7 ppm resulted in ≥90% deceases in lifespan. Repeated exposure of rats and hamsters to 1 ppm for 10 days resulted in decreases in lifespan, extreme irritability, and subarachnoid hemorrhage (rats only) (Drew et al. 1975).

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Bis(chloromethyl)ether (BCME)
CAS Numbers:	542-88-1
Date:	December, 1989 March, 2017—Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Intermediate
MRL:	0.0003 ppm
Critical Effect:	Respiratory damage
Reference:	Leong et al. 1981
Point of Departure:	NOAEL of 0.1 ppm
Uncertainty Factor:	100
LSE Graph Key:	10
Species:	Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.0003 ppm was derived for BCME. The MRL is based on a NOAEL of 0.1 ppm for the lack of respiratory effects in rats exposed to BCME for 6 months (Leong et al. 1981). The NOAEL was adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: A small number of studies have evaluated the toxicity of BCME following intermediate-duration inhalation studies; most of the studies focused on the carcinogenicity of BCME. In the only study examining a wide range of potential noncancerous endpoints, Leong et al. (1981) did not report non-neoplastic alterations in the major tissues and organs examined in rats exposed concentrations as high as 0.1 ppm for 6 months. Additional findings reported in this study included an increase in the incidence of nasal tumors and increases in mortality in the post-exposure period in rats exposed to 0.1 ppm and increases in pulmonary adenomas in mice dying post-exposure in the 0.1 ppm group. At 1 ppm, respiratory distress and weight loss were observed in mice exposed for 82 exposure days (Leong et al. 1971) and subarachnoid hemorrhage and extreme irritability were observed in rats and hamsters exposed for 30 days (Drew et al. 1975); increases in mortality were observed in all three species. The available data suggest that the respiratory tract and nervous system maybe sensitive targets of toxicity for BCME. An acute-duration study in rats and hamsters support the identification of the respiratory tract as a sensitive target. Increases in lung weight and tracheal hyperplasia were observed in rats and hamsters exposed to 0.7 ppm for 7 hours and followed for a lifetime (Drew et al. 1975). At 2.1 ppm, tracheal and bronchial hyperplasia and squamous metaplasia (rats only) were also observed.

Selection of the Principal Study: The Leong et al. (1981) study was selected as the principal study because it identified a NOAEL for respiratory effects, the presumed critical effect.

Summary of the Principal Study:

Leong BKJ, Kociba RI, Jersey GC. 1981. A lifetime study of rats and mice exposed to vapors of bis(chloromethyl) ether. Toxicol Appl Pharmacol 58:269-281

Groups of 120 male Sprague Dawley rats were exposed to 1, 10, or 100 ppb (0.001, 0.01, or 0.1 ppm) bis(chloromethyl)ether 6 hours/day, 5 days/week for 6 months and observed over a lifetime; a control group of 120 rats were held under ambient conditions without chamber exposure. The following parameters were used to assess toxicity: body weight (weekly for 3 months and monthly thereafter),

hematology evaluation (in 10 rats/group at 12 weeks in control and 0.1 ppm groups, in all groups at day 1 post-exposure, in 4 rats/group on post-exposure day 5, and in the 4 rats/group in control, 0.001, and 0.01 ppm groups at study week 104), organ weight (heart, brain, liver kidneys, and testes in 4 rats/group sacrificed 1 day post-exposure) and histopathology of the major tissues and organs, including the nasal cavity, in 4 rats/group sacrificed 1 or 5 days post-exposure and in rats dying early.

The percentages of animals dying during the exposure period were 0.8, 1.7, 0.8, and 3.3% in the control, 0.001, 0.01, and 0.1 ppm groups, respectively. Although statistical significance was not reported, a Fisher Exact test conducted by ATSDR did not find a statistically significant increase in mortality during the exposure period. Most animals in the 0.1 ppm group died during the first 7 post-exposure months. No increases in post-exposure mortality were observed in the 0.001 or 0.01 ppm groups. No significant alterations in body weight gain, hematological alterations, or organ weight were observed. No treatment-related non-neoplastic lesions were observed in rats sacrificed 1 or 5 days post-exposure. A significant increase in the incidence of nasal esthesioneuroepitheliomas was observed during the post-exposure period. Evidence of respiratory infection was observed in animals in the 0.1 ppm group sacrificed due to morbidity during the exposure period. Similar infectious lesions were observed in the controls and 0.001 and 0.01 ppm groups. The investigators noted that cultures often revealed the presence of *Corynebacterium kutscheri*.

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 ppm for the lack of respiratory effects was selected as the basis of the MRL.

Adjustment for Intermittent Exposure: The NOAEL was adjusted for intermittent exposure (6 hours/day, 5 days/week)

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

Uncertainty Factor: The human equivalent NOAEL was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As noted previously, acute-duration inhalation studies have also identified the respiratory tract as a sensitive target of toxicity.

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(chloromethyl)ether (BCME)
CAS Numbers: 542-88-1
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 BCME.

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(chloromethyl)ether (BCME)
CAS Numbers: 542-88-1
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: No acute-duration oral studies were identified for BCME.

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(chloromethyl)ether (BCME)
CAS Numbers: 542-88-1
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 BCME.

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bis(chloromethyl)ether (BCME)
CAS Numbers: 542-88-1
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: No chronic-duration oral studies were identified for BCME.

Agency Contact (Chemical Manager): Nickolette Roney, M.P.H.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BCME

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 BCME.

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 BCME. 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 BCME 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 BCME 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
Cancer

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

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 BCME (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 BCME. 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 BCME 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	((77382IHE37[rn] OR 542-88-1[rn] OR "Bis(Chloromethyl) Ether"[MeSH] OR "Bis(Chloromethyl) Ether"[nm]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[mhda])) OR (("sym-Dichloromethyl ether"[tw] OR "1,1'-Dichlorodimethyl ether"[tw] OR "alpha,

Table B-2. Database Query Strings

Database search date	Query string
	alpha'-Dichlorodimethyl ether"[tw] OR "Bis(chloromethyl) ether"[tw] OR "Chloro(chloromethoxy)methane"[tw] OR "Chloromethyl ether"[tw] OR "Dichlordimethylaether"[tw] OR "Dimethyl-1,1'-dichloroether"[tw] OR "Monochloromethyl ether"[tw] OR "Oxybis(chloromethane)"[tw] OR "sym-Dichloro-dimethyl ether"[tw] OR "sym-Dichloromethyl ether"[tw] OR "1,1'-oxybis(1-chloro-Methane"[tw] OR "Bis(chloromethyl)ether"[tw] OR "Dichloromethyl ether"[tw]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[crdat] OR 1987/01/01 : 3000[edat]))
Toxline	
03/2017	("sym-dichloromethyl ether" OR "1 1'-dichlorodimethyl ether" OR "alpha alpha'-dichlorodimethyl ether" OR "bis (chloromethyl) ether" OR "chloro (chloromethoxy) methane" OR "chloromethyl ether" OR "dichlordimethylaether" OR "dimethyl-1 1'-dichloroether" OR "monochloromethyl ether" OR "oxybis (chloromethane) " OR "sym-dichloro-dimethyl ether" OR "sym-dichloromethyl ether" OR "1 1'-oxybis (1-chloro-methane" OR "bis (chloromethyl) ether" OR "dichloromethyl ether" OR 542-88-1 [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 14:37:16 ON 17 MAR 2017 CHARGED TO COST=EH011.13.01.01 L49 583 SEA 542-88-1 L50 571 SEA L49 NOT TSCATS/FS L51 508 SEA L50 NOT PATENT/DT L52 206 SEA L51 AND PY>=1987 ACTIVATE TOXQUERY/Q --------- L53 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L54 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L55 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L56 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L57 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L58 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L59 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L60 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L61 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L62 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L63 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L64 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR

Table B-2. Database Query Strings

Database search date	Query string
	TERATOGEN?)
	L65 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L66 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L67 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L68 QUE (ENDOCRIN? AND DISRUPT?)
	L69 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L70 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L71 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L72 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L73 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L74 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L75 QUE (NEPHROTOX? OR HEPATOTOX?)
	L76 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L77 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L78 QUE L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR
	L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR L67 OR L68 OR L69 OR
	L70 OR L71 OR L72 OR L73 OR L74 OR L75 OR L76 OR L77
	L79 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?)
	L80 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L81 QUE L78 OR L79 OR L80
	L82 QUE (NONHUMAN MAMMALS)/ORGN
	L83 QUE L81 OR L82
	L84 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L85 QUE L83 OR L84

	L86 158 SEA L52 AND L85
	L87 18 SEA L86 AND MEDLINE/FS
	L88 28 SEA L86 AND BIOSIS/FS
	L89 99 SEA L86 AND CAPLUS/FS
	L90 13 SEA L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L91 145 DUP REM L87 L88 L90 L89 (13 DUPLICATES REMOVED)
	L*** DEL 18 S L86 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 18 S L86 AND MEDLINE/FS L92 18 SEA L91 L*** DEL 28 S L86 AND BIOSIS/FS L*** DEL 28 S L86 AND BIOSIS/FS L93 23 SEA L91 L*** DEL 99 S L86 AND CAPLUS/FS L*** DEL 99 S L86 AND CAPLUS/FS L94 91 SEA L91 L*** DEL 13 S L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 13 S L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L95 13 SEA L91 L96 127 SEA (L92 OR L93 OR L94 OR L95) NOT MEDLINE/FS SAVE TEMP L96 CHLOROM/A D SCAN L96

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 542-88-1
NTP	
03/2017	"542-88-1" OR "sym-Dichloromethyl ether" OR "1,1'-Dichlorodimethyl ether" OR "alpha,alpha'-Dichlorodimethyl ether" OR "Bis(chloromethyl) ether" OR "Chloro(chloromethoxy)methane" OR "Chloromethyl ether" OR "Dimethyl-1,1'-dichloroether" OR "Monochloromethyl ether" OR "Oxybis(chloromethane)" OR "sym-Dichloro-dimethyl ether" OR "sym-Dichloromethyl ether" OR "1,1'-oxybis(1-chloro-Methane" OR "Bis(chloromethyl)ether" OR "Dichloromethyl ether"
NIH RePORTER	
05/2017	Active projects "sym-Dichloromethyl ether" OR "1,1'-Dichlorodimethyl ether" OR "alpha,alpha'-Dichlorodimethyl ether" OR "Bis(chloromethyl) ether" OR "Chloro(chloromethoxy)methane" OR "Chloromethyl ether" OR "Dichlordimethylaether" OR "Dimethyl-1,1'-dichloroether" OR "Monochloromethyl ether" OR "Oxybis(chloromethane)" OR "sym-Dichloro-dimethyl ether" OR "sym-Dichloromethyl ether" OR "1,1'-oxybis(1-chloro-Methane" OR "Bis(chloromethyl)ether" OR "Dichloromethyl 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): 310

- Number of records identified from other strategies: 25
- Total number of records to undergo literature screening: 335

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on BCME:

- 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.

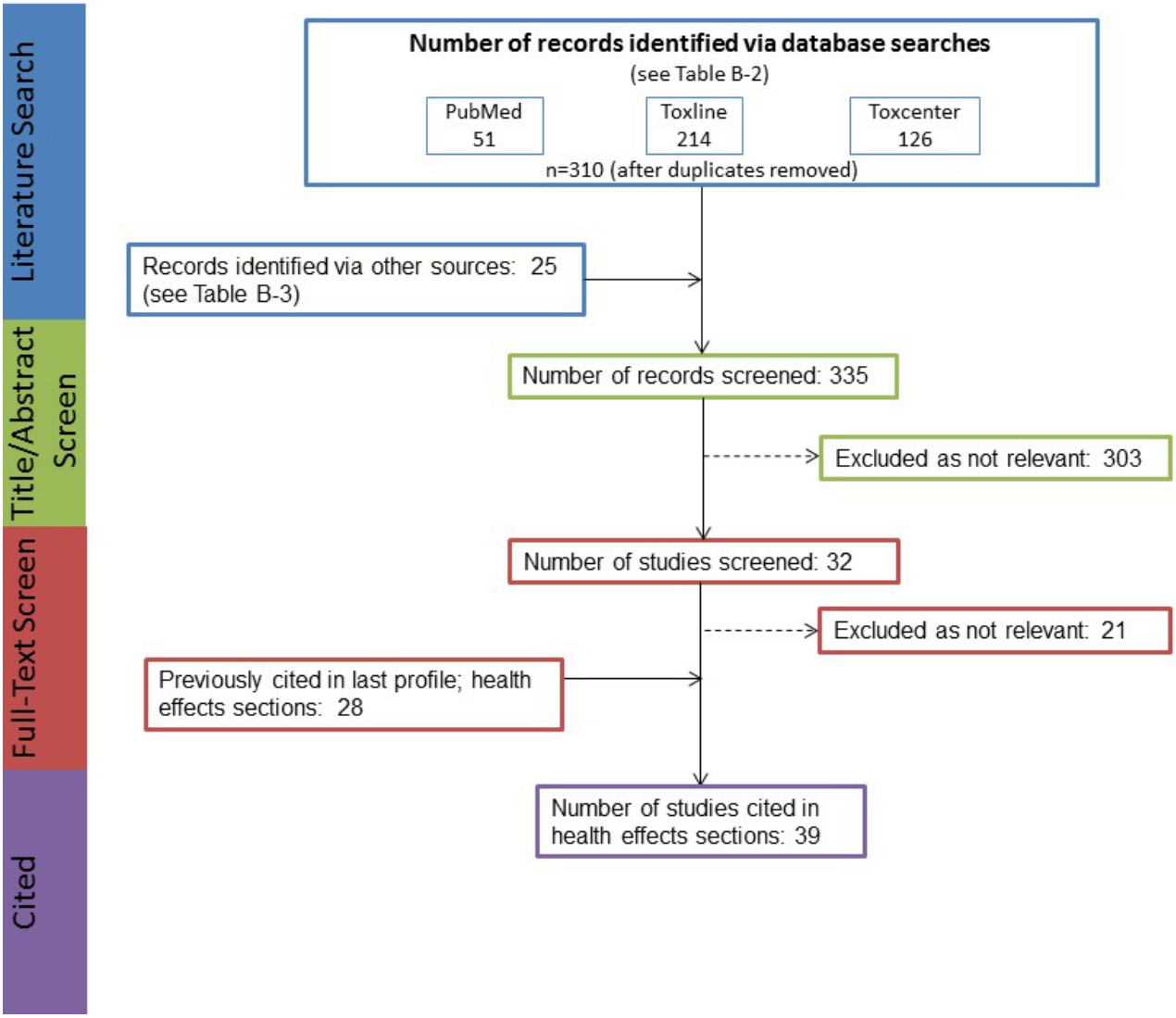
- Number of titles and abstracts screened: 335
- Number of studies considered relevant and moved to the next step: 32

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: 32
- Number of studies cited in the health effects sections of the existing toxicological profile (December, 1989): 28
- Total number of studies cited in the health effects sections of the updated profile: 39

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 BCME



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.

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.

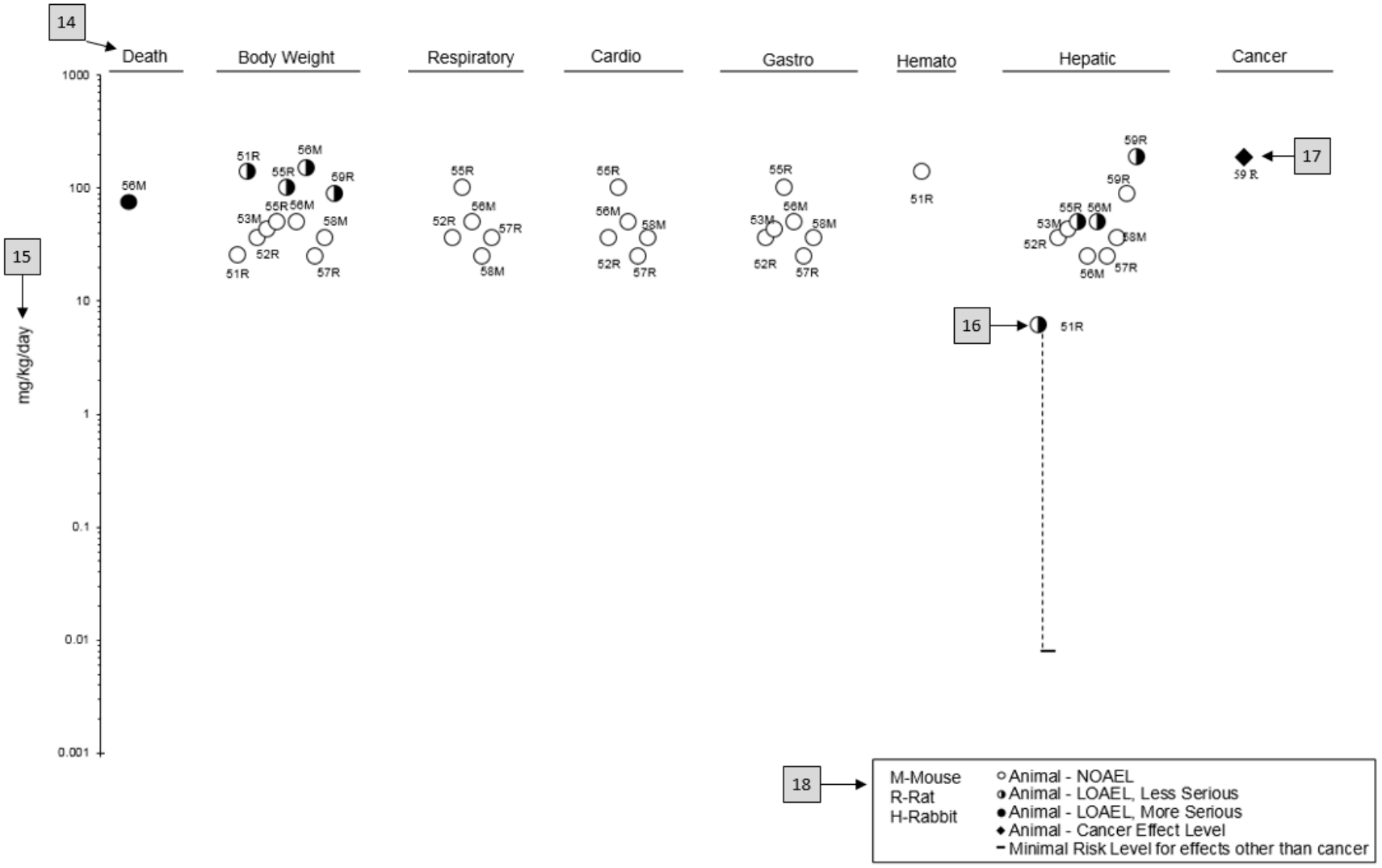
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[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).

1

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

13 → Chronic (≥365 days)



1

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) ≥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