TOXICOLOGICAL PROFILE FOR BROMODICHLOROMETHANE

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

In collaboration with:

U.S. Environmental Protection Agency (EPA)

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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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Acting Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS BROMODICHLOROMETHANE?

Bromodichloromethane (BDCM) is a colorless, heavy, nonburnable liquid. BDCM does not usually exist as a liquid in the environment. Rather, it usually is found evaporated in air or dissolved in water.

Most BDCM in the environment is formed as a by-product when chlorine is added to drinking water to kill disease-causing organisms. Small amounts of BDCM are also made in chemical plants for use in laboratories or in making other chemicals. A very small amount (less than 1% of the amount coming from human activities) is formed by algae in the ocean.

BDCM evaporates quite easily, so most BDCM that escapes into the environment from chemical facilities, waste sites, or drinking water enters the atmosphere as a gas. BDCM is slowly broken down (about 90% in a year) by chemical reactions in the air. Any BDCM that remains in water or soil may also be broken down slowly by bacteria.

Further information on the properties and uses of BDCM, and how it behaves in the environment, may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO BROMODICHLOROMETHANE?

For most people, the most likely means of exposure to BDCM is by drinking chlorinated water. Usually the levels in drinking water are between 1 and 10 ppb (parts per billion). BDCM is also found in some foods and beverages such as ice cream or soft-drinks that are made using chlorinated water, but this is probably not a major source of exposure. BDCM has been found in chlorinated swimming pools, where exposure might occur by breathing the vapors or through the skin. Exposure to BDCM might also occur by breathing BDCM in the air in or near a laboratory or factory that made or used BDCM. However, BDCM is not widely used in this country, so this is not likely for most people. Average levels of BDCM in air are usually quite low (less than 0.2 ppb). Another place where human exposure might occur is near a waste site where BDCM has been allowed to leak into water or soil. In this situation, people could be exposed by drinking the water or by getting the soil on their skin. BDCM has been found in water and soil at some waste sites (about 1% to 10% of those tested), usually at levels of 1 to 50 ppb. Further information on how people might be exposed to BDCM is given in Chapter 5.

1. PUBLIC HEALTH STATEMENT

1.3 HOW CAN BROMODICHLOROMETHANE ENTER AND LEAVE MY BODY?

Studies in animals show that almost all BDCM swallowed in water or food will enter the body by moving from the stomach or intestines into the blood. It is likely that BDCM would also move from the lungs into the blood if it were breathed in and would cross the skin if skin contact occurred, but this has not been studied. Bromodichloromethane leaves the body mostly by being breathed out through the lungs. Smaller amounts leave in the urine and feces. BDCM removal is fairly rapid and complete (about 95% in 8 hours), so it does not usually build up in the body. Further information on how BDCM enters and leaves the body is given in Chapter 2.

1.4 HOW CAN BROMODICHLOROMETHANE AFFECT MY HEALTH?

The effects of BDCM depend on how much is taken into the body. In animals, the main effect of eating or drinking large amounts of BDCM is injury to the liver and kidneys, These effects can occur within a short time after exposure. High levels can also cause effects on the brain, leading to incoordination and sleepiness. There is some evidence that BDCM can be toxic to developing fetuses, but this has not been well-studied. Studies in animals show that intake of BDCM for several years in food or water can lead to cancer of the liver, kidney and intestines. Although effects of BDCM have not been reported in humans, effects would probably occur if enough BDCM were taken into the body. Further information on how BDCM can affect the health of humans and animals is presented in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO BROMODICHLOROMETHANE?

Methods are available to measure low levels of BDCM in human blood, breath, urine and fat, but not enough information is available to use such tests to predict if any health effects might result. Because special equipment is needed, these tests are not usually done in doctors' offices. Because BDCM leaves the body fairly quickly, these methods are best suited to detecting recent exposures. Further information on how BDCM can be measured in exposed humans is presented in Chapter 6.

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

Tables l-l through l-4 show the relationship between exposure to BDCM and known health effects. Minimal Risk Levels (MRLs) are also included in Table 1-3. These MRLs were derived from animal data for both short-term and longer-term exposure, as described in Chapter 2 and in Table 2-l. These MRLs provide a basis for comparison with levels that people might encounter either in food or drinking water. If a person is exposed to BDCM at an amount below the MRL, it is not expected that harmful noncancer health effects will occur. Because these levels are based only on information currently available, some uncertainty is always associated with them. 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. Further information on the levels of BDCM that have been observed to cause health effects in animals is presented in Chapter 2.

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

The U.S. Environmental Protection Agency (EPA) has set a Maximum Contaminant Level in drinking water of 0.10 ppm (parts per million) for the combination of BDCM and a group of similar compounds (trihalomethanes). Most water samples in the U.S. have BDCM levels lower than this. The Food and Drug Administration (FDA) has set the same limit for bottled water, but no tolerance limits have been set for BDCM in food. Because it has such limited use in industry, there is no Occupational Safety and Health Administration standard for BDCM. Further information on regulations concerning BDCM is presented 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

1. PUBLIC HEALTH STATEMENT

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

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 BDCM are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term human exposure to air containing specific levels of BDCM are not known.

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

TABLE 1-2. Animal Health Effects from Breathing BDCM

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 animal exposure to air containing specific levels of BDCM are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term animal exposure to air containing specific levels of BDCM are not known.

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

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
1.3		Estimated Minimal Risk Level (based on studies in animals; see Section 1.6 for discussion)
Levels in Water (ppm)		The health effects resulting from short-term human exposure to water containing specific levels of BDCM are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
0.6		Estimated Minimal Risk Level (based on studies in animals; see Section 1.6 for discussion)
Levels in Water (ppm)		The health effects resulting from long-term human exposure to water containing specific levels of BDCM are not known.

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

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

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
280	14 days	Liver injury in mice.
570	14 days	Kidney injury in mice.
1,000	10 days	Impaired fetal development in rats.
1,200	14 days	Death in mice.
Levels in Water (ppm)		The health effects resulting from short-term animal exposure to water containing specific levels of BDCM are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
190	2 years	Kidney injury in mice.
380	2 years	Liver injury in mice.
Levels in Water (ppm)		The health effects resulting from long-term animal exposure to water containing specific levels of BDCM are not known.

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

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 BDCM. Its purpose is to present levels of significant exposure for BDCM 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 BDCM 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 (MRLs) 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 1980d), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or experimental animals following inhalation exposure to BDCM:

2.2.1.1 Death

2.2.1.2 Systemic Effects

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

2. HEALTH EFFECTS

2.2.2 Oral Exposure

No studies were located regarding health effects in humans associated with ingestion of BDCM. Figure 2-l and Table 2-l summarize the health effects observed in experimental animals following oral exposure to BDCM. These effects are discussed below.

2.2.2.1 Death

Most estimates of acute oral LD_{50} values for BDCM in rodents range between 400 and 1000 mg/kg (Aida et al. 1987; Chu et al. 1980; Bowman at al. 1978). Typical pathological changes observed in acutely poisoned animals include fatty infiltration of liver and hemorrhagic lesions in kidney, adrenals, lung and brain (Bowman et al. 1978). In a 14-day repeated-dose study in mice, all animals dosed with 150 mg/kg/day died (NTP 1987). This dose has been converted to an equivalent concentration of 1,200 ppm in food for presentation in Table l-4. Males appear to be slightly more susceptible to the lethal effects of BDCM than females, both in rats (Aida et al. 1987; Chu et al. 1980, 1982a; NTP 1987), and in mice (Bowman et al. 1978; NTP 1987).

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

2.2.2.2 Systemic Effects

No studies were located regarding effects on the respiratory, cardiovascular, gastrointestinal, musculoskeletal, or dermal systems in humans or animals following oral exposure to BDCM.

Hematological Effects. Hemoglobin and hematocrit were significantly reduced in male rats following a single dose of 390 mg/kg of BDCM (Chu et al. 1982a). The basis of this effect was not investigated. Exposure in drinking water for 90 days to a dose of 213 mg/kg/day caused no effect on lymphocyte levels in either males or females (Chu et al. 1982b). A slight reduction in lymphocyte count was noted in females 90 days after exposure ceased, which the authors felt might be related to endogenous release of steroids. Rats fed BDCM in their diets at intake levels of 130 mg/kg/day for 24 months exhibited no hematological changes compared to controls (Tobe et al. 1982).

2. HEALTH EFFECTS

TABLE 2-1. Levels of Significant Exposure to BDCM - Oral

Graph Key	Species (Route)[a]	Exposure Duration/ Frequency	Syst. Effect	NOAEL mg/kg/day	LOAEL (Effect) Less Serious mg/kg/day	LOAEL (Effect) Serious mg/kg/day	Reference
ACUTE EXPOSURE							
Death							
1	rat (G)	1 dose				430 LD50M 510 LD50F	Aida et al. 1987
2	rat (G)	1 dose		390		916 LD50M 969 LD50F	Chu et al. 1980
3	mouse (G)	14 d		75		150 100% died	NTP 1987
4	mouse (G)	1 dose		300		600	NTP 1987
5	mouse (G)	1 dose				450 LD50M 900 LD50F	Bowman et al. 1978
Systemic							
6	rat (G)	10 d	Hepatic		50 liver wt.		Ruddick et al. 1983
7	rat (G)	14 d	Renal		600 reddened medullae		NTP 1987
8	rat (G)	1 dose	Hepatic	300	1250 pale color		NTP 1987
9	rat (G)	1 dose	Renal	390			Chu et al. 1982a
10	rat (G)	1 dose	Hemato		390 decreased hematocrit		Chu et al. 1982a
11	rat (G)	1 dose	Hepatic	396	495 GPT	990 GPT	Hewitt et al. 1983
12	mouse (G)	14 d	Renal	75	150 reddened medullae		NTP 1987
13	mouse (G)	14 d	Renal		250 BUN		Munson et al. 1982
14	mouse (G)	14 d	Hepatic		125 fibrinogen		Munson et al. 1982
15	mouse (G)	14 d	Hepatic		37[b] microscopic lesions		Condie et al. 1983
16	mouse (G)	14 d	Renal		74 PAH inhib.	148 microscopic lesions	Condie et al. 1983

2. HEALTH EFFECTS

TABLE 2-1. - continued

Graph Key	Species (Route)		Exposure Duration/ Frequency[a]	Syst. Effect	NOAEL mg/kg/day	LOAEL (Effect) Less Serious mg/kg/day	LOAEL (Effect) Serious mg/kg/day	Reference
17	mouse	(G)	14 d	Hepatic		125 liver wt. inc.		Munson et al. 1982
18	mouse	(G)	14 d	Renal	300			NTP 1987
Neurological								
19	rat	(G)	1 dose				1500 ataxia	Chu et al. 1980
20	rat	(G)	14 d			600 hyperactive		NTP 1987
21	mouse	(G)	1 dose			273 coordination		Balster and Borzelleca 1982
22	mouse	(G)	1 dose			600 lethargy		NTP 1987
23	mouse	(G)	14 d		11.6			Balster and Borzelleca 1982
Developmental								
24	rat	(G)	10 d d. 6-10 of gest.				50 fetotox.	Ruddick et al. 1983
INTERMEDIATE EXPOSURE								
Death								
25	rat	(W)	28 d		120			Chu et al. 1982a
26	mouse	(G)	13 wk 5d/wk		100			NTP 1987
Systemic								
27	rat	(W)	28 d	Renal	120			Chu et al. 1982a
28	rat	(W)	90 d	Hepatic		7 lesions		Chu et al. 1982b
29	rat	(W)	28 d	Hepatic	120			Chu et al. 1982a
30	rat	(G)	13 wk 5d/wk	Hepatic	150		300 lesions	NTP 1987
31	rat	(W)	28 d	Hemato	120			Chu et al. 1982a
32	rat	(W)	90 d	Hemato	213			Chu et al. 1982b
33	rat	(G)	13 wk 5d/wk	Renal	150		300 lesions	NTP 1987

2. HEALTH EFFECTS

TABLE 2-1. - continued

Graph Key	Species (Route)	Exposure Duration/ Frequency[a]	Syst. Effect	NOAEL mg/kg/day	LOAEL (Effect) Less Serious mg/kg/day	LOAEL (Effect) Serious mg/kg/day	Reference
34	mouse (G)	13 wk 5d/wk	Hepatic	100		200 lesions	NTP 1987
35	mouse (G)	13 wk 5d/wk	Hepatic	100			NTP 1987
36	mouse (G)	13 wk 5d/wk	Renal	50		100 focal necrosis	NTP 1987
CHRONIC EXPOSURE							
Neurological							
37	mouse (G)	30 d		100			Balster and Borzelleca 1982
38	mouse (G)	90 d		11.6			Balster and Borzelleca 1982
39	mouse (G)	60 d			100 operant behavior		Balster and Borzelleca 1982
Death							
40	rat (G)	104 wk 5d/wk		100			NTP 1987
41	mouse (G)	104 wk 5d/wk		50			NTP 1987
Systemic							
42	rat (G)	104 wk 5d/wk	Hepatic		50 fatty degen.	100 lesions	NTP 1987
43	rat (F)	24 mo	Renal	220			Tobe et al. 1982
44	rat (F)	24 mo	Hemato	220			Tobe et al. 1982
45	rat (G)	104 wk 5d/wk	Renal		50 cytomegaly		NTP 1987
46	rat (F)	24 mo	Hepatic	41	220 GPT		Tobe et al. 1982
47	mouse (G)	104 wk 5d/wk	Renal		25[c] cytomegaly		NTP 1987
48	mouse (G)	104 wk 5d/wk	Renal	150			NTP 1987
49	mouse (G)	104 wk 5d/wk	Hepatic		50 fatty degn.		NTP 1987

2. HEALTH EFFECTS

TABLE 2-1. - continued

Graph Key	Species	(Route)[a]	Exposure Duration/ Frequency	Syst. Effect	NOAEL mg/kg/day	LOAEL (Effect) Less Serious mg/kg/day	LOAEL (Effect) Serious mg/kg/day	Reference
Cancer								
50	rat	(W)	180 wk 7d/wk				150 CEL (liver tumors)	Tumasonis et al. 1985
51	rat	(G)	104 wk 5d/wk				50 CEL (intestinal carcinoma)	NTP 1987
52	mouse	(G)	104 wk 5d/wk				50 CEL (renal carcinoma)	NTP 1987
53	mouse	(G)	104 wk 5d/wk				75 CEL (liver tumors)	NTP 1987

[a]G = Gavage; W = Drinking Water, F = Feed.
[b]Used to derive acute oral MRL: dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive chronic oral MRL: dose adjusted for intermittent exposure and divided by uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.018 mg/kg/day. This MRL has been converted to an equivalent concentration in food (0.6 ppm) for presentation in Table 1-3.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg/kg/day = milligram/kilogram/day; (G) = gavage; LD50 = lethal dose, 50% mortality; d = day; wt. = weight; hemato = hematological; GPT = glutamate-pyruvate transaminase; BUN = blood urea nitrogen; PAH = para-amino hippuric acid; inhib. = inhibition; inc. = increased; fetotox = fetotoxicity; gest = gestation; (W) = drinking water; wk = week; degen = degeneration; (F) = food; mo = month; CEL = cancer effect level.

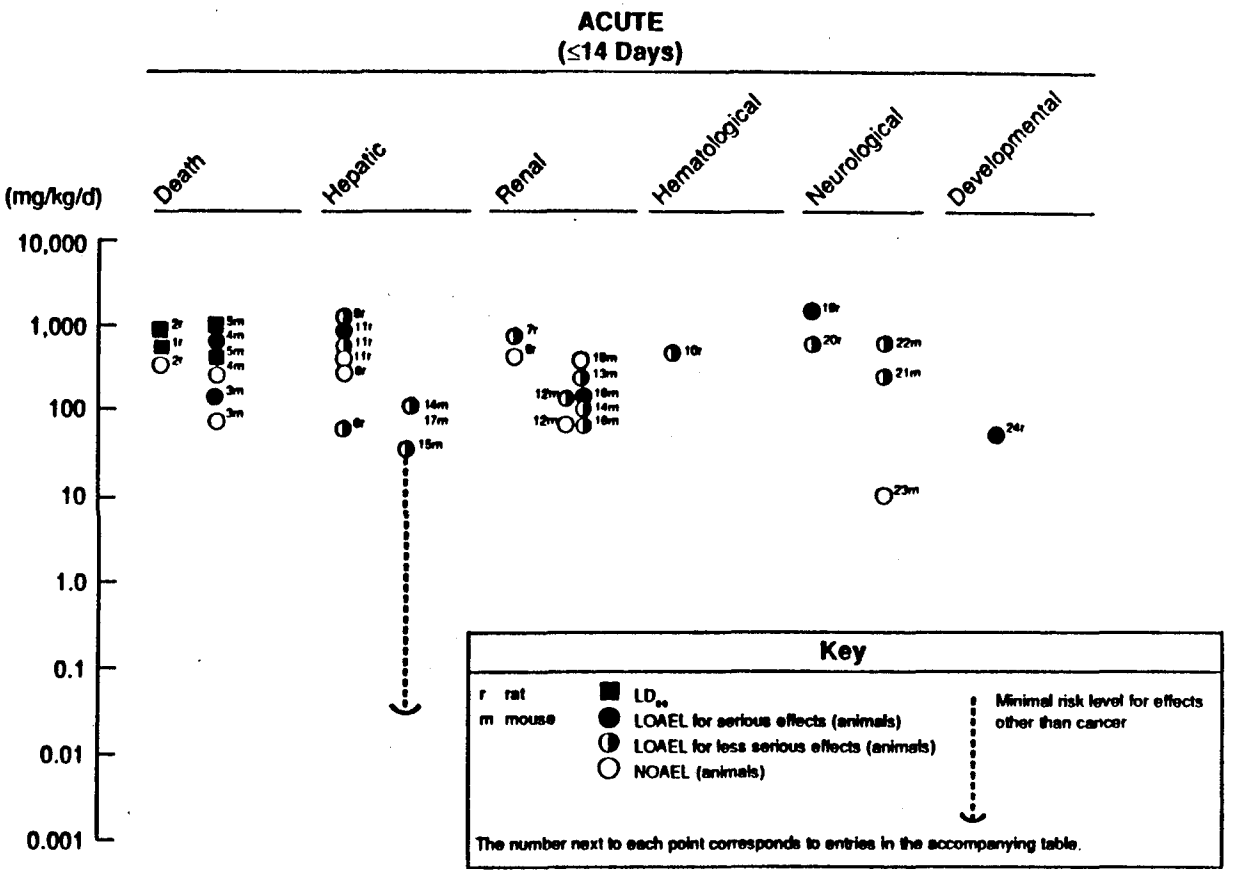


FIGURE 2-1. Levels of Significant Exposure to BDCM – Oral

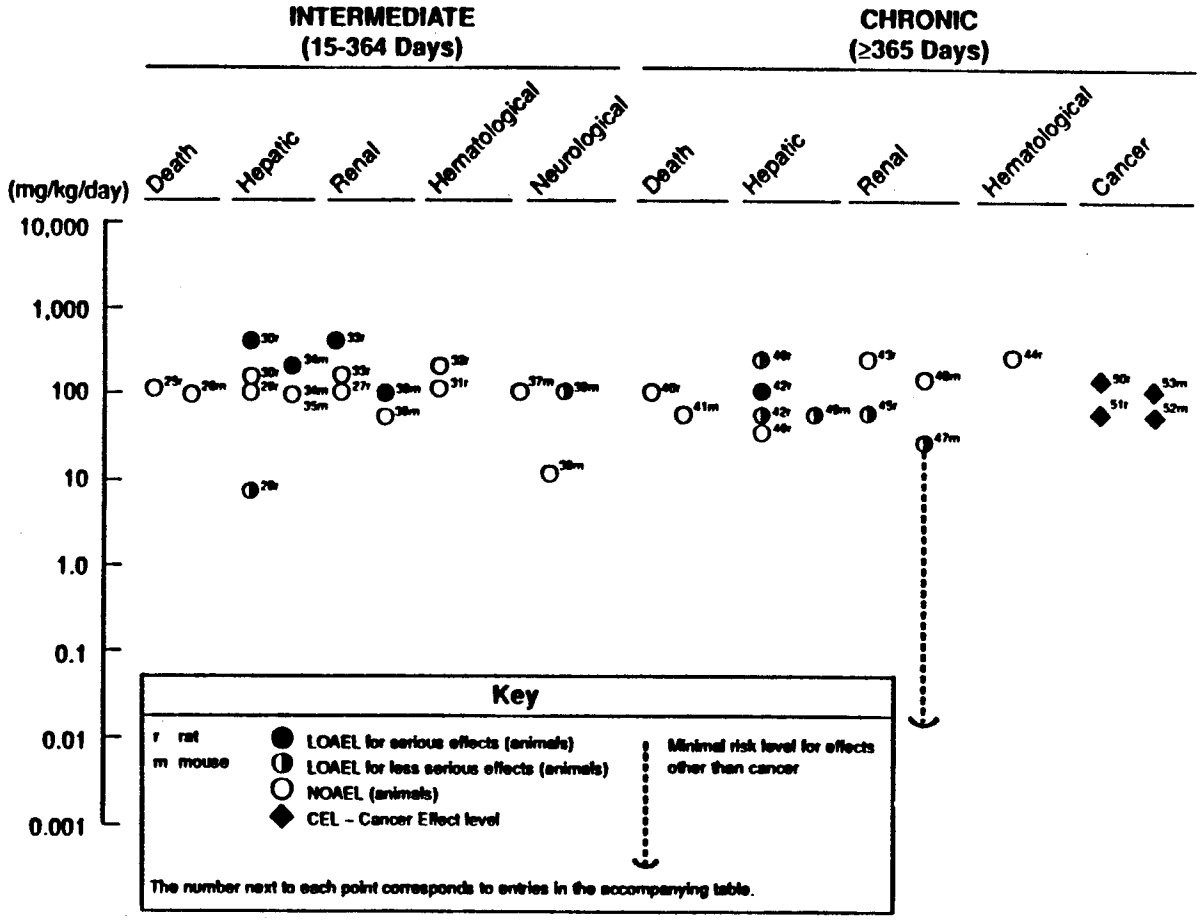


FIGURE 2-1. (con't)

2. HEALTH EFFECTS

Hepatic Effects. A number of studies in animals indicate that the liver is susceptible to injury by BDCM. Typical signs include increased liver weight, pale discoloration, increased levels of hepatic tissue enzymes in serum, decreased levels of secreted hepatic proteins (fibrinogen) in blood, and focal areas of inflammation or degeneration. In acute (single dose) studies, these effects have been noted at doses of around 1,250 mg/kg or higher (NTP 1987). It should be noted that this dose level causes death within two weeks (NTP 1987).

In subchronic studies (10 to 14 days) in mice and rats, mild effects on liver have been noted at doses as low as 37 mg/kg/day (Condie et al. 1983) and 50 mg/kg/day (Ruddick et al. 1983). Effects included slightly increased liver weights (Ruddick et al. 1983) and microscopic changes that were rated as "minimal" (Condie et al. 1983). The effects become more pronounced at doses of 125 to 300 mg/kg/day (Condie et al. 1983; Munson et al. 1982). The dose of 37 mg/kg/day has been converted to an equivalent concentration of 280 ppm in food for presentation in Table 1-4.

Although hepatic effects at doses of 40 to 50 mg/kg/day are minimal, it appears that this is the approximate threshold for the appearance of more marked effects at higher doses, so the dose of 37 mg/kg/day (Condie et al. 1983) has been used to derive the acute MRL for BDCM. Based on this value, an acute oral MRL of 0.037 mg/kg/day was calculated, as described in the footnote in Table 2-1. This MRL has been converted to an equivalent concentration in food (1.3 ppm) for presentation in Table 1-3.

Most longer-term studies report signs of liver injury in rats or mice at doses of 50 to 200 mg/kg/day (Dunnick et al. 1987; NTP 1987; Tobe et al. 1982). These doses are not significantly different from those observed to cause hepatic injury in acute and short-term studies, suggesting that there is a relatively low tendency toward cumulative injury to liver.

An exception is the study of Chu et al. (1982b), where statistically significant effects on liver were noted in rats exposed to doses as low as 7 mg/kg/day for 90 days. However, these effects were minimal (the authors assigned a severity score of 2 on a scale of 1 to 10) and showed essentially no dose-response tendency. Because this observation is of uncertain significance and is inconsistent with NOAEL

estimates from other intermediate and chronic studies, it has not been selected for calculation of a longer-term MRL. The chronic dose level of 50 mg/kg/day (NTP 1987) has been converted to an equivalent concentration of 380 ppm in food for presentation in Table l-4.

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

Renal Effects. Studies in animals reveal that the kidney is also susceptible to injury by BDCM, typically at dose levels similar to those that effect the liver. For example, in 14-day studies, Munson et al. (1982) observed increases in blood urea nitrogen (BUN) in mice dosed with 250 mg/kg/day, and Condie et al. (1983) reported decreased uptake of p-aminohippurate (PAH) into kidney slices from mice dosed with 74 to 148 mg/kg/day. Similarly, Ruddick et al. (1983)observed increased renal weight in rats dosed with 200 mg/kg/day for 10 days. The dose of 74 mg/kg/day has been converted to an equivalent concentration of 570 ppm in food for presentation in Table l-4.

In longer-term studies, areas of focal necrosis were observed in the proximal tubular epithelium in male mice exposed for 13 weeks to doses of 100 mg/kg/day, and cytomegaly was noted following chronic exposure to 25 mg/kg/day (Dunnick et al. 1987; NTP 1987). Female mice were somewhat less susceptible than males. In rats, cytomegaly and nephrosis were observed in both males and females at chronic exposure levels of 50 to 100 mg/kg/day (NTP 1987). The dose of 25 mg/kg/day has been converted to an equivalent concentration of 190 ppm in food for presentation in Table l-4. This dose has also been selected as the most appropriate value for calculation of the chronic MRL for BDCM. Based on this value, a chronic oral MRL of 0.018 mg/kg/day was calculated, as described in the footnote in Table 2-l. This MRL has been converted to an equivalent concentration in food (0.6 ppm) for presentation in Table l-3.

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

2.2.2.3 Immunological Effects

The effects of BDCM on the immune system have not been thoroughly studied. Munson et al. (1982) administered BDCM to mice for 14 days, and observed a decrease in female mice in the number of antibody forming

cells in spleen and a decrease in the hemagglutination titer at doses of 125 to 250 mg/kg/day. The authors felt that the humoral immune system may have potential to serve as an early indicator of halomethane toxicity.

2.2.2.4 Neurological Effects

No studies were located regarding histological or electrophysiological effects of BDCM on the nervous system. Rats and mice administered oral doses of 150 to 600 mg/kg often display acute signs of CNS depression, including lethargy, labored breathing, sedation and flaccid muscle tone (NTP 1987; Aida et al. 1987; Balster and Borzelleca 1982; Chu et al. 1980). These effects tend to reverse after a period of several hours.

To determine whether BDCM exposure resulted in any longer-lasting . changes in behavior, Balster and Borzelleca (1982) performed a series of tests in mice 24 hours or more after the last of a series of doses of BDCM. Exposure to doses of 1.2 to 11.6 mg/kg/day for 14 to 90 days had no effect on tests of coordination, strength, endurance or exploratory activity, and 90 days exposure to 100 mg/kg/day did not effect passiveavoidance
learning. Exposure to 100 or 400 mg/kg/day for go-days did result in an acute effect on operant behavior (decreased pressing of a lever that presented food), but this change tended to diminish over the exposure period, suggesting there was no progressive effect and that partial tolerance developed.

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

2.2.2.5 Developmental Effects

Ruddick et al. (1983) reported an increased incidence of sternebral anomalies in fetuses from rats that had been exposed to BDCM at doses of 50 to 200 mg/kg/day on days 6 to 15 of gestation (the critical period for organogenesis). No other dose-related visceral or skeletal anomalies were observed. The authors interpreted the sternebral anomalies to be evidence of a fetotoxic (rather than a teratogenic) effect. These doses also resulted in significant maternal toxicity, as evidenced by a 40% reduction in body weight gain. The dose of 50 mg/kg/day has been converted to an equivalent concentration of 1,000 ppm in food for presentation in Table l-4.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following oral exposure to BDCM.

2.2.2.7 Genotoxic Effects

An increased frequency of sister chromatic exchange (SCE) in mice exposed to BDCM was reported by Morimoto and Koizumi (1983). Statistically significant increases in SCEs in bone marrow cells were observed in animals dosed with 50 or 100 mg/kg/day for 4 days. Mice given the highest dose tested, 200 mg/kg/day for 4 days, died and could not be evaluated for SCEs in bone marrow cells.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following chronic oral exposure to BDCM per se. There are several epidemiological studies that indicate there may be an association between ingestion of chlorinated drinking water (which typically contains BDCM) and increased risk of cancer in humans (Gottlieb et al. 1981; Kanarek and Young 1982; Marienfeld et al. 1986), but such studies cannot provide information on whether any effects observed are due to BDCM or to one or more of the hundreds of other byproducts that are also present in chlorinated water.

However, chronic oral studies in animals provide convincing evidence that BDCM is carcinogenic. In rats, increased frequency of liver tumors was observed in females exposed to 150 mg/kg/day for 180 weeks (Tumasonis et al. 1985), and kidney tumors were observed in both males and females exposed to 100 mg/kg/day (NTP 1987; Dunnick et al. 1987). Incidences of renal tumors were 13/50 and 15/50 in males and females, respectively. Tumors of the large intestine were also observed in rats, at incidences of 13/50 and 45/50 in males exposed to 50 and 100 mg/kg/day, and at an incidence of 12/47 in females dosed at 100 mg/kg/day. In mice, renal tumors were observed in males dosed with 50 mg/kg/day, and hepatic tumors were observed in females dosed with 75 or 150 mg/kg/day. Increased intestinal tumors were not observed in mice (Dunnick et al. 1987; NTP 1987).

2.2.3 Dermal Exposure

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

2. HEALTH EFFECTS

2.2.3.1 Death

2.2.3.2 Systemic Effects

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 RELEVANCE TO PUBLIC HEALTH

Oral exposure studies in animals identify the central nervous system, the liver, the kidney and the intestine as the principal target tissues of BDCM. Effects on the central nervous system (lethargy, sedation) are observed mostly following large doses, and are likely the result of a direct narcotic or anaesthetic effect similar to other related chemicals (e.g., chloroform, carbon tetrachloride).

Effects on the liver and kidney include increased organ weight, focal areas of inflammation or degeneration, and decreased function. These effects tend to appear in both tissues at roughly similar doses, usually between 25 and 100 mg/kg/day. This indicates that both tissues are approximately equally susceptible to BDCM. The doses which lead to renal and hepatic injury following intermediate or chronic exposure are generally similar to those causing acute effects (e.g., see Figure 2-l), suggesting that there is a relatively low tendency toward cumulative injury for these noncarcinogenic endpoints. This is probably because both the liver and the kidney are able to repair damaged cells or replace dead cells within a short period after exposure.

BDCM exposure has also been observed to result in developmental toxicity (Ruddick et al. 1983). However, data are available only for doses that cause significant maternal toxicity, so it is not possible to judge whether-developmental effects are likely to occur in animals or humans exposed at lower dose levels.

2. HEALTH EFFECTS

The greatest reason for concern with BDCM exposure is evidence from animal studies that BDCM is carcinogenic. Compared with other trihalomethanes (THMs), BDCM causes the widest spectrum of neoplasms in rats and mice, and is the only THM observed to cause intestinal tumors (Dunnick et al. 1987). In addition, BDCM has been found to be mutagenic in some (but not all) *in vitro* gene mutation and sister chromatid exchange assays (summarized in Table 2-2). BDCM has also been reported to cause increased sister chromatid exchange in bone marrow cells of mice exposed *in vivo* (Morimoto and Koizumi 1983). These positive carcinogenicity and genotoxicity studies indicate that exposure to BDCM in chlorinated water or near waste sites might contribute to increased risk of cancer in humans.

Several studies indicate that there are differences in susceptibility to BDCM between species and between sexes. With regard to lethality, for example, male mice are more susceptible than female mice, and both male and female mice are more susceptible than rats. Male mice are also more susceptible to the renal effects of BDCM than females, while in rats, males respond to BDCM with renal cytomegaly and females develop nephrosis. Intestinal tumors are observed in both male and female rats, but not in mice. The basis of these differences is not known, but may possibly be attributed to differences in disposition and metabolism of BDCM between sexes and species. That significant differences exist have been demonstrated by Mink et al, (1986) and Smith et al. (1985), as discussed below in Section 2.6.

Because of the differences in dose susceptibility and tissue specificity observed between sexes and species in animal studies, it is difficult to extrapolate the observations in animals to humans. Until an improved understanding of the mechanistic or toxicokinetic basis of these variables is achieved, it is prudent to assume that the same effects observed in animals will be observed in humans ingesting comparable dose levels.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

BDCM was not detected in samples of human fat studied in the National Human Adipose Tissue Survey (NHATS) (EPA 1986c), and was not detected in the blood of 250 patients studied by Antoine et al. (1986).

TABLE 2-2. Genotoxicity of BDCM

End Point	Species/ Test System	Result	Reference
Gene Mutation	Salmonella (4 strains)	Negative, with and without activation	NTP 1987
Gene Mutation	Saccharomyces XVI85-14C reversion	Negative, with activation; weakly positive, without activation	Nestmann and Lee 1985
Gene Mutation	Saccharomyces D7 gene conversion	Negative, with activation; weakly positive, without activation	Nestmann and Lee 1985
Gene Mutation	Mouse lymphoma	Positive, with activation; negative, without activation	NTP 1987
Chromosomal aberrations	Chinese Hamster ovary (CHO) cells	Negative, with and without activation	NTP 1987
Sister Chromatid Exchange	CHO cells	Negative, with and without activation	NTP 1987
Sister Chromatid Exchange	Human lymphocytes	Delayed cell turnover; moderate activity	Morimoto and Koizumi 1983
Sister Chromatid Exchange	Human lymphoid cells	Elevation in frequency of SCE's	Sobti 1984
Sister Chromatid Exchange	Rat liver cells	Increased 50% above control	Sobti 1984

2. HEALTH EFFECTS

A BDCM concentration of 14 ng/ml was found in a blood sample from one resident living near a waste site in New York (Barkley et al. 1980), but the significance of this isolated observation is difficult to judge. No other studies were located regarding levels of BDCM in human tissues and fluids.

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

No studies were located regarding the relationship between environmental levels of BDCM and levels of BDCM in human tissues or fluids or the occurrence of any adverse health effects. Epidemiological studies which indicate there may be an association between consumption of chlorinated water (which contains BDCM) and increased risk of cancer are consistent with, but do not establish, the hypothesis that BDCM increases cancer risk in humans, since chlorinated water contains hundreds'of other chemicals as well.

2.6 TOXICOKINETICS

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

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

No studies were located regarding absorption following inhalation exposure to BDCM. By analogy with other similar chemicals, it seems likely that BDCM would be well absorbed across the lung in both humans and animals.

2.6.1.2 Oral Exposure

Female monkeys, dosed with radioactive BDCM by gavage, excreted 2% of the administered radioactivity in feces, indicating that gastrointestinal'absorption was essentially complete (Smith et al. 1985). In mice, absorption was also rapid and extensive (Mink et al. 1986). Within eight hours of administration, 90% of the administered radioactivity was excreted in urine or expired air, indicating that

absorption was at least 90% complete. In rats, BDCM was not absorbed as readily as in mice and monkeys with only about 60% of the orally administered dose appearing in the expired air and urine (Mink et al. 1986).

2.6.1.3 Dermal Exposure

No studies were located regarding absorption following dermal exposure to BDCM. By analogy with other similar chemicals, it seems likely that BDCM will be absorbed across the skin.

2.6.2 Distribution

2.6.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to BDCM.

2.6.2.2 Oral Exposure

When BDCM was administered to rats by gavage, the compound was slow to leave the stomach (Smith et al. 1985). Three hours after administration, 21.5% of the dose was still in the stomach. Fat, muscle, and liver each contained from 1.8 to 2.8% of the dose, with lower levels in other tissues.

2.6.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to BDCM.

2.6.3 Metabolism

Pathways of BDCM metabolism have not been characterized. Studies in mice indicate that carbon dioxide is a major endproduct in that species, accounting for 81% of the administered dose (Mink et al. 1986). In rats, only 14% of the administered dose was expired as carbon dioxide, and 42% as the parent compound (Mink et al. 1986). As discussed previously, toxicology studies in rats and mice showed that BDCM was more toxic to mice than to rats, and it is possible that these toxicokinetic differences in metabolism may contribute to these differences.

2. HEALTH EFFECTS

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals following inhalation exposure to BDCM.

2.6.4.2 Oral Exposure

The major route of excretion of BDCM in rats, mice, and monkeys is expiration through the lung, either as parent BDCM, or as volatile metabolites such as CO_2 (Mink et al. 1986; Smith et al, 1977; Smith et al. 1985). Excretion via the urine accounts for only a minor fraction of the administered dose (1.4% in rats, 2.2% in mice, and 2% to 6% in monkeys) (Mink et al. 1986; Smith et al. 1985).

Fecal excretion in monkeys accounted for less than 2% of the administered dose 72 hours after dosing (Smith et al. 1985). In rats, Smith et al. (1985) found no detectable amounts of radiolabelled BDCM or metabolites in the feces, but the feces were evaluated only up to 6 hours after administration of BDCM. The shortness of the time interval does not give an accurate assessment of the feces as a route of excretion for BDCM, since 37% of the administered dose in the rats was accounted for in the gastrointestinal tract. No data were available on fecal excretion in mice.

The half-life of BDCM in rats and mice was estimated to be 1.5 and 2 hours, respectively (Mink et al. 1986), and the half-life in monkeys was 4 to 6 hours (Smith et al. 1977). This indicates that BDCM is effectively excreted and that tissue accumulation of BDCM is unlikely.

2.6.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to BDCM.

2.7 INTERACTIONS WITH OTHER CHEMICALS

Hewitt et al. (1983) reported that pretreatment of rats with an oral dose of acetone dramatically increased the hepatic and renal toxicity of an oral dose of BDCM given 18 hours later. This is very similar to the well-documented potentiation of CCl_4 by a variety of alcohols, ketones and other chemicals, suggesting that BDCM and CCl_4 may

exert their toxicity through common mechanisms. Because of the widespread use of alcohols and ketones in industry and in consumer products, this sort of potentiation could be quite important.

A study in rats by Wester et al. (1985) evaluated the effects of ingestion of a mixture of 11 halogenated hydrocarbon contaminants of drinking water, including BDCM. No effects were observed after 25 months of exposure, but the doses employed were so low (0.003 to 0.28 mg/kg/day for BDCM) that this observation does not constitute strong evidence that BDCM does not interact with other chemicals.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No studies were located regarding human populations that are unusually susceptible to BDCM. Because BDCM is known to cause liver injury in animals, humans with preexisting liver diseases (e.g. , hepatitis, cirrhosis) may be particularly susceptible to the hepatotoxic effects of BDCM. Likewise, humans with preexisting kidney diseases may be susceptible to BDCM. By analogy with CCl_4, persons who are heavy drinkers and/or take certain drugs that affect the liver may also be particularly susceptible to the effects of BDCM.

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 BDCM 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. HEALTH EFFECTS

2.9.1 Existing Information on Health Effects of BDCM

As summarized in Figure 2-2, there are no data on the health effects of BDCM in humans. In animals, there are a number of studies of health effects following oral exposure, and information exists for most endpoints except reproduction. However, no animal toxicity data exist for inhalation or dermal exposure to BDCM.

2.9.2 Data Needs

Single Dose Exposure. There are a number of single dose studies in animals by the oral route, and the range of intake doses leading to lethal and most sublethal effects is reasonably well defined. However, the mechanism of toxicity has not been studied. Such studies would be useful in revealing why there are significant differences in susceptibility between males and females, and whether this is pertinent to the evaluation of human health risk from BDCM. Studies by the oral route are likely to be most relevant, but studies of acute inhalation and dermal toxicity would also be useful, since humans may be exposed by these pathways while bathing or swimming.

Repeated Dose Exposure. Existing studies of health effects in animals administered repeated oral doses of BDCM indicate that there is a relatively low tendency toward cumulative toxicity and that chronic noncarcinogenic effects resemble short-term effects. However, the threshold dose for noncarcinogenic effects is not known with certainty. For example, the study by Chu et al. (1982b) identified minimal effects on the liver at doses of 7 mg/kg/day or higher, while other studies (NTP 1987; Tobe et al. 1982) did not detect effects at doses 6- to 20-times higher. Thus, additional studies to define long-term no-effect levels with greater certainty would help improve risk assessments for BDCM.

Chronic Exposure and Carcinogenicity. Several studies have indicated that chronic oral exposure to BDCM increases cancer risk in animals. Tumors were observed in both liver and kidney tissues (known to be target tissues from subchronic studies of this chemical), and tumors were also observed in the large intestines in rats. This is an unusual tumorigenic response in rats, and the basis for the susceptibility of the large intestine is not known. Further studies would be valuable to reveal the basis for this tissue selectivity, and to obtain improved dose-response data to allow reliable quantitative cancer risk assessment.

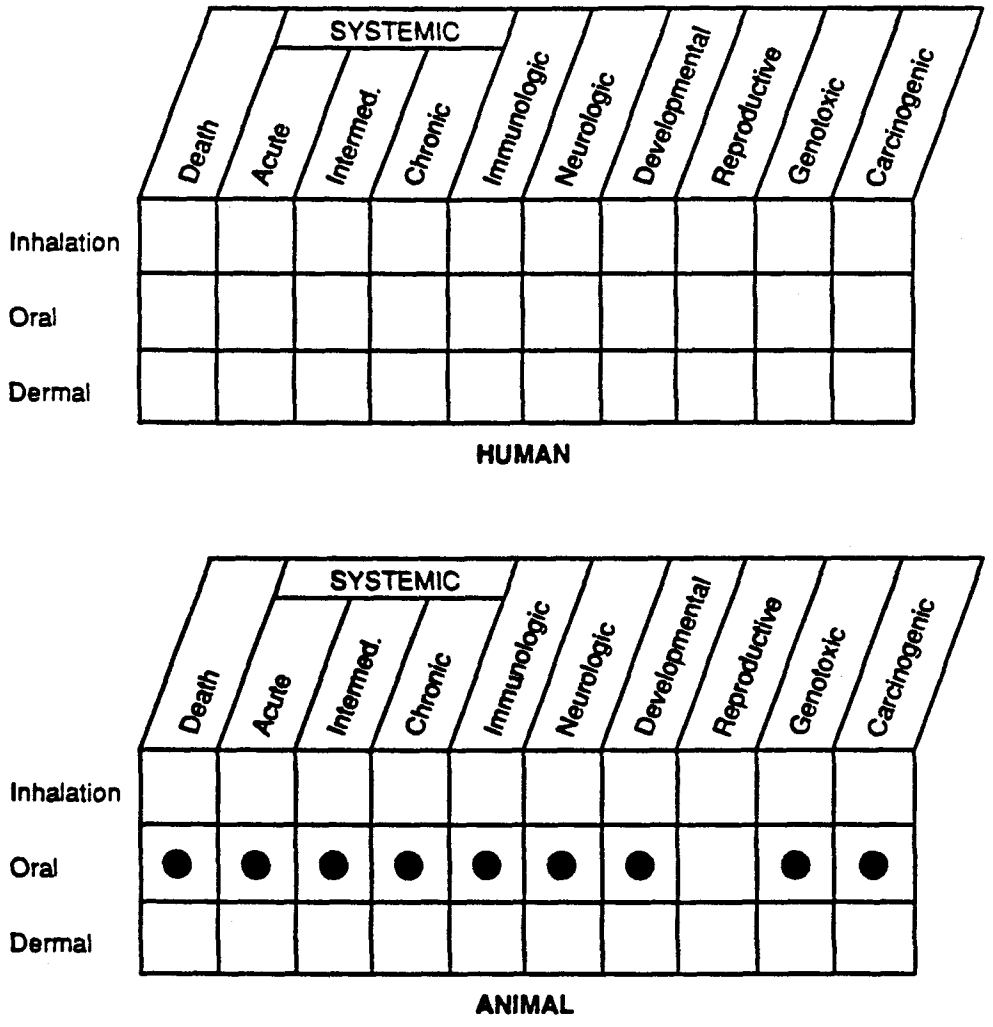


FIGURE 2-2. Existing Information on Health Effects of BDCM

2. HEALTH EFFECTS

Genotoxicity. An in vivo mutagenicity study in mice indicated that BDCM has potential to cause genetic damage, and in vitro studies also suggest that BDCM has genotoxic potential. Additional in vitro and in vivo studies to evaluate the genotoxicity of BDCM and to identify the mechanism of genotoxic damage in intact mammalian cells would be valuable.

Reproductive Toxicity. No studies were located regarding effects of BDCM on reproduction. Multigeneration studies in animals to evaluate effects of BDCM on reproduction would be valuable.

Developmental Toxicity. One study in rats (Ruddick et al. 1983) indicates that BDCM is fetotoxic at doses that cause maternal toxicity, but effects at lower doses were not evaluated. Additional developmental studies at lower doses and in several other species would be helpful in evaluating more fully the potential of BDCM to cause effects on the developing organism.

Immunotoxicity. Limited data from subchronic oral studies in mice indicate that BDCM adversely affects the immune system. However, the data do not define the threshold for the effect with certainty, nor do the data reveal whether the function of the immune system is significantly impaired. Further studies on the immunotoxicity of BDCM in animals would be valuable in establishing the no-effect level and the relevance to human health.

Neurotoxicity. High doses of BDCM affect the CNS like other halocarbons, causing depressed function and anesthesia. Limited data indicate that repeated exposures may lead to transient effects on behavior, but this has not been investigated in detail. Further neurobehavioral,studies using more sensitive operant measures would help define the exposure levels that lead to these effects, and whether any permanent neurological changes occur.

Epidemiological and Human Dosimetry Studies. No epidemiological studies were located regarding human health effects from exposure to BDCM per se. Epidemiological studies of cancer frequency in populations consuming chlorinated drinking water have been performed, but since BDCM levels tend to vary in concert with the levels of other trihalomethanes and numerous other byproducts of disinfection, it is unlikely that studies of this sort will be able to provide information on the risks contributed specifically by BDCM.

2. HEALTH EFFECTS

Biomarkers of Disease. Since no cases of human disease due to BDCM exposure have been reported, it is not possible to identify biomarkers of disease in humans. Assuming that hepatic and renal injury similar to that observed in animals might occur in exposed humans, early signs of these effects could be detected by standard clinical methods such as serum enzyme levels, PAH clearance, and so on. These tests would not be specific for BDCM, however, and would only detect effects after injury to the tissues has occurred. Efforts to identify a sensitive and specific biomarker of BDCM-induced disease would be helpful.

Disease Registries. No disease registry exists for BDCM-induced diseases in humans. Since the effects observed in animals (hepatic and renal injury, cancer of liver, kidney and intestines) are common diseases in humans, it is likely that a registry of individuals with these diseases would contain only a small number of cases that might be attributable solely to BDCM exposure.

Bioavailability from Environmental Media. No studies were located on the relative bioavailability of BDCM in different environmental media. Based on the physical properties of BDCM, it is not expected that bioavailability would vary widely between water, soil, food, and other media. Studies to investigate this would, nevertheless, be helpful.

Food Chain Bioaccumulation. BDCM is biosynthesized by a variety of marine macroalgae, but whether BDCM from this source or other sources enters the food chain has not been studied. While the relatively rapid metabolism and excretion of BDCM in laboratory animals suggest that marked bioaccumulations is not likely, information on BDCM uptake and retention by fish, plants, and other food sources would be helpful.

Absorption, Distribution, Metabolism, and Excretion. Currently there are no toxicokinetic studies on BDCM following inhalation exposure. Consequently, it would be helpful to determine the fraction of BDCM that is absorbed via inhalation and to investigate whether any significant differences in metabolism or retention exist between inhalation and oral exposures. Similarly, there are no toxicokinetic data regarding dermal exposure to BDCM. Although direct dermal contact with concentrated BDCM is unlikely, dermal contact with water containing BDCM is very common. Consequently, information on dermal absorption rates from aqueous solutions would be helpful.

Most toxicokinetic studies were conducted prior to the findings of cancer in the large intestine of male and female rats following chronic

ingestion of BDCM. Since tumors in the gastrointestinal tract are uncommon in rats, additional toxicokinetic studies focusing on BDCM metabolism and distribution in this tissue would be valuable in understanding the metabolic pathways for BDCM and how the metabolism may be related to the mechanism of toxicity and carcinogenicity of BDCM.

Detailed studies of the enzymic pathways of BDCM metabolism and of the intermediates formed would also be valuable. Metabolic activation to yield highly toxic intermediates is known to be a critical step in the toxicity of some similar compounds (e.g., CCl_4). Investigations to determine whether similar pathways are involved in BDCM toxicity might help resolve many of the special aspects of the toxicity of this compound.

Comparative Toxicokinetics. Since BDCM toxicity appears to differ significantly between sexes and species, additional toxicokinetic studies in several species would be valuable. Such studies would aid in understanding the differences in toxicity between species, and could help identify the most appropriate animal species for use as a model for humans.

2.9.3 On-going Studies

Dr. James Mathews (Research Triangle Institute) is currently performing studies of the dose-dependency of absorption, metabolism and clearance of BDCM following oral exposure of rodents. This research is sponsored by the National Toxicology Program.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

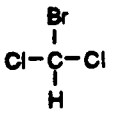
Table 3-l lists common synonyms, trade names and other pertinent identification information for BDCM.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of BDCM

	Value	References
Chemical Name	Bromodichloromethane	NLM 1988
Synonyms	Dichlorobromomethane; Monobromodichloromethane; Methane, bromodichloro-	NLM 1988
Trade Name (s)	--[a]	
Chemical Formula	$CHBrCl_2$	Verschueren 1977
Chemical Structure		EPA 1983
Identification Numbers:		
CAS Registry	75-27-4	NLM 1988
NIOSH RTECS	PA5310000	HSDB 1988
EPA Hazardous Waste	ND	HSDB 1988
OHM-TADS	ND	HSDB 1988
DOT/UN/NA/IMCO Shipping	ND	HSDB 1988
HSDB	4160	NLM 1988
NCI	C55243	NLM 1988

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 BDCM

Property	Value	References
Molecular weight	163.83	Weast 1985
Color	colorless	Verschueren 1977
Physical State	liquid	Verschueren 1977
Melting point, °C	-57.1	Weast 1985
Boiling point, °C	90	Weast 1985
Density, 20/4	1.980	Weast 1985
Odor	ND[a]	
Odor threshold Water Air	ND	
Solubility Water, mg/L	4,500	Mabey et al. 1982
Organic Solvents	soluble	Weast 1985
Partition coefficients Log octanol/water	2.1	Mabey et al. 1982
Log k_{oc}	1.8	Mabey et al. 1982
Vapor Pressure, mm Hg (20°C)	50	Mabey et al. 1982
Henry's Law Constant, atm m^3/mol	2.41E-03	Mabey et al. 1982
Autoignition temperature, °C	ND	
Flash point	ND	
Flammability limits	ND	
Conversion Factors ppm (v/v) to mg/m^3 in air (20 °C)	1 ppm = 6.70 mg/m^3	Verschueren 1977
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3 = 0.15 ppm	

[a] No data located.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

BDCM is produced commercially by the reaction of dichloromethane with aluminum bromide. Small quantities of BDCM are currently produced in the United States, but quantitative production volumes are not available.

4.2 IMPORT

No data on imports or exports of BDCM were located. Little, if any, of either is expected.

4.3 USE

In the past, BDCM has been used as a solvent for fats, waxes, and resins, as a flame retardant, as a heavy liquid for mineral and salt separations, and as a fire extinguisher fluid ingredient (Sax 1984). At present, the principal use of BDCM is as a chemical intermediate for organic synthesis and as a laboratory reagent (Sittig 1985; Verschueren 1983). BDCM is not listed as a current ingredient in fire extinguishers, solvents or other commercial products (Gosselein et al. 1984).

4.4 DISPOSAL

Bromodichloromethane is categorized as a hazardous waste constituent (40 CFR 261 App. VIII) and, therefore, must be disposed of in accordance with RCRA regulations. Acceptable disposal methods include incineration using liquid injection, rotary kiln or fluidized bed techniques. At the present time, land disposal of BDCM is also permitted, although trihalomethanes are being evaluated for land disposal prohibition.

BDCM has been detected in the raw and treated wastewater of numerous industries (EPA 1983), but no quantitative data on amounts of BDCM disposed of to the environment were located. BDCM has been detected at 7% of chemical waste sites investigated under Superfund (CLPSD 1988).

4. PRODUCTION, IMPORT, USE AND DISPOSAL

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 BDCM 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, Use, Release and Disposal. The minimal commercial use of BDCM is reflected in the absence of available production data. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to BDCM.

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

The major source of BDCM in the environment is formation as a byproduct during chlorination of water, and many people are exposed to low levels of BDCM in their drinking water. Industrial use of BDCM is sufficiently limited that exposures to industrial emissions outside the workplace are not expected to be of general concern. BDCM has been detected in water and soil at some chemical waste sites, and human exposure may potentially occur in such cases.

BDCM is a volatile chemical, so most of the BDCM that is formed in water or released by industry tends to evaporate into air. BDCM does not adsorb strongly to soils or sediments, nor does it tend to bioaccumulate in fish or other animals.

In the atmosphere, BDCM is thought to undergo slow destruction through oxidative pathways, with a half-life of about two to three months. BDCM remaining in soil or water may undergo microbial degradation. However, these fate processes have not been studied in detail.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

No studies were located regarding industrial release of BDCM into air. Because of the low volume of BDCM currently in use, it is expected that releases from industrial activities are probably small.

5.2.2 Water

The principal source of BDCM in the environment is from chlorination of water. EPA (1980a) estimated that over 800 kkg (1 kkg = 1 metric ton) are produced annually in this way. It is presumed that essentially all of this is ultimately released into the environment, mainly through volatilization. This may occur either indoors (e.g., while showering, washing, cooking, etc.) or outdoors after discharge of the water to the surface.

5. POTENTIAL FOR HUMAN EXPOSURE

Class et al. (1986) observed trace levels (<l parts per trillion (ppt)) of BDCM and other brominated methanes in seawater and in the air above the ocean at several locations in the Atlantic. The presence of BDCM can be attributed to biosynthesis and release of BDCM by macroalgae (Class et al. 1986; Gschwend et al. 1985). BDCM from this source accounts for less than 1% of the anthropogenic burden of bromomethanes in the atmosphere (Class et al. 1986).

BDCM has been detected in wastewater from a number of industrial discharges and municipal wastewater treatment facilities, usually at concentrations between 1 and 100 μg/L (Staples et al. 1985; Perry et al. 1979; Dunovant et al. 1986). These levels of BDCM are similar to those found in many chlorinated drinking water supplies (see Section 5.4.2, below), and probably most discharges of this sort do not represent a major source of BDCM release to the environment.

5.2.3 Soil

No studies were located regarding release of BDCM to soil.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Because of the relatively high vapor pressure of BDCM (50 mm Hg at 20°C), the principal transport process in the environment is volatilization (Class et al. 1986; Gschwend et al. 1985). Over 99% of all BDCM in the environment is estimated to exist in air (EPA 1980a).

Volatilization from surface waters depends on factors such as turbulence and temperature. The volatilization half-life from rivers and streams has been estimated to range from 33 minutes to 12 days, with a typical half-life of 35 hours (Kaczmar et al. 1984). Volatilization rates from surface soils have not been studied in detail, but Wilson et al. (1981) found that about 50% of BDCM applied to a soil column in the laboratory escaped by volatilization.

BDCM may be removed from air by washout in rainfall (Class et al. 1986), but the average rate of this transport process has not been estimated. It is expected that BDCM removed from air in this way would be largely returned to air through volatilization.

5. POTENTIAL FOR HUMAN EXPOSURE

BDCM is moderately soluble in water (4,500 mg/L), and significant transport of BDCM can occur in water, especially in groundwater where volatilization is restricted. This transport pathway may be important at waste sites or other locations where BDCM spills lead to groundwater contamination.

In soil, the relatively low log octanol-water partition coefficient (Kow) indicates that adsorption is not likely to be a dominant factor, and that BDCM spilled into soil will be relatively mobile and may migrate into groundwater (EPA 1985a; Piet et al. 1981). In support of this, Wilson et al. (1981) found that BDCM was not significantly retarded during percolation through a column of sandy soil.

The moderate solubility and low log Kow indicate that bioaccumulation of BDCM by fish or other aquatic species is likely to be minor, but no estimate of a bioaccumulation factor in aquatic species was located.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Pathways responsible for BDCM destruction in the atmosphere are not well studied, but probably involve oxidative reaction with hydroxyl radicals or singlet oxygen (EPA 1980a; Mabey et al. 1982). Direct photochemical decomposition is not likely to be significant (EPA 1980a). The typical atmospheric lifetime of BDCM has been estimated to be two to three months (EPA 1980a). This relatively persistent tropospheric halflife of BDCM suggests that a small percentage of the BDCM present in air will eventually diffuse into the stratosphere where it will be destroyed by photolysis. In addition, long-range global transport is possible.

5.3.2.2 Water

Hydrolysis of BDCM in aqueous media is very slow, with an estimated rate constant at neutral pH of 5.76×10^{-8} hr^{-1} (Mabey et al. 1982). This corresponds to a half-life of more than 1,000 years.

Biodegradation in aqueous media may be significant in some cases. For example, Tabak et al. (1981) reported 35% transformation after seven days incubation in a medium inoculated with sewage. Repeated culturing lead to increased losses, indicating gradual adaptation of the degradative microbes.

5. POTENTIAL FOR HUMAN EXPOSURE

Under aquatic conditions where volatilization cannot occur, biodegradation may be the predominant mechanism for degradation of BDCM. Bouwer et al. (1981) and Bouwer and McCarty (1983a) studied the degradation of BDCM under aerobic and anaerobic conditions in both static and continuous flow systems inoculated with mixed methanogenic bacterial cultures from sewage. Degradation was found to be very limited under aerobic conditions, but essentially complete within 2 days under anaerobic conditions. Slow degradation (50% to 70% in 16 weeks) occurred in sterile media, indicating that a chemical mechanism (hypothesized to be reductive dehalogenation) was operative in addition to the rapid microbial degradation. Microbial degradation was also observed under anaerobic conditions in media inoculated with denitrifying bacteria (Bouwer and McCarty 1983b).

5.3.2.3 Soil

Biodegradation of BDCM in soil has not been studied, but studies in aqueous media indicate that biodegradation might occur under anaerobic conditions (Bouwer et al. 1981; Bouwer and McCarty 1983a, 1983b; Tabak et al. 1981). This suggests that, in regions of soil where volatilization is restricted, biodegradation could be a major removal process.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Ambient air monitoring data compiled by Brodzinsky and Singh (1983) identified BDCM at four of six sites investigated. Concentrations ranged from 0.76 to 180 ppt, with a mean value of 1.1 ppt. BDCM levels from four sites monitored in California were reported to range from 20 to 100 ppt (Shikiya et al. 1984). BDCM was not detected in a survey of bromine-containing gasses in the atmosphere at the South Pole (Rasmussen and Khalil 1984), although trace levels (1 ppt) were detected in air at several locations in the Atlantic Ocean (Class et al. 1986). This was judged by the authors to be due to releases from macroalgae.

5.4.2 Water

BDCM occurs in water primarily as a by-product of chlorination. Surveys of BDCM levels in chlorinated public drinking water systems across the United States have revealed that BDCM is present in most

systems at concentrations averaging around 1 to 20 μg/L, but ranging up to 125 μg/L in some cases (Coleman *et* al. 1975; EPA 1979; Furlong and D'itri 1986; Symons et al. 1975).

The concentration of BDCM in chlorinated water depends on reaction conditions during the chlorination process. Important parameters include temperature, pH, bromide ion concentration in the source water, fulvic and humic substance concentration in the water, and the chlorination treatment practices (EPA 1985b). The amount of BDCM tends to increase as a function of increasing organic content and bromide ion in the source water (Bellar et al. 1974; Argue110 et al. 1979). Studies by Brett and Calverly (1979) and Argue110 et al. (1979) indicate that BDCM levels increased by 30 to 100% in water system distribution pipes, presumably because formation continues as long as a chlorine residual and organic precursors remain.

BDCM is also formed in chlorinated swimming pools. Beech et al. (1980) measured THM levels in several swimming pools in Miami, and found total THM concentrations averaged from 120 to 660 μg/L. In freshwater pools, most of the total THM was chloroform, with BDCM levels ranging from 13 to 34 μg/L. In saltwater pools, bromoform was the principal THM present, and BDCM concentrations were roughly the same as in freshwater pools.

Monitoring studies of groundwater and surface water at chemical waste sites indicate that BDCM is a relatively infrequent contaminant. BDCM was detected at only 4 of 818 sites on the National Priority List (NPL) , and at 7% of a number of other sites being investigated under Superfund (CLPSD 1988). The average concentration of BDCM in groundwater at these sites was 30 μg/L. Quantitative data for surface water were not available.

5.4.3 Soil

No studies were located on BDCM levels in ambient soil. Because of its volatility, it is likely that BDCM would be present only at low levels in most soils. BDCM was detected in 2% of soil samples taken near chemical waste sites being investigated under Superfund (CLPSD 1988), but quantitative estimates of soil concentration are not available.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4.4 Other Media

BDCM is not a common contaminant of food, occurring only in trace quantities in some samples. A market basket study of 39 food items detected BDCM in one dairy composite at 1.2 ppb and in butter at 7 ppb (Entz et al. 1982). A study of BDCM in food processing water and processed foods revealed no detectable levels except in ice cream at one processing plant (0.6 to 2.3 ppt) (Uhler and Diachenko 1987). Soft drinks have been found to contain BDCM (Abdel-Rahman 1982; Entz et al. 1982), but usually at concentrations (0.1 to 6 μg/L) below those found in municipal water supplies. Cooking foods in water containing BDCM is unlikely to lead to contamination, since BDCM would rapidly volatilize (Kool et al. 1981).

BDCM is biosynthesized by marine macroalgae, and has been measured in these organisms at 7-22 ng/g dry weight (Gschwend et al. 1985). Whether BDCM enters and accumulates in the food chain from this source appears to be unlikely, but has not been studied.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The estimated exposure of the general human population to BDCM from drinking water, assuming a median BDCM concentration of 0.014 mg/L and a water intake for an adult of 2.18 L/day, would be 0.03 mg/day (EPA 1980a). Low levels of exposure might also occur by inhalation of BDCM volatilized from chlorinated water (e.g., while showering, cooking, or swimming), or by dermal contact with such water. Based on a chemical structure analogy to chloroform, an estimated dermal exposure to BDCM in a child swimming two hours/day in a saline pool would typically be 0.003 mg/day, with a maximum of 0.04 mg/day (Beech 1980). Higher exposure levels might occur through ingestion of water contaminated with BDCM near a waste site, but available data suggest that this is not a common occurrence.

No studies were located on human exposure levels in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The environmental medium most likely to be contaminated with BDCM is chlorinated water, so any person with above-average contact with such water could have above-average exposures. This includes individuals-who drink very large quantities of water, such as diabetics, workers in hot climates, and so on. It may also include persons with swimming pools or saunas, where exposure could occur by inhalation (especially if the pool

or sauna is indoors) or by dermal contact. Since BDCM levels depend on the organic content of the source water before chlorination, persons whose water source is high in organics are likely to have finished water with higher-than-average BDCM levels.

People working in chemical plants or laboratories where BDCM is made or used would also have potentially high exposures to the chemical, most likely by inhalation exposure. Persons living near waste sites may have potentially high exposure to BDCM, but this can only be evaluated on a case-by-case basis.

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 BDCM 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 of BDCM have been determined (see Table 3-2), and further studies on these parameters do not appear to be essential.

Environmental Fate. There are very few quantitative data on the environmental fate and transport of BDCM, and most evaluations are based, entirely or in part, on extrapolations from studies of other similar compounds such as chloroform. Consequently, studies to obtain reliable quantitative rate values for the key fate processes of BDCM would be valuable. Of particular importance would be studies on the volatilization of BDCM from chlorinated drinking water, and on the atmospheric reactions of BDCM. Studies of chemical and biological transformation and degradation rates in soil and water under conditions comparable to those around waste sites would also be helpful.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Levels in Environmental Media. Data are available on BDCM levels in drinking water and on how these levels depend on water organic content and treatment conditions. Nevertheless, continued monitoring will be valuable in revealing whether changes in drinking water treatment and disinfection procedures are effective in reducing levels of BDCM and other contaminants.

Studies of BDCM levels in air (especially indoor air) in the vicinity of open bodies of chlorinated water would also be helpful. This would include water treatment plants, swimming pools, and perhaps even home bathtubs or showers. In view of the ready volatilization of BDCM from water, airborne levels in such locations might be significant.

Further monitoring of groundwater, soil and ambient air in the vicinity of chemical waste sites is also needed to determine whether emissions of BDCM from such sites adds significantly to total BDCM exposure.

Exposure Levels in Humans. Current data on BDCM levels in air are not adequate to estimate inhalation exposure in ambient air or the workplace. Collection of such information would be helpful in evaluating the relative contribution of this exposure pathway to the total intake of BDCM. Similar data would be useful for airborne levels of BDCM around swimming pools (especially indoor pools). Data on the presence of BDCM in drinking water appears to be adequate for estimating exposure from consumption of water immediately after taking it from the tap. However, it would be helpful to know how rapidly the BDCM would volatilize from a glass of water or from a bathtub full of water, and what concentration would then be in the breathing zone of occupants of the house.

Exposure Registries. No registry exists for humans known to have been exposed to BDCM. Although exposure to BDCM through drinking water is common, a registry of humans exposed in this way is not likely to help identify BDCM-related diseases in humans, since exposure to BDCM in water are usually low and typically involve exposure to other trihalomethanes and many other byproducts of disinfection as well. A registry of individuals exposed to BDCM during manufacture or use of this chemical might be helpful in identifying possible health effects in humans, although the size of the exposed population is believed to be small.

5. POTENTIAL FOR HUMAN EXPOSURE

5.7.2 On-going Studies

No information was located on any on-going studies on the potential for human exposure to BDCM.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for BDCM and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

As a volatile organohalide, BDCM may be measured with good sensitivity and specificity using gas-chromatographic methods employing halide-specific or election-capture detection. Methods available for separation of BDCM from biological samples prior to analysis include headspace analysis, purge-and-trap collection, solvent extraction, and direct collection on resins.

Headspace analysis offers speed, simplicity, and good reproducibility for a particular type of sample. However, partitioning of the analyte between the headspace and the sample matrix is dependent upon the nature of the matrix and must be determined separately for different kinds of matrices (Walters 1986).

Purge-and-trap collection is well suited to biological samples that are soluble in water (Peoples et al. 1979), and is readily adapted from techniques that have been developed for the analysis of BDCM and other VOCs in water and wastewater. This method consists of bubbling inert gas through a small volume of the sample and collecting the vapor in a trap packed with sorbent. The analytes are then removed from the trap by heating it and backflushing the analytes onto a gas chromatographic column (Pankow et al. 1988). The two materials most widely used for adsorption and thermal desorption of volatile organic compounds collected by the purge-and-trap technique are Carbotrap, consisting of graphitized carbon black, and Tenax,a porous polymer of 2,6-diphenyl-p-phenylene oxide (Fabbri et al. 1987).

Solvent extraction of volatile components from biological fluids is usually performed using dimethyl ether (Zlatkis and Kim 1976). Homogenization of tissue with the extractant and lysing of cells improves extraction efficiency. When, as is often the case, multiple analytes are being determined using solvent extraction, selective extraction and loss of low-boiling compounds can cause errors. Supercritical fluid extraction using pure carbon dioxide or carbon dioxide with additives offers some exciting potential for the extraction of organic analytes such as BDCM from biological samples (Hawthorne 1988).

Analytical methods for the determination of BDCM in biological samples are given in Table 6-1.

6. ANALYTICAL METHODS

TABLE 6-1. Analytical Methods for BDCM in Biological Samples

Sample type	Extraction/cleanup	Detection	Limit of detection	References
Adipose tissue	Purge from liquified fat at 115°C, trap on silica gel, thermal desorption	GC/HSD	<0.8 µg/L	Peoples et al. 1979
Bile acids	NR	GC/ECD	NR	Brechbuehler et al. 1977
Breath, blood, and urine	NR	GC/MS	NR	Barkley et al. 1980
Blood serum	Purge from water-serum mixture containing antifoam reagent at 115°C, trap on Tenax/ silica gel, thermal desorption	GC/HSD	<0.8 µg/L	Peoples et al. 1979
Biofluids[a]	Dilute with water, sealed vial, collection of headspace vapors	GC/ECD	NR	Suitheimer et al. 1982
Grain[b]	Extract with acetone/ water (5/1), dry, inject acetone solution	GC/ECD	NR	AOAC 1984

Abbreviations: GC = gas chromatography; HSD = halide selective detector; ECD = electron capture detector; NR = not reported; MS = mass spectrometry.

[a]This method for volatiles by headspace chromatography can be adapted to bromodichloromethane although the procedure does not list it specifically as an analyte.

[b]Method for carbon tetrachloride, but applicable to bromodichloromethane because of their similar properties.

6. ANALYTICAL METHODS

6.2 ENVIRONMENTAL SAMPLES

BDCM may be isolated from environmental samples using the same methods and principles used for biological samples, followed by gas chromatographic analysis. The most convenient procedure for most liquid and solid samples is the purge-and-trap method. A similar procedure is used for air, involving passing the air through an adsorbent canister, followed by thermal desorption.

Analytical methods for the determination of BDCM in environmental samples are given in Table 6-2.

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 BDCM 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 Compounds and Metabolites in Biological Materials. Methods are available for the determination of BDCM in biological samples, but there is a need for development of validated standard methods of analysis with well-defined limits of detection, such as those that exist for water and wastewater (EPA 1982a, EPA 1982b) and for solid wastes (EPA 1986a, EPA 1986b).

Animal studies show that BDCM is excreted via the lungs as parent compound or carbon dioxide. Small amounts of carbon monoxide have also been measured in animals after administration of BDCM (Anders et al. 1978). Other metabolites of BDCM have not been identified. Since carbon dioxide and carbon monoxide are not specific to BDCM, measurement of these metabolites is not likely to provide a good index of BDCM exposure.

6. ANALYTICAL METHODS

TABLE 6-2. Analytical Methods for BDCM in Environmental Media

Sample type	Extraction/cleanup	Detection	Limit of detection	References
Air[a]	Coconut shell charcoal sorption carbon disulfide desorption	GC/FID	10 µg per sample	NIOSH 1984
Air	Sorption	GC/CLMD	$3x10^{-13}$ g/sec	Yamada et al. 1982
Air and water	NR	GC/MS	NR	Barkley et al. 1980
Drinking water	Purge and trap	GC/MWED	<1 µg/L	Quimby et al. 1979
Water	Purge and trap	GC/MS	10 µg/L	EPA 1980c
Water	Purge and trap	GC/HSD	0.12 µg/L	EPA 1982a
Water	Purge and trap	GC/MS	2.2 µg/L	EPA 1982b
Water	Purge and trap	GC/HSD	0.5 µg/L	APHA 1985a
Water	Purge and trap	GC/MS	<0.27 µg/L	APHA 1985b
Water	Solvent extraction (isooctane)	GC/HSD	1 µg/L	ASTM 1988
Contaminated soil	Purge and trap	GC/HSD	1.0 µg/kg	EPA 1986a
Wastes, non-water miscible	Purge and trap	GC/HSD	125 µg/kg	EPA 1986a
Solid waste	Purge and trap	GC/MS	5 µg/kg	EPA 1986b

Abbreviations: GC = gas chromatography; FID = flame ionization detector; CLMD = chemiluminescence detection; NR = not reported; MS = mass spectrometry; MWED = microwave emission detector; HSD = halogen-specific detector.

[a]This method for halogenated hydrocarbons can be adapted to bromodichloromethane although the procedure does not list it specifically as an analyte.

6. ANALYTICAL METHODS

Methods for Biomarkers of Exposure. No biomarkers of exposure to BDCM are currently known. By analogy with CCl_4, it is possible that BDCM may be metabolized to reactive intermediates that form covalent adducts with cellular macromolecules. If so, immunoassays and 32 P-post labeling assays might be capable of identifying and quantifying these adducts, although levels would likely be very low. Efforts to identify such adducts and to develop appropriate measurement techniques would be valuable for determining exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. BDCM can be analyzed in water, air, and waste samples with good selectivity and sensitivity. However, since BDCM may be carcinogenic in humans, very low levels in water, air or other media may be of concern, so improvements in sensitivity would be valuable.

6.3.2 On-going Studies

The development of supercritical fluid (SCF) extraction holds great promise for analysis of nonpolar organic analytes such as BDCM. Current research in this area has been summarized by Hawthorne (1988). Research is ongoing to develop a "Master Analytical Scheme" for organic compounds in water (Michael et al. 1988), which includes BDCM as an analyte. The overall goal is to detect and quantify organic compounds at 0.1 μg/L (1 ppb)in drinking water, 1 μg /L in surface waters, and 10 μg/L in effluent waters. A comprehensive review of the literature leading up to these efforts has been published (Pellizzari et al. 1985).

The introduction of capillary column chromatography has markedly improved both sensitivity and resolution of gas chromatographic analysis, but because of the very small quantities of sample required, has made sample delivery more difficult. One of the more promising approaches to sample introduction using capillary columns with purgeand-trap collection is the use of cryofocusing. Basically, this procedure consists of collecting purged analyte on a short section of the capillary column cooled to a low temperature (e.g., -l00°C), followed by heating and backflushing of the sample onto the analytical column. Several compounds closely related to BDCM have been determined in water by this method (Washall and Wampler 1988), including mefhylene chloride, chloroform, chlorobromomethane and bromoform.

6. ANALYTICAL METHODS

Methods are also being developed for in situ measurement of organohalide levels in water. This has been demonstrated for chloroform-contaminated well water using remote fiber fluorimetry (RFF) and fiber optic chemical sensors (FOGS) (Milanovich 1986). With this approach, fluorescence of basic pyridine in the presence of organohalide (the Fujiwara reaction) is measured from a chemical sensor immersed in the water at the end of an optical fiber. If conditions can be found under which BDCM undergoes a Fujiwara reaction, its determination might be amendable to this approach.

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of BDCM and other volatile organic compounds in blood. These methods use purge and trap methodology and magnetic mass spectrometry which gives detection limits in the low parts per trillion range.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse effects in exposed people, a number of regulations and advisory values have been established for BDCM by various national and state agencies. These values are summarized in Table 7-1. No international values were located.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to BDCM

Agency	Description	Value	References
	National		
Regulations			
a. Water			
EPA ODW	Maximum Contaminant Level (MCL) for Total Trihalomethanes	0.10 mg/L	40 CFR 141.12
	Monitoring Required for All Systems	NA[a]	40 CFR 141.40 EPA 1987a
EPA OSW	Groundwater Monitoring List (Appendix IX)	NA	40 CFR 264 EPA 1987b
EPA OWRS	General Permits Under the National Pollutant Discharge Elimination System (NPDES)	NA	40 CFR 122 Appendix D Table II
	General Pretreatment Regulations for Existing and New Sources of Pollution (halomethanes)	NA	40 CFR 403
FDA	Permissible Level in Bottled Water (Total Trihalomethanes)	0.10 mg/L	21 CFR 103.35
b. Non-specific Media			
EPA OERR	Reportable Quantity	5000 lb	40 CFR 302.4 EPA 1985a
Guidelines			
EPA OWRS	Ambient Water Quality Criteria to Protect Human Health[b]		EPA 1980b
	Ingesting Water and Organisms		
	10^{-5}	1.9 µg/L	
	10^{-6}	0.19 µg/L	
	10^{-7}	0.019 µg/L	
	Ingesting Organisms Only		
	10^{-5}	157 µg/L	
	10^{-6}	15.7 µg/L	
	10^{-7}	1.57 µg/L	
EPA	Reference Dose (RfD)	2E-2 mg/kg/d	EPA 1988
	State Regulations and Guidelines		
State Environmental Agencies	Drinking Water Standards and Guidelines		FSTRAC 1988
	Illinois	1.0 µg/L	
	Vermont	100 µg/L	

[a]Not applicable.

[b]Because of its carcinogenic potential, the EPA-recommended concentration for BDCM in ambient water is zero. However, because attainment of this level may not be possible, levels which correspond to upper bound incremental lifetime cancer risks of 10^{-5}, 10^{-6} and 10^{-7} are estimated. Since no quantitative data are available on the cancer risk from BDCM, the values are assumed to be equal to those for chloroform.

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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 (LO) (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(LO) (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.

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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.

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.

9. GLOSSARY

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 BDCM. The panel consisted of the following members: Dr. Sheldon Murphy, Professor of Environmental Health, University of Washington; Dr. Joseph Gould, Research Scientist, Georgia Institute of Technology; Dr. Nancy Reiches, Director of Research, Riverside Methodist Hospital, Columbus, Ohio; and Dr. Sanford Bigelow, President, MultiSciences, Inc. These experts collectively have knowledge of BDCM'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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