TOXICOLOGICAL PROFILE FOR BIS(CHLOROMETHYL)ETHER

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

In collaboration with:

U.S. Environmental Protection Agency

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FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the most significant hazardous substances were published in the Federal Register on April 17, 1987, and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> (A) An examination, summary and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (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 which present a significant risk to human health of acute, subacute, or chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every 3 years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that

describes a hazardous substance's toxicological properties. Other literature is presented but 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.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. 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 protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

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. We plan to revise these documents as additional data become available.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers 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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Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS BIS(CHLOROMETHYL) ETHER?

Bis(chloromethy1) ether (BCME) is a man-made chemical with a strong, unpleasant odor. It is a clear liquid at room temperature, but it readily evaporates into air. BCME undergoes chemical reactions easily, so it is broken down very rapidly when it comes into contact with water. Consequently, any BCME that might escape from a chemical plant or a chemical waste site into water or moist soil would be destroyed within a few minutes. BCME that escapes into air is also broken down by reacting with water and other chemicals, but this takes a few hours.

BCME was used in the past to make several types of polymers, resins and textiles. However, because BCME is believed to cause cancer in humans, these uses have been stopped. BCME is now used only in small amounts inside fully enclosed systems in chemical plants. More information on the properties and uses of BCME is presented in Chapters 3 and 4.

1.2 HOW MIGHT I BE EXPOSED TO BIS(CHLOROMETHYL)ETHER?

Since BCME has such limited use in the United States, chances for exposure to BCME are low. Some BCME can form as an impurity during the production of other chemicals, so exposure might occur in chemical plants that make or use these chemicals. Also, some BCME may exist in chemical waste sites, although this is not certain. Because BCME evaporates easily, the most likely way to be exposed to BCME in the workplace or around a waste site is by breathing air containing BCME vapors. However, information on levels of BCME which exist in air is not available.

More information on possible ways that people can be exposed to BCME is presented in Chapter 5.

1.3 HOW CAN BIS(CHLOROMETHYL) ETHER ENTER AND LEAVE MY BODY?

Because BCME is so quickly broken down by water, most BCME that contacts the body is quickly changed into other chemicals (formaldehyde and hydrochloric acid) before it passes through the outermost layer of cells contacted (e.g., the cells that line the nose, windpipe and lungs). Some BCME may enter into the blood or internal tissues, but this has not been studied and the amount may be too small to measure.

More information on how BCME enters the body is presented in Chapter 2.

1.4 HOW CAN BIS(CHLOROMETHYL) ETHER AFFECT MY HEALTH?

Studies of people exposed to BCME in the workplace show that breathing of BCME vapors causes irritation to the nose, throat, and lungs. Contact with the liquid is also highly irritating to skin. In animals, breathing in high levels of BCME causes swelling and bleeding in the lung and can cause death. Workers exposed to BCME have been shown to have a higher-than-expected incidence of lung cancer. This observation is supported by studies in animals which also show that BCME can cause cancer. More information on the harmful effects of BCME is presented in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO BIS(CHLOROMETHYL) ETHER?

Because BCME is broken down so rapidly in the body, there are no specific tests to determine if a human has been exposed to this compound. The only available medical tests are physical examination of the nose and throat, chest X-ray, and examination of the sputum for abnormal cell types. Unfortunately, these tests are not specific for this compound, and would reveal effects of the compound only after damage to the tissues had already occurred. More information on ways to measure BCME is provided in Chapter 6.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables l-1 through 1-4 show the relationship between exposure to BCME and known health effects besides cancer. Chapter 2 provides information on levels that have been shown to cause cancer in animals.

Although no direct information is available from studies in humans, a Minimal Risk Level (MRL) is included in Table l-l., This MRL was derived from animal data for long-term exposure, as described in Chapter 2 and in Table 2-1. The MRL provides a basis for comparison with levels that people might encounter in the air or in food or drinking water. If a person is exposed to BCME at an amount below the MRL, it is not expected that harmful noncancer health effects will occur. Because this level is based only on information currently

1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing BCME*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to air containing specific levels of BCME are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
0.0003	15 days or more	Estimated minimal risk level (based on studies in animals; see Section 1.6 for discussion).

* See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-2. Animal Health Effects from Breathing BCME

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
0.7	7 hr	Lung injury in rats and hamsters
1.0	3 days (6 hr/d)	Death in rats and hamsters
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
0.1	6 months	Increased number of deaths in in rats (due to nasal tumors)
1.0	82 days	Impaired breathing, injury to lungs in mice

* These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking BCME*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to food containing specific levels of BCME are not known. However, because BCME is rapidly destroyed when it comes into contact with other substances, it is unlikely that BCME would be found in food.
Levels in Water (ppm)		BCME is rapidly destroyed in water, so exposure by drinking water containing BCME is of little concern.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term human exposure to food containing specific levels of BCME are not known. However, because BCME is rapidly destroyed when it comes into contact with other substances, it is unlikely that BCME would be found in food.
Levels in Water (ppm)		BCME is rapidly destroyed in water, so exposure by drinking water containing BCME is of little concern.

* See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking BCME

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term animal exposure to food containing specific levels of BCME are not known. However, because BCME is rapidly destroyed when it comes into contact with other substances, it is unlikely that BCME would be found in food.
Levels in Water (ppm)		BCME is rapidly destroyed in water, so exposure by drinking water containing BCME is of little concern.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term animal exposure to food containing specific levels of BCME are not known. However, because BCME is rapidly destroyed when it comes into contact with other substances, it is unlikely that BCME would be found in food.
Levels in Water (ppm)		BCME is rapidly destroyed in water, so exposure by drinking water containing BCME is of little concern.

available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the presence, absence or level of risk of cancer.

No information exists for either animals or humans on toxic effects following oral exposure (Tables l-3 and l-4), but oral exposure is of little concern since BCME breaks down in water or moist foods and exposure is not likely by this route. Direct skin contact with even small amounts (less than a drop) of the liquid form of BCME causes severe skin irritation at the site of contact. Further information on the exposure levels that have been found to cause harmful health effects in humans and animals is presented in Chapter 2.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has taken a series of steps to reduce the risk of human exposure to BCME. The Occupational Safety and Health Administration (OSHA) regulates BCME as a potential human carcinogen. An average concentration of 1 part per billion (ppb) is considered to be the highest acceptable level in the workplace, and strict controls have been established to minimize exposure to this compound. The U.S. Environmental Protection Agency (EPA) has developed standards which limit the amount of this compound that can be discharged into water or air or disposed of at waste sites, Further information on regulations concerning BCME is provided in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have further questions or concerns, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to BCME. Its purpose is to present levels of significant exposure for BCME based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of BCME and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in

humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MELs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980c), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

A number of cases of inhalation exposure of humans to BCME have occurred in the workplace. However, data on BCME concentrations in workplace air are rarely available, and exposure to BCME often occurs in conjunction with exposure to other chemicals, particularly chloromethyl methyl ether (CME). Consequently, there are no reliable dose-response data in humans. The effects of inhalation of BCME have been investigated in animals, with principal emphasis on carcinogenic effects. Available data on the health effects of inhalation of BCME are summarized in Table 2-l and Figure 2-l and are discussed below.

2.2.1.1 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 2.2.1.7.

2. HEALTH EFFECTS

TABLE 2-1. Levels of Significant Exposure to BCME - Inhalation

Graph Key	Species	Exposure Duration/ Frequency	Syst. Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	rat	1 exp. 7hr		0.7		2.1	Drew et al. 1975
2	rat	3 d 6hr/d				1.0	Drew et al. 1975
3	rat	1 exp. 7hr				7 LC50	Drew et al. 1975
4	mouse	1 exp. 6 hr				5.3 LC50	Leong et al. 1971
5	hamster	1 exp. 7 hr		0.7		2.1	Drew et al. 1975
6	hamster	3d 6hr/d				1.0	Drew et al. 1975
7	hamster	1 exp. 7hr				7 LC50	Drew et al. 1975
Systemic							
8	rat	1 exp. 7 hr	Resp			0.7 edema	Drew et al. 1975
9	hamster	1 exp. 7 hr	Resp			0.7 edema	Drew et al. 1975
Neurological							
10	rat	10 d 6 hr/d				1 subarach. hemorrhage	Drew et al. 1975
INTERMEDIATE EXPOSURE							
Systemic							
11	rat	6 mo 6hr/d 5d/wk	Resp	0.1[a]			Leong et al. 1981
			Cardio	0.1			
			Gastro	0.1			
			Hemato	0.1			
			Musc/skel	0.1			
			Hepatic	0.1			
			Derm/Oc	0.1			
			Other	0.1			

TABLE 2-1. - continued

Graph Key	Species	Exposure Duration/ Frequency	Syst. Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
12	mouse	82 d 6hr/d 5d/wk	Resp			1 edema	Leong et al. 1971
Neurological							
13	rat	6 mo 6hr/d 5d/wk		0.1			Leong et al. 1981
Reproductive							
14	rat	6 mo 6hr/d 5d/wk		0.1			Leong et al. 1981
Cancer							
15	rat	6 mo 6hr/d 5d/wk				0.1 CEL (nasal tumors)	Leong et al. 1981
16	rat	4 wk 5d/wk 6hr/d				0.1 CEL (nasal, lung tumors)	Kuschner et al. 1975

[a]Used to derive intermediate MRL; dose 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. This value is presented in Table 1-1.

NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse effect level; ppm = parts per million; exp = exposure; hr = hour; d = day; LC_{50} = lethal concentration, 50% mortality; Resp. = Respiratory; Subarach = subarachnoid; mo = month; wk = week; Cardio = cardiovascular; gastro = gastrointestinal; hemato = hematological; musc/skel = muscular/skeletal; derm/oc = dermal/ocular; CEL = cancer effect level.

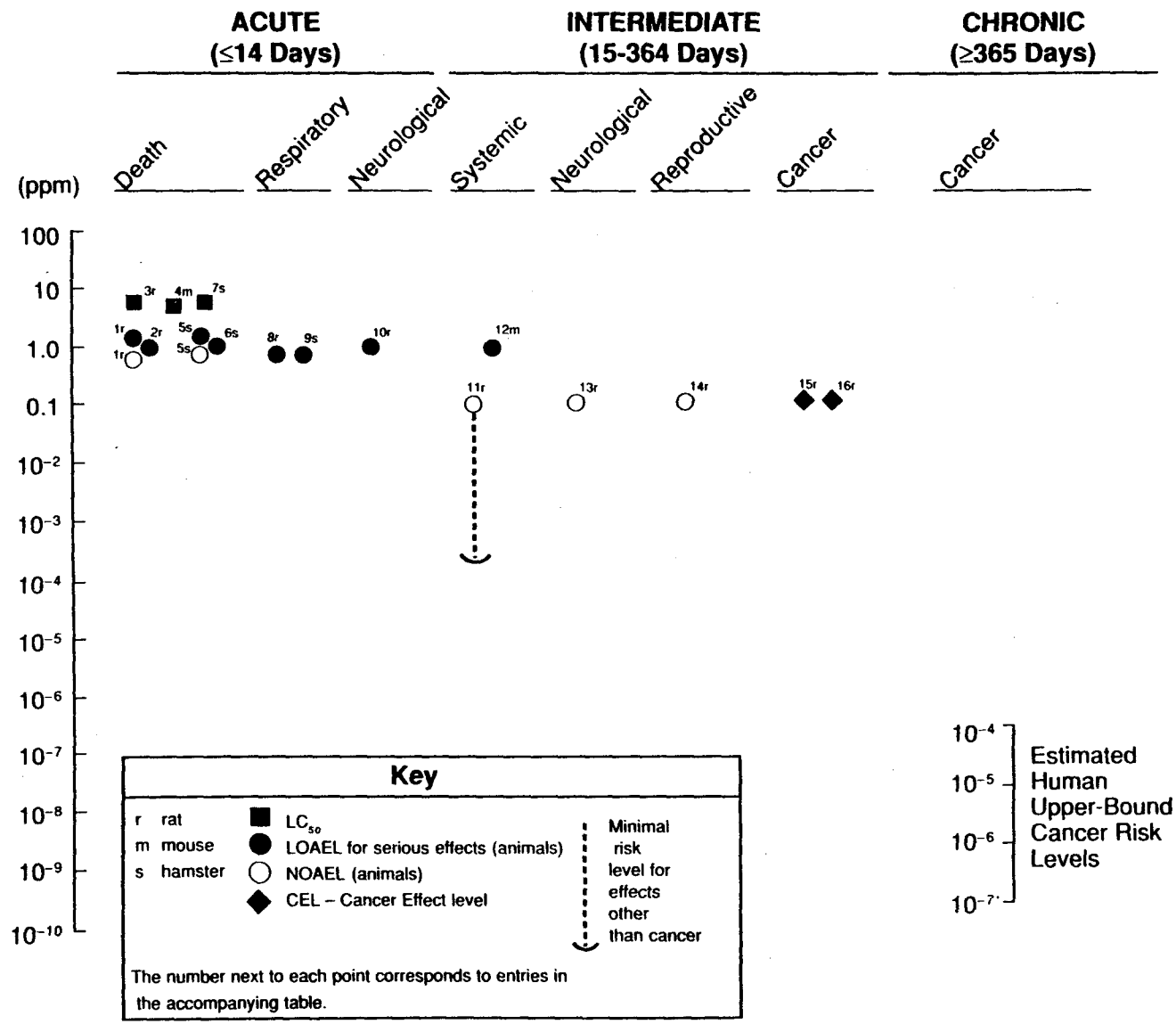


FIGURE 2-1. Levels of Significant Exposure to BCME – Inhalation

In rats, 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-hr exposure to 0.7 ppm did not cause acute or delayed mortality in rats or hamsters, but a single exposure to 2.1 ppm lead to marked reduction in life span in both species (Drew et al. 1975). Repeated exposures (6 hr/d) to 1 ppm lead to a duration dependent increase in mortality. In rats, 3 exposures to 1 ppm lead to 50% mortality after about 20 weeks, and 10 exposures lead to 100% mortality within 10 weeks. In hamsters, 3 exposures caused 50% mortality after about one year, and 30 exposures caused 100% mortality within about 10 weeks (Drew et al. 1975). The data on lethality following three exposures to 1 ppm have been presented in Table 1-2. Exposure to as little as 0.1 ppm caused increased mortality in rats when exposure was extended to six months (Leong et al. 1981), primarily because of the occurrence of nasal tumors (see Section 2.2.1.7, below).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Respiratory Effects. As noted above, BCME is acutely irritating to the lungs, causing congestion, edema and hemorrhage in rats and hamsters at exposure levels of 0.7 ppm and higher (Drew et al. 1975). This value has been presented in Table 1-2.

Exposure of mice to BCME at 1.0 ppm (6 hr/d, 5 d/wk) for 82 days caused marked respiratory distress (Leong et al. 1971), while exposure of rats to 0.1 ppm (6 hr/d, 5 d/wk) for six months did not result in edema, hemorrhage or any effects on the histological appearance of the lung (Leong et al. 1981). The value of 0.1 ppm has been used to calculate the intermediate inhalation MRL value of 0.0003 ppm, as shown in Figure 2-1 and described in the footnote in Table 2-1. This value has also been presented in Table 1-1.

In humans, exposure to vapors of chloromethyl methyl ether (CME) containing BCME as a contaminant lead to increased incidence of chronic bronchitis, manifest as chronic cough and impaired respiratory function

(Weiss and Boucot 1975; Weiss 1976). 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.

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

Other Systemic Effects. Systemic effects other than on the lungs have not been observed following inhalation exposure to BCME. Leong et al. (1981) observed no effects on cardiovascular, hematological, gastrointestinal, musculoskeletal, endocrine and subcutaneous tissues in rats exposed to 0.1 ppm for six months (6 hr/day, 5 days/week). This is consistent with the hypothesis that rapid hydrolysis of BCME precludes direct action at tissues beyond the respiratory epithelium. The resulting hydrolysis product (formaldehyde and HCl) are presumably absorbed and distributed throughout the body, but at levels sufficiently low that no effect from these degradation products are expected.

2.2.1.3 Neurological Effects

Leong et al. (1981) reported that exposure of male rats to 0.1 ppm for six 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 to 30 times to 1 ppm of BCME, and concluded that this was evidence of central nervous system effects. However, these symptoms were probably due to treatment-related stress associated with the dis-comfort 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. As detailed in Section 2.2.1.7 (below), nasal tumors of neural cells esthesioneuroepitheliomas) have been noted in rats exposed to 0.1 ppm for 5-6 months (Kuschner et al. 1975: Leong et al. 1981).

2.2.1.4 Immunological Effects

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

2.2.1.5 Developmental Effects

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

2.2.1.6 Reproductive Effects

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

Leong et al. (1981) found no histological evidence of injuries to the testes of rats exposed to 0.1 ppm of BCME in air for six months. However, no tests of reproductive function were performed, and rio tests were performed on females.

2.2.1.7 Genotoxic Effects

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

2.2.1.8 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 (Figueroa et al. 1973; Thiess et al. 1973; Sakabe 1973; Albert et al. 1975; Weiss and Boucot 1975; DeFonso and Kelton 1976; Lemen et al. 1976; Weiss 1976; Pasternack et al. 1977; Reznik et al. 1977; Weiss 1982; Roe 1985; Maher and DeFonso 1987; Collingwood et al. 1987). 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 to CME and other chemicals as well, the consistent findings strongly support the conclusion that BCME is a lung carcinogen in humans. Although quantitative data on exposure levels were not available, increased risk as a function of exposure duration and/or qualitative estimates of exposure intensity was noted in some cases (DeFonso and Kelton 1976). A high proportion of the respiratory tumors were oat cell

TABLE 2-2. Lung Cancer Mortality in Workers Exposed to BCME and Technical Grade Chloromethyl Methyl Ether

Exposed Population	Duration of Exposure	Number of Observed Lung Cancer Deaths	Number of Expected Lung Cancer Deaths	Increased Risk (Obs./Exp.) (P value)	Reference
669 chemical plant workers	<1 yr (n=389)	3	2.1	1.2	DeFonso and Kelton 1976
	1-5 yr (n=170)	5	1.3	3.8 (P<0.05)	
	≥ 5 yr (n=101)	11	1.1	9.6 (P<0.01)	
	Total (n=669)	19	5.0	3.8 (P<0.01)	
1446 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
136 anion-exchange plant workers	≥5 years	5	0.54	9.24 (P<0.01)	Lemen et al. 1976

carcinomas (Lemen et al. 1976; Figueroa et al. 1973; Weiss et al. 1979). Some tumors appeared after only 5 to 10 years of exposure (Weiss and Boucot 1975; Weiss 1976) in young workers (Figueroa et al. 1973; Reznick et al. 1977).

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% to 86%) of respiratory tract tumors in exposed rats, and some tumors developed in animals that had been exposed for periods as short as two 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 to 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 are mice or rats. However, Drew et al. (1975) observed nasal tumors after two years in two hamsters that had been exposed only one to three times to 1.0 ppm BCME. Hamsters exposed for 10 times or more to 1.0 ppm had shortened lifespans, so tumors may not have had time to develop.

Based on the evidence reviewed above, EPA has concluded that BCME is a known human carcinogen (EPA Group A). Employing the data of Kuschner et al. (1975), EPA (1988) has calculated an upper bound cancer potency factor (q_1^*) of 220 $(mg/kg/day)^{-1}$. Assuming that a 70-kg adult inhales 20 m^3/day, the concentrations of BCME associated with upper bound human risk levels of 10^{-4}, 10^{-5}, 10^{-6} and $l0^{-7}$ are $3.4 \times l0^{-7}$, 3.4×10^{-8}, $3.4 \times l0^{-9}$ and 3.4×10^{-l0} ppm, respectively. These values, and doses which have been observed to cause cancer, are plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

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).

TABLE 2-3. Inhalation Carcinogenicity of BCME in Animals

Species Strain	Exposure Level, ppm	Exposure Duration/ Frequency	Respiratory Tumors[a]	Tumor Types	References
Rats Sprague-Dawley	0.1	2 weeks (10 exposures)	1/41 (2%)	Nasal esthesio-neuroepithelioma, lung squamous-cell carcinoma	Kuschner et al. 1975
		4 weeks (20 exposures)	3/46 (6%)		
		8 weeks (40 exposures)	4/18 (22%)		
		12 weeks (60 exposures)	4/18 (22%)		
		16 weeks (80 exposures)	15/34 (44%)		
		20 weeks (100 exposures)	12/20 (60%)		
Rats Sprague-Dawley	0.0	6 months	0/112 (0%)	Nasal neuroepithelioma	Leong et al. 1981
	0.001	6 hr/day, 5 day/wk	0/113 (0%)		
	0.01		0/111 (0%)		
	0.1		96/111(86%)		
Mice A/H	0	21 weeks	20/49 (41%)	Lung adenomas	Leong et al. 1971
	1	6 hr/day, 5 day/wk	26/50 (55%)[b]		
Mice Ha/ICR	0.0	6 months	9/86 (10%)	Pulmonary adenomas	Leong et al. 1981
	0.001	6 hr/day, 5 day/wk	5/54 (9%)		
	0.01		3/37 (8%)		
	0.1		8/27 (30%)		
Hamsters Golden Syrian	0.1	67 weeks 6 hr/day, 5 day/wk	1/100 (1%)	Lung carcinoma	Kuschner et al. 1975
Hamsters Golden Syrian	0.7	1 day (6 hr/d)	1/25 (4%)	Nasal esthesioneuro-epithelioma	Drew et al. 1975
		3 day (6 hr/d)	1/25 (4%)		
		10 day (6 hr/d)	0/25 (0%)		
		30 day (6 hr/d)	0/25 (0%)		

[a]Observation, after exposure, was for lifetime or until animals were moribund.
[b]A significantly higher number of tumors per tumor-bearing mouse was found in BCME-exposed versus control mice.

2. HEALTH EFFECTS

No studies were located regarding the following effects in humans or animals following oral exposure to BCME:

2.2.2.2 Systemic Effects

2.2.2.3 Neurological Effects

2.2.2.4 Immunological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

2.2.3 Dermal Exposure

2.2.3.1 Death

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.

2.2.3.2 Systemic Effects

Dermal/Ocular Effects. 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 lead to moderate erythema and marked necrosis, and a primary dermal irritation score of 6 was assigned (Union Carbide 1968). A dose of 5 /μL (7 mg) applied to the eye of rabbits produced severe cornea1 necrosis (Union Carbide 1968).

Other Systemic Effects. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic or renal effects in humans or animals following dermal exposure to BCME.

No studies were located regarding the following effects in humans or animals following dermal exposure to BCME:

2.2.3.3 Neurological Effects

2.2.3.4 Immunological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

The first report of the carcinogenicity of BCME was that of Van Duuren et al. (1968). Following dermal exposure (skin painting), BCME was found to produce skin papillomas and carcinomas in over 50% of mice tested after 325 days of treatment. 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).

2.3 RELEVANCE TO PUBLIC HEALTH

Available data indicate that the toxic effects of BCME are restricted to the epithelial tissue where exposure occurs, and this is consistent with the short half-life of BCME in aqueous media. Since exposure is most likely to occur by inhalation, the tissues at greatest risk of injury are those of the respiratory tract. In particular, inhalation of BCME leads to acute irritation, hemorrhage and edema of the lung, and resulting respiratory distress can lead to acute or delayed mortality.

At present, opportunities for exposure to levels of BCME causing acute lung injury are considered to be remote. However, low levels of exposure may still occur, and these are of concern because of the high carcinogenic potency of BCME. Nasal and lung tumors have been observed

in animals following both intermediate and chronic exposure to BCME vapor, and epidemiological studies in exposed workers strongly suggest that BCME causes lung tumors in humans as well. This is supported by the carcinogenic activity of BCME following dermal and parenteral exposure in animals (Gargus et al. 1969; Van Duuren et al. 1968, 1969, 1972; Zajdela et al. 1980).

An important aspect of the carcinogenicity of BCME is that chronic exposure is not required for tumorigenesis. Respiratory tumors have been noted in rats after as few as 20 exposures, and, although the results are not statistically significant, nasal tumors occurred in a few animals after only one to three exposures. Although no cases of human cancer have been noted after acute exposures, the latency in exposed workers is shorter for BCME than for most other carcinogens, and lung cancer can develop at an early age relative to lung cancer in United States cigarette smokers. In addition, the respiratory tumors produced in humans are predominantly oat-cell carcinomas, a particularly rapid-growing and highly lethal tumor. These observations emphasize the marked carcinogenic hazard of BCME.

BCME is a powerful alkylating agent (Van Duuren et al. 1968), and as such would be expected to react readily with DNA and be a powerful genotoxin. However, in vitro tests of mutagenicity have yielded mixed results (Table 2-4), and no effect on bone marrow chromosomes were observed in rats exposed to BCME vapors for six months (Leong et al. 1981). Reaction of BCME with DNA in vitro did not affect the melting temperature or the buoyant density of the DNA, nor did it yield isolatable products on reaction with purines or DNA as did other alkylating agents (Van Duuren et al. 1972). These observations suggest that BCME may be hydrolyzed so quickly in an aqueous environment (such as a cell) that interaction with nucleic acids is very limited. However, the data do not establish that low levels of binding do not occur.

The hydrolysis products of BCME are formaldehyde and HCl. Since formaldehyde has been shown to produce nasal tumors in rats (Albert et al. 1982; Sellakumar et al. 1985), it is possible that at least some of the carcinogenic potential of BCME may be due to this degradation product. However, it is apparent from the difference in potency (BCME is much more potent than formaldehyde) that this cannot be the sole mechanism of carcinogenicity. It is also possible that BCME,

TABLE 2-4. Summary of *In Vitro* Genotoxicity Studies on BCME

Test System	Dose or Concentration	Exogenous Activation	Results	Reference
S. typhimurium (TA 1535, TA 1538, TA 98)	NR[a]	+	No increase in reversion frequency (less than 2-fold increase)	Anderson and Styles 1978
S. typhimurium (TA 100)	20 µg/plate	+	3-fold increase in reversion frequency	Anderson and Styles 1978

[a]Not reported

formaldehyde and HCl interact synergistically within the cell, but there are no data to clearly support this possibility. Rather, studies by Albert et al. (1982) and Sellakumar et al. (1985) indicate that inhalation exposure of rats to mixtures of formaldehyde and HCl results in little change in the frequency of nasal tumors compared with exposure to formaldehyde alone. However, one animal in this study developed an esthesioneuroepithelioma, a rare kind of tumor which is characteristic of BCME exposure.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

No studies were located regarding the presence of BCME in human tissues and fluids. It is expected that BCME does not endure 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.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS

As previously noted, there are no data available on the levels of BCME or its metabolites in tissues of humans or animals. Although there are a number of epidemiological studies involving occupational exposure to BCME, there are no data on the concentrations of BCME to which workers were exposed. Consequently, there is no information on the relationship between environmental levels of BCME and any health effect or tissue level in exposed humans.

2.6 TOXICOKINETICS

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

2.7 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.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No evidence was located to suggest that any one group of humans are 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.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on Health Effects of BCME

As shown in Figure 2-2, no data exist on the effects of BCME in humans, except for data on lung cancer risk following inhalation exposure. In animals, there are limited data on the effects of inhalation exposure, but only one observation is available for oral exposure (an estimate of the oral LD_{50}). This is probably not a major limitation, since BCME is not stable in water or moist foods. There are

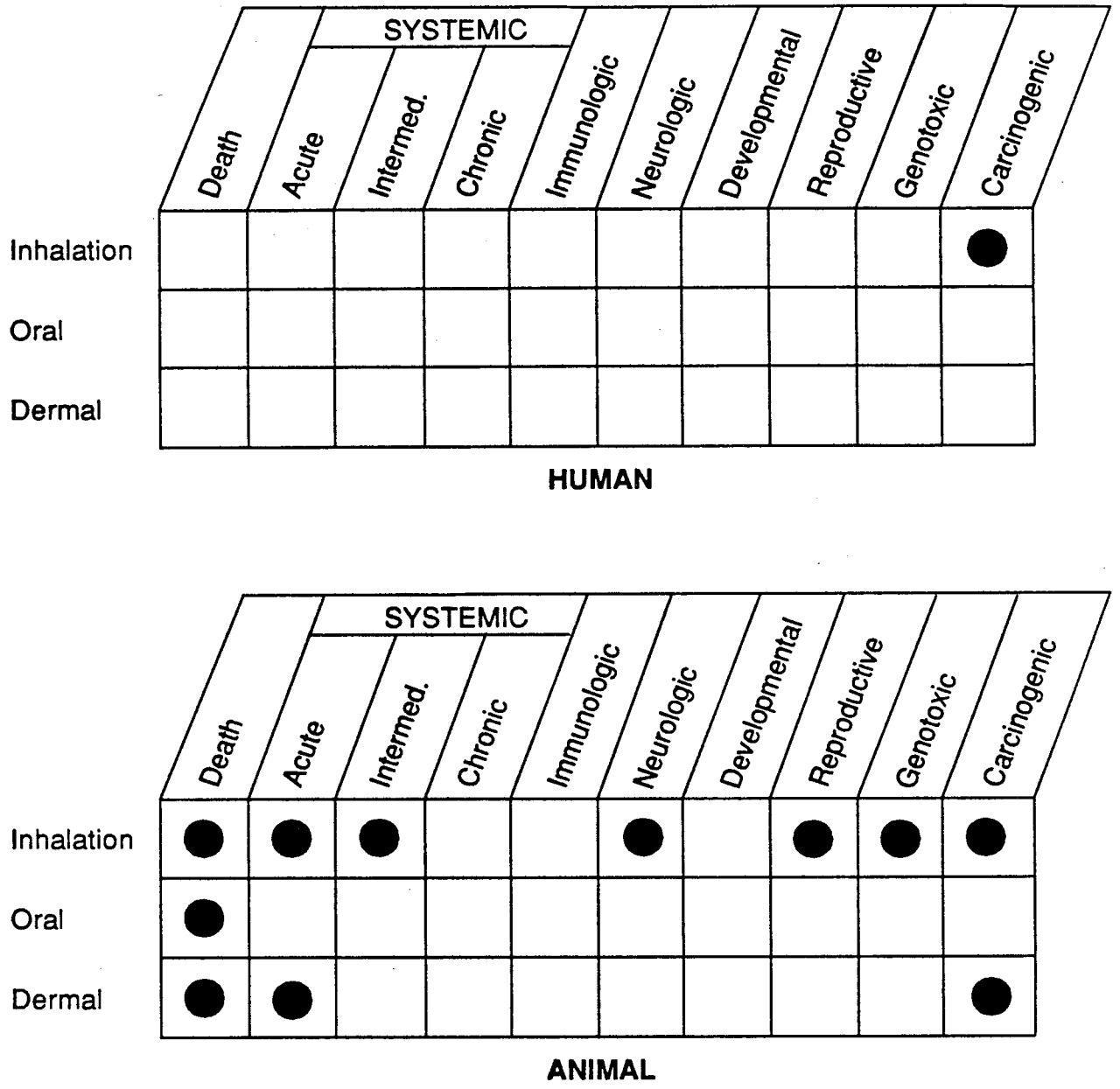


FIGURE 2- 2. Existing Information on Health Effects of BCME

limited data on dermal lethality and direct dermal and ocular irritation, but none on any systemic effects following dermal exposure. Most research has focused on the carcinogenic effects of inhaled BCME, since this is the most common route of human exposure.

2.9.2 Data Needs

Single Dose Exposure. 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 does-response curve for sub- lethal effects on the lung has not been determined, and further studies to identify the acute NOAEL would be valuable. Due to the rapid hydrolysis of BCME, effects are not likely to occur in nonepithelial tissues, but careful studies to investigate this would still be appropriate.

Repeated Dose Exposure. 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, while 1.0 ppm leads to significant injury to lung in mice. Further studies to confirm these estimates and to determine both NOAEL and LOAEL values in each species would be useful in the protection of occupationally exposed workers.

Chronic Exposure and Carcinogenicity. 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 which 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 which 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 lead 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 affects of BCME on the nervous system would be useful, including tests both of functions (behavior, electrophysiological tests, etc.) and of structure (histopathology).

Epidemiological 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 Disease. No biomarkers are known that are specific for BCME-induced lung injury. Standard chemical examination of nose and throat can provide an index of local irritation, and examination of sputum for abnormal cell types can provide information on the state of the respiratory epithelium. However, these tests cannot distinguish BCME-induced effects from effects caused by smoking or exposure to other chemicals, and can only discover changes after damage to the tissue has already occurred. Continued efforts to devise more sensitive and more specific early biomarkers of disease (especially lung cancer) would be valuable.

Disease Registries. There is no registry of humans with BCMEinduced disease. The identities of individuals who have died from lung cancer (particularly oat cell carcinoma) can be found by searching death certificates, but it is expected that only a small fraction of all such cases would be related to BCME exposure. Creation of a disease registry for BCME would be valuable in helping to establish a clearer understanding of the association between BCME exposure and lung cancer.

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 Bioaccumulations. 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.

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 (see Table 2-3).

2.9.3 Ongoing Studies

No information was located regarding ongoing research on the health effects of BCME.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

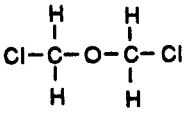
Table 3-1 lists common synonyms, trade names and other pertinent identification information for BCME.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of BCME.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of BCME

Property	Value	References
Chemical Name	Bis(chloromethyl) ether	NLM 1988
Synonyms	Oxybis(chloromethane); dichlorodimethyl ether; monochloromethyl ether	NLM 1988
Trade Name (s)	--(a)	
Chemical Formula	$C_2H_4Cl_2O$	Weast 1985
Chemical Structure		
Identification Numbers:		
CAS Registry	542-88-1	NLM 1988
NIOSH RTECS	KN1575000	HSDB 1988
EPA Hazardous Waste	P016	NLM 1988
OHM-TADS	8200174	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN2249	NLM 1988
HSDB	501	NLM 1988
NCI	--(a)	

CAS - Chemical Abstracts Service
NIOSH - National Institute for Occupational Safety and Health
RTECS - Registry of Toxic Effects of Chemical Substances
OHM-TADS - Oil and Hazardous Materials/Technical Assistance Data System
DOT/UN/NA/IMCO - Department of Transportation/United Nations/North America/ International Maritime Dangerous Goods Code
HSDB - Hazardous Substances Data Bank
NCI - National Cancer Institute

(a)-- = No data located.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of BCME

Property	Value	References
Molecular weight	114.96	Weast 1985
Color	colorless	Windholz 1983
Physical state	liquid	Windholz 1983
Melting point, °C	-41.5	Weast 1985
Boiling point, °C	104	Weast 1985
Density, 20/4	1.328	Weast 1985
Odor	--[a]	
Odor threshold Water Air, ppm	 -- --	
Solubility Water, mg/L, 25°C	 22,000[b]	 Mabey et al. 1982
Organic solvents	miscible	Weast 1985
Partition coefficients Log octanol/water	 -0.38[b]	 Mabey et al. 1982
Log k_{oc}	0.08	Mabey et al. 1982
Vapor pressure, mm Hg, 20°C	30	Mabey et al. 1982
Henry's law constant, atm-m^3/mol	2.1×10^{-4}	Mabey et al. 1982
Autoignition temperature, °C	--	
Flash point, °C	19	HSDB 1988
Flammability limits	--	
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]-- = data not located.
[b]Calculated values. Due to the rapid hydrolysis of BCME in water, significant concentrations in water would not be expected to occur.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 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). Available information indicates that BCME is no longer produced for sale in the United States (EPA 1980a; USITC 1987; HSDB 1988), although at least one facility manufactures BCME as a non-isolated, site-limited intermediate used in the production of other chemicals (Brothers 1989; Ress 1977). BCME is produced as a contaminant during the manufacture of chloromethyl methyl ether, usually at estimated levels of approximately 0.5 to 5% (DeFonso and Kelton 1976).

4.2 IMPORT

No data were located on imports of BCME.

4.3 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 flameretardant fabrics (EPA 1980a). These applications have been discontinued, and no uses of BCME other than as a nonisolated intermediate were identified.

4.4 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).

4.5 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research

designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort,ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

4.5.1 Data Needs

Production, Import, Use 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.

According to the Emergency Planning and Community Right to Know Act
of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and
emission.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

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. Inhalation of BCME in ambient air might also occur near such a facility, but there is no evidence that this occurs. Exposure through other media (water, food, soil) is unlikely to be significant.

5.2 RELEASES TO THE ENVIRONMENT

No information was located on the amount of BCME released to air, water or soil. Because BCME is readily volatile at room temperature, emissions into the atmosphere could occur, but OSHA regulations require that processes involving BCME be contained (OSHA 1974). Releases into water could occur but would be of little significance, due to the rapid hydrolysis of BCME in water.

5.3 ENVIRONMENTAL FATE

5.3.1 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.

5.3.2 Transformation and Degradation

5.3.2.1 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 halflife 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 to 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 to 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:

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

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.

5.3.2.2 Water

BCME is rapidly hydrolyzed in water to yield formaldehyde and HCl, with a hydrolysis rate constant of 0.018 sec^{-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.

5.3.2.3 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.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 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.

5.4.2 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.

5.4.3 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.

5.4.4 Other Media

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

5. POTENTIAL FOR HUMAN EXPOSURE

5.5 GENERAL POPULATION AND OCCUPATIONAL 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).

5.6 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.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

5.7.1 Data Needs

Physical and Chemical Properties. The physical and chemical properties most important in evaluating the environmental fate of BCME have been determined (see Table 3-2). Although some of these values (eg, 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.

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.

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 exists 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 at 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.

Exposure Registries. No exposure registries exist for humans exposed to BCME. Although the exposed population is likely to be quite small, creation of such a registry would provide the opportunity to obtain valuable additional data on the health effects of BCME.

5.7.2 Ongoing Studies

No information was located regarding any ongoing studies on the occurrence of BCME in the environment or the potential for human exposure to BCME.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

There is little need or opportunity to measure BCME in biological samples because of its rapid hydrolysis in water to yield formaldehyde and chloride. The abundance of chloride and, to a lesser extent, of formaldehyde, in biological materials precludes use of these hydrolysis products as an index of exposure to BCME. Therefore, the analysis of BCME in biological samples from exposed humans is virtually impossible.

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of BCME in environmental samples are currently confined to monitoring of air. It is possible, to monitor BCME in air at extremely low levels, and several analytical methods have detection limits of a few tenths of a ppb. Most methods for the analysis of BCME in air call for collecting samples on a solid adsorbent, followed by thermal desorption and gas chromatographic analysis. A typical procedure (ASTM 1987) uses a sampling tube packed with Chromosorb 101 adsorbent through which up to 25 L of air can be drawn for a period as long as 24 hours. For analyte determination, the sampling tube is attached to a gas chromatograph so that carrier gas can be passed through it and through the analytical column. With the carrier gas flowing, the collection column is heated to 150°C for four minutes and the analyte flows onto the analytical column, which is maintained at room temperature. Following desorption of the BCME, the analytical column is heated to 130°C with a programmed temperature increase and the eluted BCME is detected and measured quantitatively by mass spectrometry.

It has been noted (Travenius 1982) that common adsorption methods of sampling BCME from air are prone to giving inaccurate results because of hydrolysis of the analyte by coadsorbed water. For this reason, most procedures for methods involving collection of BCME on solid adsorbents require that samples in collection tubes be processed within a few days and protected from humidity.

Methods for determination of BCME in air are given in Table 6-l.

6. ANALYTICAL METHODS

TABLE 6-1. Analytical Methods for BCME in Environmental Media

Sample type	Extraction/cleanup	Detection	Limit of Detection	References
Air	Adsorption on Chromosorb 101, thermal desorption	GC/MS	<1 ppb	ASTM 1987
Air	Direct injection without preconcentration	GC/OEEC	<2 ppb	Kallos 1981
Air	Collect on Tenax GC, thermal desorption, cryofocussing	CCGC/MS	NR	Krost et al. 1982
Air	Collect on Porapak Q	GC/MS	<1 ppb	Muller et al. 1981
Air	NR	MS	0.1 ppb	Collier 1972
Air	Collect on Chromosorb 101	GC/MS	0.5 ppb	NIOSH 1977
Air	Impinger	GC/ECD	0.5 ppb	NIOSH 1977
Air	Collect on Porapak Q	Colorimetric	0.2 ppb	Norpoth et al. 1981

Abbreviations: CCGC, capillary column gas chromatography; ECD, electron capture detector; GC, gas chromatography; MS, mass spectrometry; NR, not reported; OEEC, oxygen-enhanced electron capture detector.

6. ANALYTICAL METHODS

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

6.3.1 Data Needs

Methods for Determining Parent Compound and Metabolites in Biological Materials. 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.

Methods for Biomarkers of Exposure. No methods were located for measuring any biomarkers of exposure to BCME. Although covalent adducts of BCME with cellular proteins or DNA have not yet been reported, development of sensitive and specific immunological assays for such adducts would provide a valuable means of detecting and perhaps quantifying human exposure levels.

Methods for Determining Parent Compound and Degradation Products in Environmental Media. Air is the only environmental medium susceptibleto 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.

6.3.2 Ongoing Studies

Because of evidence that BCME is carcinogenic even at very low levels in the atmosphere, current studies of its analysis are concentrating on extending the detection limit to even lower levels. Because of its chlorine content, BCME can be measured with extreme sensitivity by electron capture detection after gas chromatographic separation of this analyte. Efforts are underway by Dr. Robert Sievers (University of Colorado, Boulder) to improve collection methods that meet the criteria of (1) highly efficient collection of BCME at sub-ppb levels in air, (2) no loss of analyte from hydrolysis resulting from atmospheric humidity, and (3) rapid, efficient, nondestructive desorption of analyte from the collection medium.

7. REGULATIONS AND ADVISORY STANDARDS

Because of its potential to cause adverse health effects in exposed people, a number of regulations and advisory values have been established for BCME by various international, national and state agencies. These values are summarized in Table 7-l.

7. REGULATIONS AND ADVISORY STANDARDS

TABLE 7-1. Regulations and Guidelines Applicable to BCME

Agency	Description	Value	References
	International		
IARC	Carcinogenic classification	Group 1[a]	IARC 1982
Regulations			
a. Air			
	National		
OSHA	Cancer-suspect agent; Specific regulations	Stringent work-place controls, record keeping and medical surveillance	OSHA 1974 29CFR 1910.1008
b. Non-specific media			
EPA OERR	Reportable quantity	1 lb	40 CFR 302.4 EPA 1985
	Reportable quantity (proposed)	10 lb	EPA 1987b
	Extremely Hazardous Substances Threshold Planning Quantity	100 lb	40 CFR 355 EPA 1987c
EPA OSW	Hazardous Waste Constituent (Appendix VIII, chloroalkyl ethers, N.O.S.)	NA[b]	40 CFR 261 EPA 1980b
Guidelines			
a. Air			
ACGIH	Threshold limit value (TLV) TWA Recognized Human Carcinogen	0.005 mg/m^3 (0.001 ppm)	ACGIH 1986
NIOSH	Recommended Exposure Limit for Occupational Exposure	Potential human carcinogen- Use 29 CFR 1910.1008	NIOSH 1986
b. Other			
EPA	Cancer weight-of-evidence Cancer potency factor[c] 10^{-6} risk level	Group A[a] 220 (mg/kg/d)$^{-1}$ 1.6 x 10^{-8} mg/m^3	EPA 1988
	State Regulations and Guidelines		
State Environmental Agencies	Drinking Water Standards and Guidelines		FSTRAC 1988
	Kansas	2.8 x 10^{-6} µg/L	

[a] Known human carcinogen, based on sufficient evidence from studies in humans and supported by studies in animals.
[b] Not applicable.
[c] The cancer potency factor (q_1*) is the estimated slope of the cancer dose response curve at very low doses.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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 (K_d) -- The amount of a chemical adsorbed by a 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.

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 time period.

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

Carcinogen -- A chemical capable of inducing cancer.

Ceiling value (CL) -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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.

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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 insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance 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) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

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

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration$_{(L0)}$ (LC $_{LO}$) -- The lowest concentration of a chemical in air which 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(L0) (LD $_{LO}$) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

9.GLOSSARY

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

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

LT50 (lethal time) -- 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.

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

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but 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.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-h shift.

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q_1^* -- The upper-bound estimate of the low-dose slope of the doseresponse
curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. 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.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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.

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TD50 (toxic dose) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

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

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for BCME. The panel consisted of the following members: Dr. Douglas Arnold, Toxicologist, Banting Research Center, Health and Welfare, Canada; Dr. James Bruckner, Director, Toxicology Programs, Department of Pharmacology and Toxicology, University of Georgia; Dr. Chon Shoaf, Research Associate, Duke University Medical Center; Dr. Dietrich Hoffman, Associate Director, American Health Foundation, Valhalla, NY; and Dr. Benjamin Van Duuren, Professor of Environmental Medicine, New York University Medical Center. These experts collectively have knowledge of BCME's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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