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.

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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.

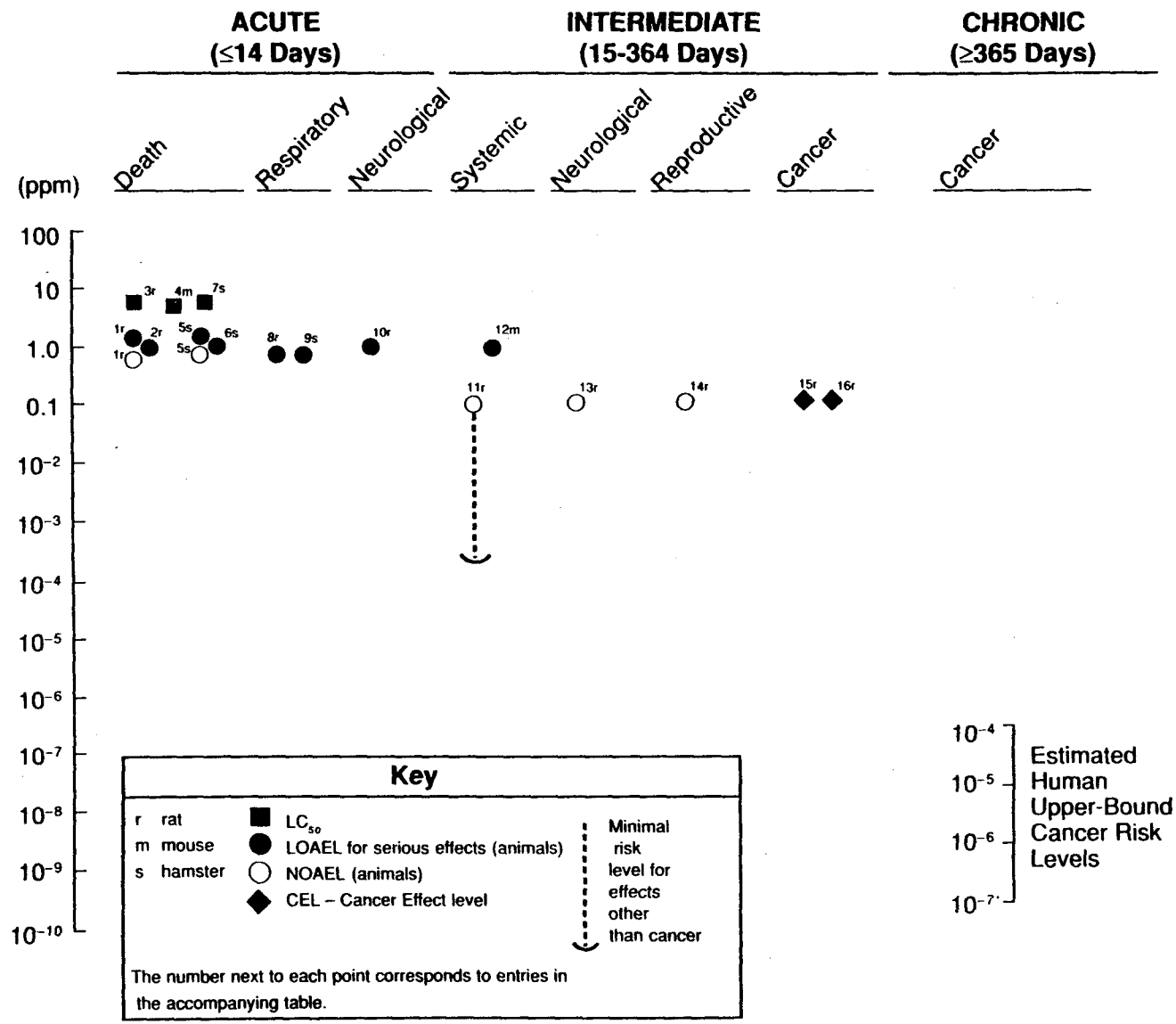

FIGURE 2-1. Levels of Significant Exposure to BCME – Inhalation

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	1/100 (1%)	Lung carcinoma	Kuschner et al. 1975
		6 hr/day, 5 day/wk			
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.

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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

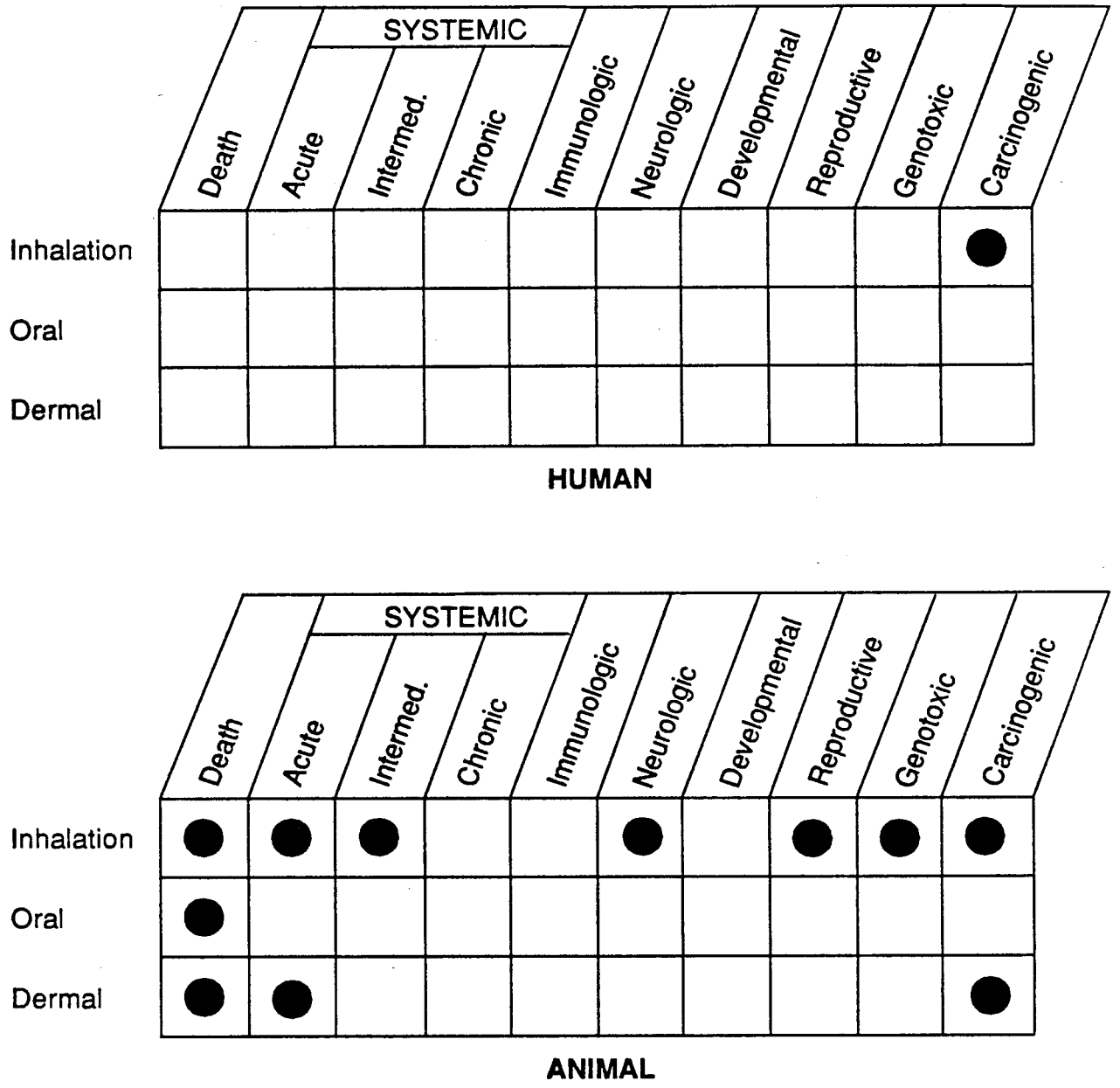

FIGURE 2- 2. Existing Information on Health Effects of BCME

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.