

## 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 ( $\leq 14$  days), intermediate (15–364 days), and chronic ( $\geq 365$  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

## 2. HEALTH EFFECTS

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.

## 2. HEALTH EFFECTS

**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.

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
<b>ACUTE EXPOSURE</b>									
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 Resp		0.7	2.1	Decreased lifespan, 36 days compared to 462 days in controls Increased relative lung weight at $\geq 0.7$ ppm; increased incidence of tracheal epithelial hyperplasia at 0.7 ppm; tracheal and bronchial hyperplasia and bronchial squamous metaplasia at 2.1 ppm
<b>Drew et al. 1975</b>									
2	Rat (Sprague-Dawley) 50 M	1, 3, or 10 days 6 hours/day	1	LE, CS	Death Neuro			1 1	Decreased lifespan in rats exposed for 3 or 10 days (168 and 21 days, respectively) compared to controls (462 days) Subarachnoid hemorrhage and extreme irritability in rats exposed for 10 days
<b>Drew et al. 1975</b>									
3	Rat (Sprague-Dawley) M	7 hours	0.94, 4.6, 6.2, 7.3, 9, 19, 74	LE	Death			7.0	LC <sub>50</sub>
<b>Drew et al. 1975</b>									
4	Hamster (Golden Syrian) M	7 hours	0.94, 4.6, 6.2, 7.3, 9, 19, 74	LE	Death			7.0	LC <sub>50</sub>
<b>Drew et al. 1975</b>									

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	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 Resp			2.1 0.7	Decreased lifespan, 68 days compared to 675 days in controls 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
<b>Drew et al. 1975</b>									
6	Hamster (Golden Syrian) 50 M	1, 3, or 10 days 6 hours/day	1	LE, CS	Death Neuro			1 1	Decreased lifespan in hamsters exposed for 3 or 10 days (471 and 137 days, respectively) compared to controls (675 days) Extreme irritability in hamsters exposed for 10 days
<b>Drew et al. 1975</b>									
7	Mouse (A/Heston) M	6 hours	2.7–10.6	LE	Death			5.3	LC <sub>50</sub>
<b>Leong et al. 1971</b>									
<b>INTERMEDIATE EXPOSURE</b>									
8	Rat (Sprague-Dawley) 50 M	30 days 6 hours/day	1	LE, CS	Death Neuro			1 1	Decreased lifespan (23 days) compared to controls (462 days) Subarachnoid hemorrhage and extreme irritability
<b>Drew et al. 1975</b>									
9	Rat	4 weeks 5 days/week; 6 hours/day			Cancer			0.1	CEL: nasal and lung tumors
<b>Kuschner et al. 1975</b>									

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	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 <sup>b</sup>			
					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
<b>Leong et al. 1981</b>									
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
<b>Leong et al. 1971</b>									
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 Cancer	0.1		0.1	Increase in pulmonary adenomas in mice dying post-exposure
<b>Leong et al. 1981</b>									

## 2. HEALTH EFFECTS

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

Figure key <sup>a</sup>	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**

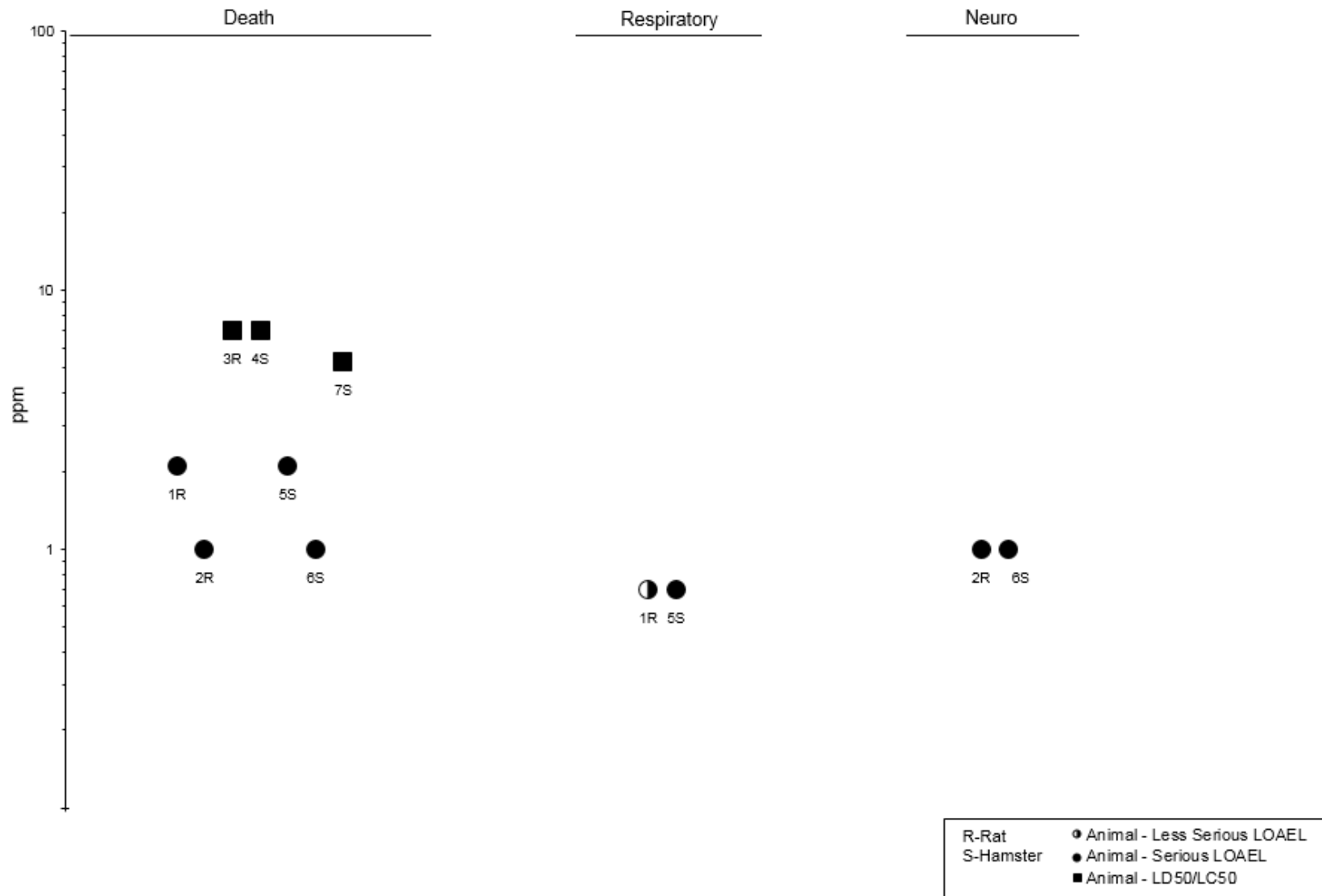
<sup>a</sup>The number corresponds to entries in Figure 2-2.

<sup>b</sup>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<sub>50</sub> = 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

2. HEALTH EFFECTS

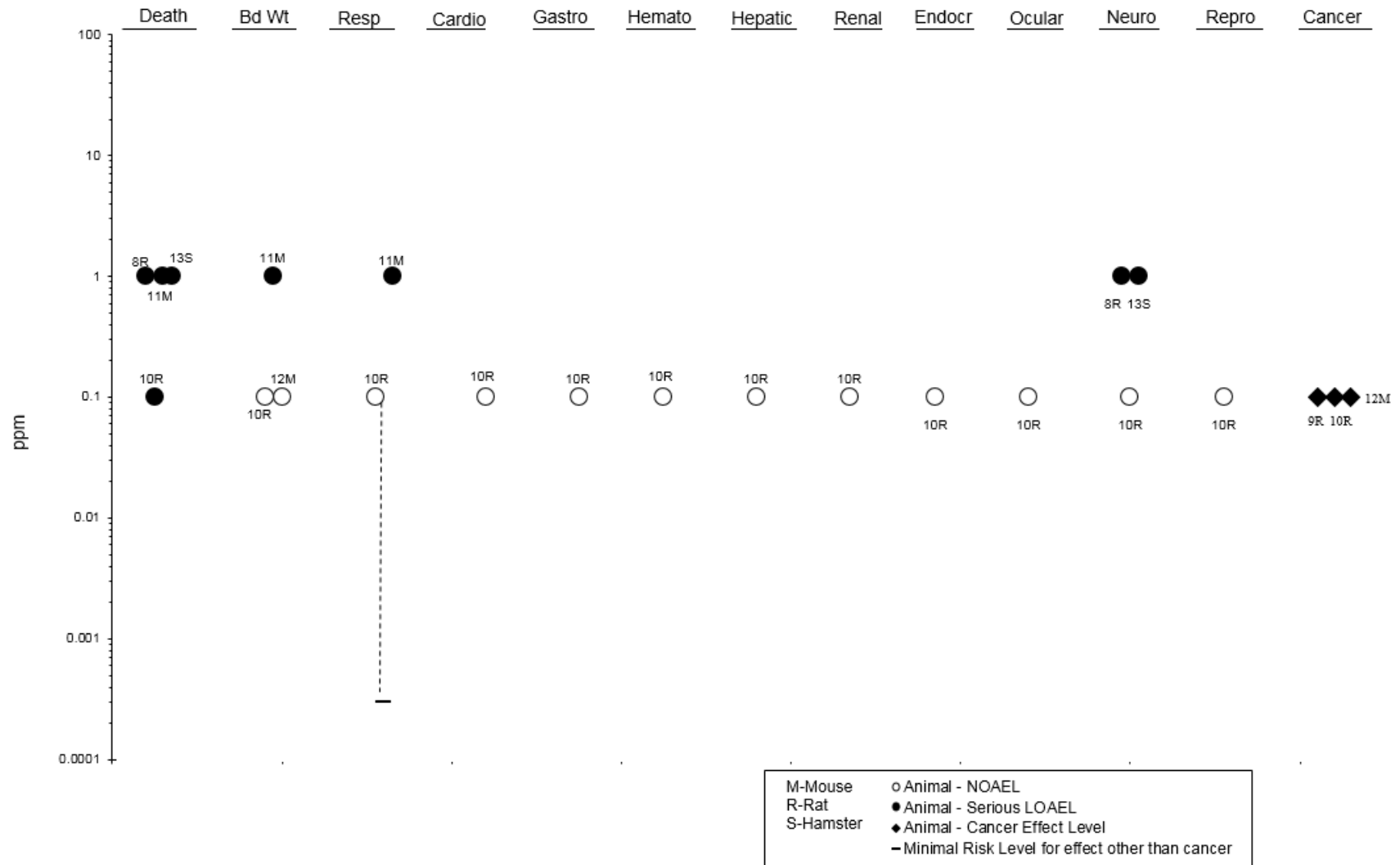
**Figure 2-2. Levels of Significant Exposure to Bis(Chloromethyl)Ether – Inhalation**  
Acute ( $\leq 14$  days)





2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Bis(Chloromethyl)Ether – Inhalation**  
Intermediate (15-364 days)



## 2. HEALTH EFFECTS

**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. HEALTH EFFECTS

**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  $\geq 0.7$  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. HEALTH EFFECTS

**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  $\mu$ L (7 mg) applied to the eye of rabbits produced severe corneal 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. HEALTH EFFECTS

### 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;

## 2. HEALTH EFFECTS

Lemen et al. 1976; Maher and DeFonso 1987; Pasternack et al. 1977; Reznick 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 (Figuroa 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 (Figuroa 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 <sup>a</sup>	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

## 2. HEALTH EFFECTS

**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 <sup>a</sup>	Reference
1,203 anion-exchange plant workers (258 exposed)	3,785 person-years at risk			5.0 (95% confidence interval 2.0–12.3) <sup>b</sup>	Gowers et al. 1993

<sup>a</sup>Observed/expected.

<sup>b</sup>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  $\geq 10$  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 <sup>a</sup>	Respiratory tumor type <sup>b</sup>	Incidence	Reference
Rat (Sprague-Dawley)	0.1	10 exposures	Nasal	1/41 (2%)	Kuschner et al. 1975
		20 exposures	esthioneuroepithelioma,	3/46 (6%)	
		40 exposures	lung squamous cell carcinoma, and other	4/18 (22%)	
		60 exposures	respiratory tract tumors	4/18 (22%)	
		80 exposures		15/34 (44%)	
		100 exposures		12/20 (60%)	

## 2. HEALTH EFFECTS

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

Species (strain)	Exposure level (ppm)	Exposure duration <sup>a</sup>	Respiratory tumor type <sup>b</sup>	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%)	

<sup>a</sup>Unless otherwise noted, exposures were for 6 hours/day, 5 days/week.

<sup>b</sup>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. HEALTH EFFECTS

**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***

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

+ = positive results; NA = not reported