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

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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).

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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

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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.

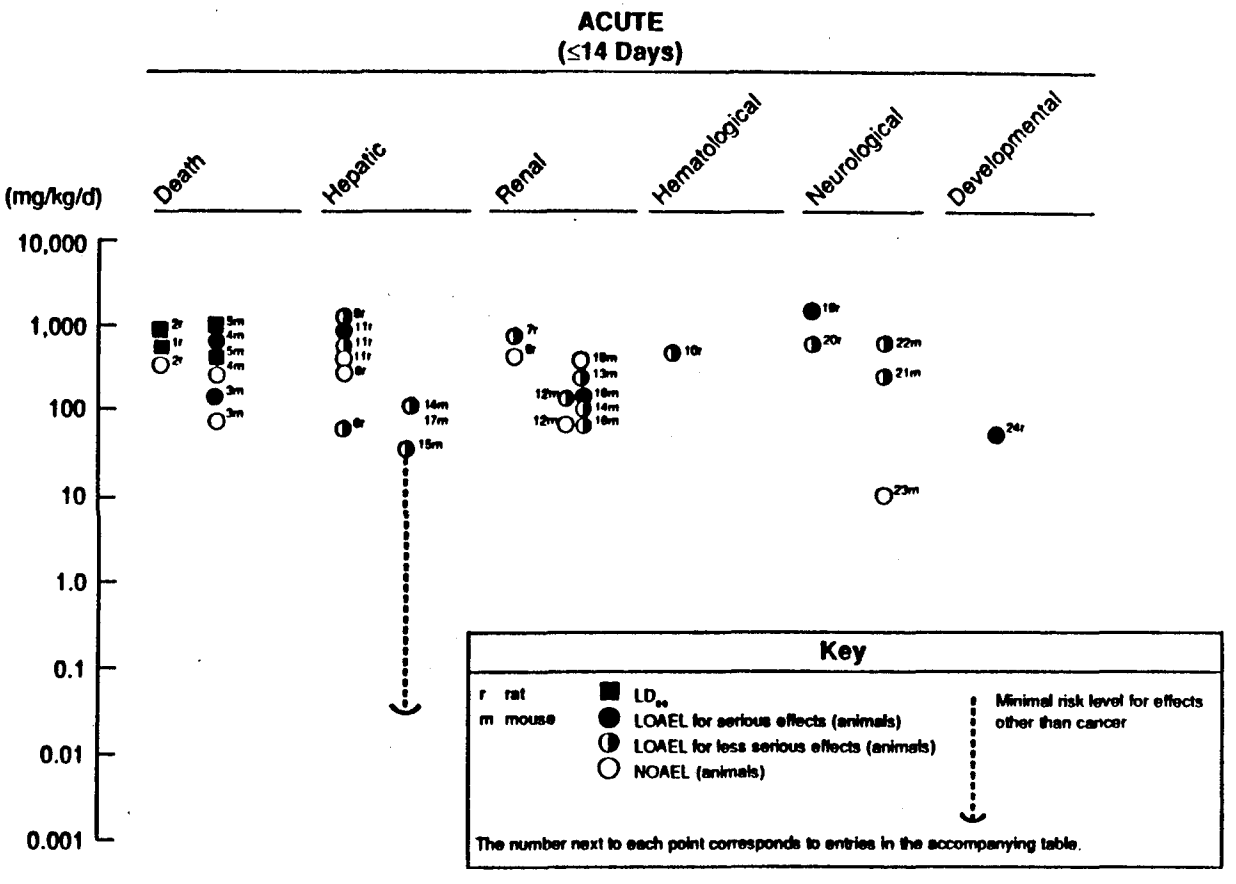

FIGURE 2-1. Levels of Significant Exposure to BDCM – Oral

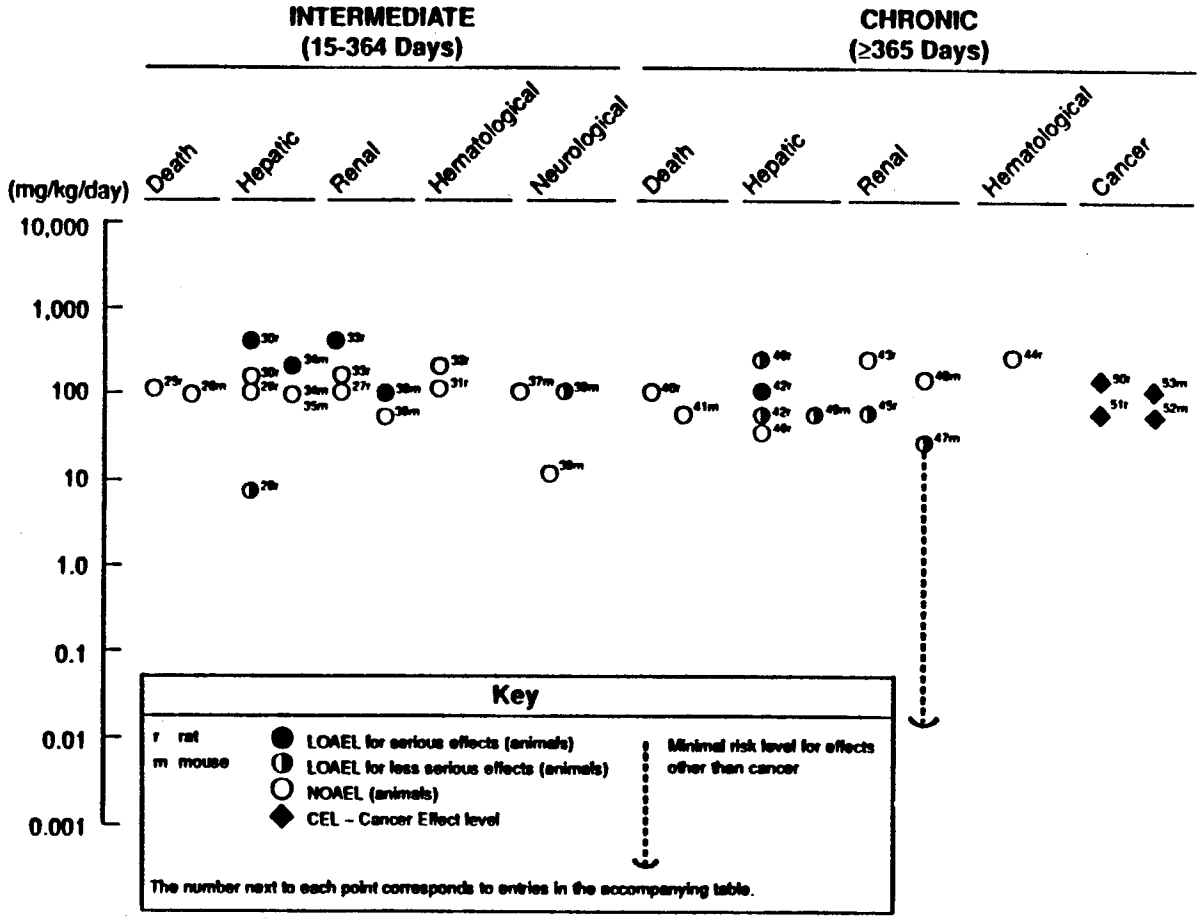

FIGURE 2-1. (con't)

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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:

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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

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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.

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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.

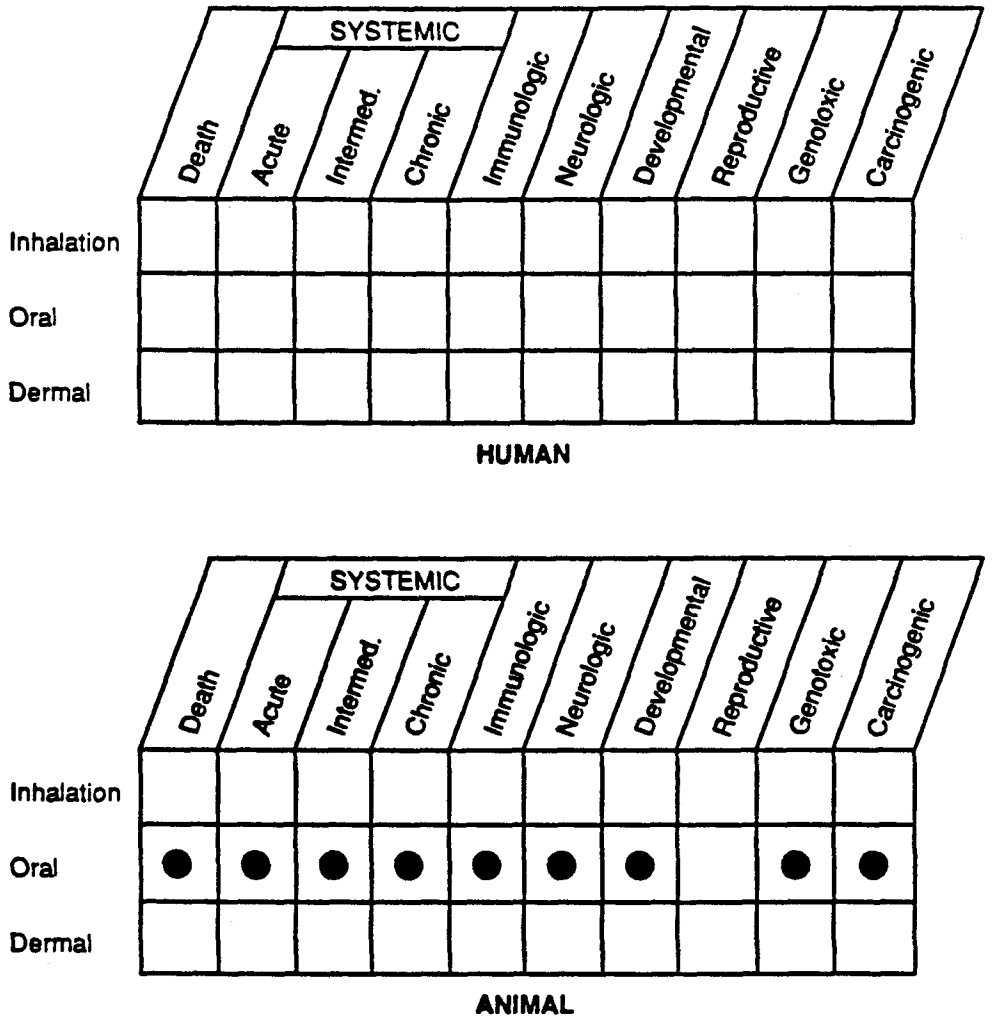

FIGURE 2-2. Existing Information on Health Effects of BDCM

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.