

Toxicological Profile for Bromodichloromethane

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;
- (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 that present a significant risk to human health of acute, intermediate, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel 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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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

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December 1989	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Bromodichloromethane (CHBrCl₂; Chemical Abstracts Service [CAS] Registry Number 75-27-4) belongs to a group of chemicals referred to as trihalomethanes; the other chemicals in this group are chloroform, bromoform, and dibromochloromethane. The major source of bromodichloromethane in the environment is its formation as a byproduct during the chlorination of water containing organic matter and bromide. Approximately 86% of the population in the United States are served by public water systems that use chlorine or chlorine-containing compounds to disinfectant water supplies; the disinfection helps protect against microbial contaminants that might otherwise cause serious water-borne diseases when exposure occurs (EPA 2016, 2015d; USGS 2010a).

The most likely source of exposure to bromodichloromethane is from chlorinated waters supplied to homes, work, and public places. Exposure can occur through ingestion, inhalation of vapors during showering or bathing, and dermal absorption during water-related activities. Bromodichloromethane levels in drinking water in the United States have been reported to range from below the detection limit to 183 µg/L (EPA 2005b). Another survey reported mean concentrations ranging from 1.0 to 20.3 µg/L (Savitz et al. 2006). Ingestion of food sources contaminated with bromodichloromethane is not an important exposure pathway because it is not frequently detected in foodstuffs and levels are typically very low. Very low levels of bromodichloromethane have been detected in ambient air, and this is not likely an exposure route of concern for the general population. The maximum arithmetic mean concentration of bromodichloromethane in outdoor air samples at 83 locations across the United States was 0.033 ppbv in 2018 (EPA 2019).

Blood bromodichloromethane level is the most commonly used biomarker of exposure; alveolar air and urine levels of bromodichloromethane are also reliable biomarkers. Studies comparing the relative contribution of different activities to blood bromodichloromethane levels found that showering was the largest contributor, followed by bathing, and then consumption of drinking water (Backer et al. 2000; Nuckols et al. 2005).

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1.2 SUMMARY OF HEALTH EFFECTS

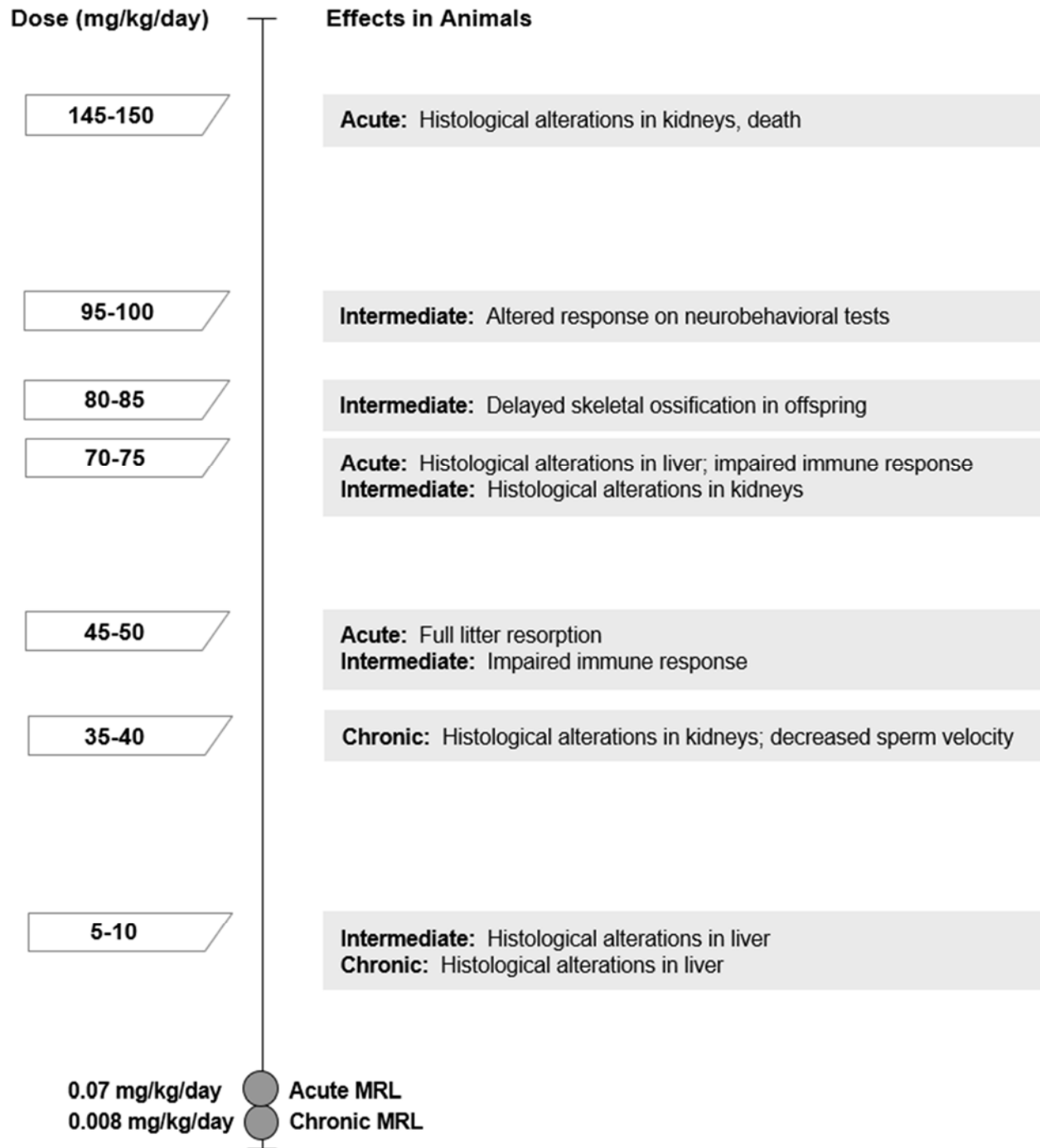
Information on the toxicity of bromodichloromethane comes primarily from oral studies in laboratory animals. Although a large number of epidemiology studies have examined the toxicity of trihalomethanes, only a small percentage have analyzed the risks associated with exposure to bromodichloromethane. These studies evaluated hepatic, reproductive, developmental, and cancer endpoints. Over 60 laboratory animal toxicity studies have been identified. More than 90% of them involve oral exposure, and no dermal studies were identified. In general, the effects observed in laboratory animal studies occurred at exposure levels that are much higher than levels typically associated with residential or environmental exposures to bromodichloromethane.

As illustrated in Figure 1-1, the most sensitive effects appear to be liver damage, kidney damage, decreases in sperm velocity, impaired immune response, and increases in resorptions. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans
- Renal effects are a suspected health effect for humans
- Immunological effects are a suspected health effect for humans
- The data are inadequate to conclude whether reproductive effects will occur in humans
- Developmental effects are a presumed health effect for humans

Hepatic Effects. Results from numerous inhalation and oral animal studies support the identification of the liver as a presumed target in humans. Oral studies in rats and mice have found marked increases in serum enzymes (e.g., alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase) and centrilobular hepatocellular vacuolar degeneration in rats following acute exposure (Condie et al. 1983; Keegan et al. 1998; Lilly et al. 1994, 1996; Thornton-Manning et al. 1994). Intermediate- and chronic-duration exposures have resulted in hepatocellular fatty degeneration or metamorphosis (Aida et al. 1992; NTP 1987). Hepatocellular degeneration was also observed in an acute-duration mouse inhalation study (Torti et al. 2001). Bile duct damage (proliferation, cholangiofibrosis, hyperplasia) has also been observed in rats following intermediate and chronic exposure (Aida et al. 1992; NTP 1987); these effects occur at higher doses than the hepatocellular effects. Animal studies found oral route-specific differences in toxicity. The available data suggest a higher toxicity when bromodichloromethane was administered via gavage in an oil vehicle compared to an aqueous vehicle (Lilly et al. 1994) and was greater when administered via gavage compared to dietary exposure (bromodichloromethane was

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Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Bromodichloromethane

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microencapsulated and added to the diet) (Aida et al. 1992). Only one epidemiology study examined hepatic outcomes and did not find a significant association between blood bromodichloromethane levels and alterations in serum alanine aminotransferase levels (Burch et al. 2015).

Renal Effects. Identification of the kidney as a suspected target in humans comes from the results of inhalation and oral studies in rats and mice. Renal tubular degeneration has been observed in mice following acute- and intermediate-duration inhalation exposure (Torti et al. 2001) and following acute-, intermediate-, and chronic-duration oral exposure (George et al. 2002; Lilly et al. 1994, 1996; NTP 1987). Acute oral studies at relatively high doses also reported increases in blood urea nitrogen, urinary glucose, and urinary protein levels (Lilly et al. 1996). No human studies examined this endpoint.

Immune Effects. Several studies have reported impaired immune responses in rats orally administered bromodichloromethane for acute or intermediate durations. Decreased immune responses to humoral and cell-mediated immune stimulants were observed in animals receiving gavage doses of bromodichloromethane (French et al. 1999; Munson et al. 1982). A comparison of lowest-observed-adverse-effect level (LOAEL) values identified in rats and mice suggest that rats may be more sensitive than mice to the immunotoxicity of bromodichloromethane. One epidemiological study examined immune endpoints and found inverse associations between bromodichloromethane levels in exhaled breath and several biomarkers of immune function (Vlaanderen et al. 2017).

Reproductive Effects. Three epidemiology studies evaluated potential reproductive targets. A decrease in menstrual cycle length, specifically the follicular phase length, was significantly associated with bromodichloromethane drinking water levels (Windham et al. 2003). Another epidemiology study found a significant association between a shorter time-to-pregnancy and an estimate of bromodichloromethane levels intake from tap water (MacLehose et al. 2008). The third study did not find an association between alterations in sperm parameters and blood bromodichloromethane levels (Zeng et al. 2013).

Although several laboratory animal studies have examined potential reproductive endpoints, additional data are needed to evaluate the adversity of the observed effects. A diminished response to luteinizing hormone levels in pregnant rats (Bielmeier et al. 2001, 2004, 2007) and decreased sperm velocity (with no change in the percentage of motile or progressive motile sperm) (Klinefelter et al. 1995) were observed in rats. It is unclear if these effects would result in a decrease in reproductive function. A 2-generation study did not find alterations in fertility in rats (Christian et al. 2001b).

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Developmental Effects. Epidemiology and laboratory animal studies have reported developmental effects associated with bromodichloromethane exposure. Inconsistent results have been observed in epidemiology studies with some studies finding decreases in birth weight and increased risk of small for gestational age (Summerhayes et al. 2012; Rivera-Núñez and Wright 2013; Wright et al. 2004) and other studies not finding these effects (Cao et al. 2016; Danileviciute et al. 2012; Hoffman et al. 2008). Epidemiology studies have also found increases in the risk of stillbirth (King et al. 2000) and spontaneous abortions (Waller et al. 1998). Other studies have found no associations with the risk of stillbirths (Rivera-Núñez et al. 2018) or cardiovascular defects (Wright et al. 2017).

In rats, increases in the occurrence of full-litter resorptions have been found following early gestational gavage administration of bromodichloromethane (Bielmeier et al. 2001; Narotsky et al. 1997). A delay in skeletal ossification was observed in rats exposed to bromodichloromethane in drinking water (Christian et al. 2001a; Ruddick et al. 1983).

Cancer Effects. The carcinogenic potential of bromodichloromethane has been evaluated in three epidemiological study and several chronic-duration oral studies in rats and mice. Epidemiological studies did not find an increased risk of colorectal cancer (Bove et al. 2007) or colon cancer (Jones et al. 2019) associated with bromodichloromethane levels in public water supplies; Jones et al. (2019) did find an association for rectal cancer. The third study did not find an association between blood bromodichloromethane levels and total cancer deaths (Min and Min 2016). Gavage administration of relatively high doses has resulted in increases in neoplastic lesions in the large intestine and kidneys of rats (NTP 1987) and livers of mice (NTP 1987). No increases in tumor incidences were observed in drinking water studies testing lower doses (George et al. 2002; NTP 2006) or at slightly higher doses in a dietary exposure study (Aida et al. 1992).

The U.S. Department of Health and Human Services categorized bromodichloromethane as reasonably anticipated to be a human carcinogen (NTP 2016), EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002), and the International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (IARC 2016).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-2, the limited available inhalation data for bromodichloromethane suggest that the liver and

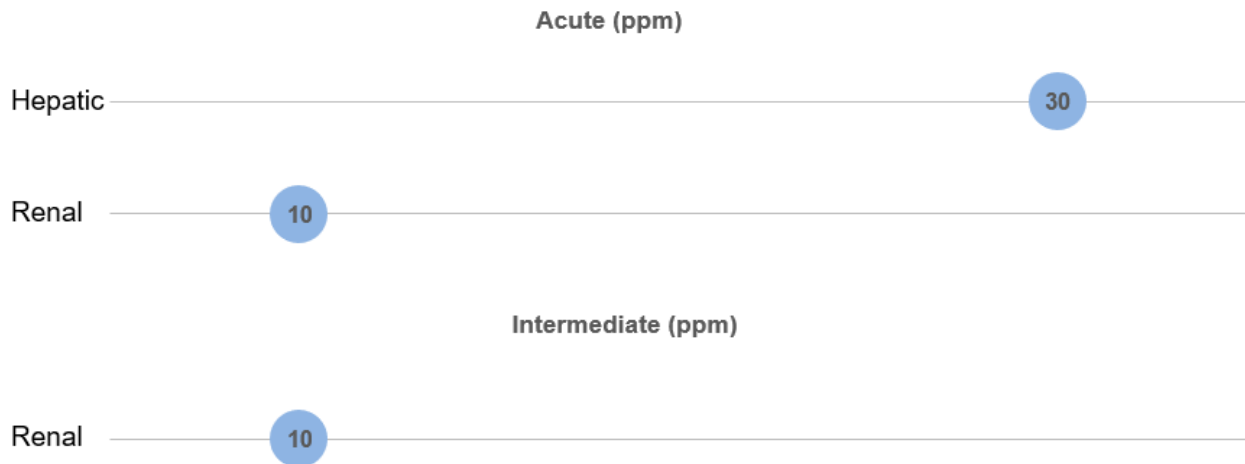
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kidney are sensitive targets of toxicity. However, other potentially sensitive endpoints, particularly developmental toxicity, have not been examined for this exposure route.

The oral database was considered adequate for derivation of acute- and chronic-duration oral MRLs for bromodichloromethane. As with inhalation exposure, the liver and kidney are sensitive targets following oral exposure to bromodichloromethane. Developmental, immunological, and reproductive endpoints also have relatively low LOAEL values, as illustrated in Figure 1-3. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of Bromodichloromethane – Inhalation

The kidney is the most sensitive target of bromodichloromethane inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



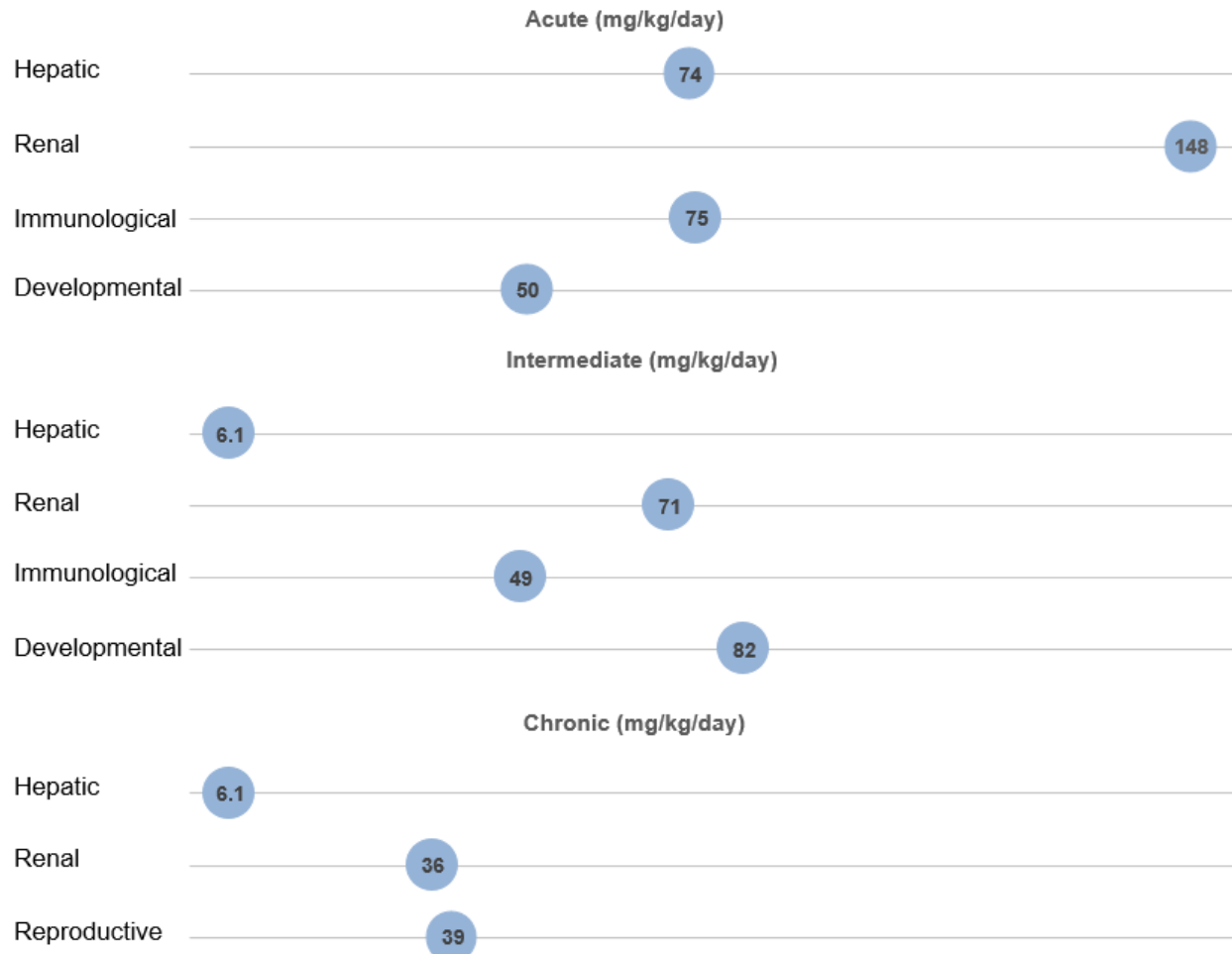
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Figure 1-3. Summary of Sensitive Targets of Bromodichloromethane – Oral

The liver is the most sensitive target of bromodichloromethane oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.

No reliable dose response data were available for humans.



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Table 1-1. Minimal Risk Levels (MRLs) for Bromodichloromethane^a

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.07	Full-litter resorption in rats	7.15 (BMDL ₀₅)	100	Narotsky et al. 1997
Intermediate	Insufficient data for MRL derivation; chronic MRL considered protective for intermediate duration exposure				
Chronic	0.008	Hepatocellular fatty degeneration in rats	0.78 (BMDL ₁₀)	100	Aida et al. 1992

^aSee Appendix A for additional information.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of bromodichloromethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤ 14 days), intermediate (15–364 days), and chronic (≥ 365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to bromodichloromethane, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to bromodichloromethane was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, and animal oral studies are presented in Table 2-3 and Figure 2-3; no dermal data were identified for bromodichloromethane.

Levels of significant exposure (LSEs) for each route and duration 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. "Serious" effects are those that

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evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of bromodichloromethane are indicated in Table 2-3 and Figure 2-3.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of bromodichloromethane have been evaluated in epidemiological and laboratory animal studies. As illustrated in Figure 2-1, most of the health effects data come from oral exposure studies in animals. Animal data are available for each health effect category and exposure duration category. The most examined endpoints were body weight (approximately 70% of the animal studies examined this endpoint), hepatic (approximately 50%), and renal (approximately 50%). Only five animal studies evaluated toxicity following inhalation exposure and these studies examined a limited number of endpoints (body weight, hepatic, renal, ocular, and other noncancer). The small number of available observational epidemiological studies only examined hepatic, immunological, reproductive, developmental, and cancer endpoints. Although some epidemiological studies suggest associations between bromodichloromethane exposure and an adverse health outcome, most of the studies are cross-sectional in design and do not establish causality. The epidemiological studies used several biomarkers of exposure including levels of bromodichloromethane measured in municipal water, blood bromodichloromethane levels, and levels of bromodichloromethane in exhaled breath. These biomarkers assess recent exposure, particularly the blood and exhaled breath since bromodichloromethane is rapidly excreted; most studies did not evaluate historical exposures. Another limitation of the epidemiological studies is that they involve co-exposure to other disinfection byproducts, which have similar targets of toxicity. Most

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studies did not statistically adjust for co-exposure to other compounds (e.g., chloroform, dibromochloromethane); thus, it is difficult to evaluate whether the observed effect was related to bromodichloromethane exposure or total exposure to disinfection byproducts, including other trihalomethanes.

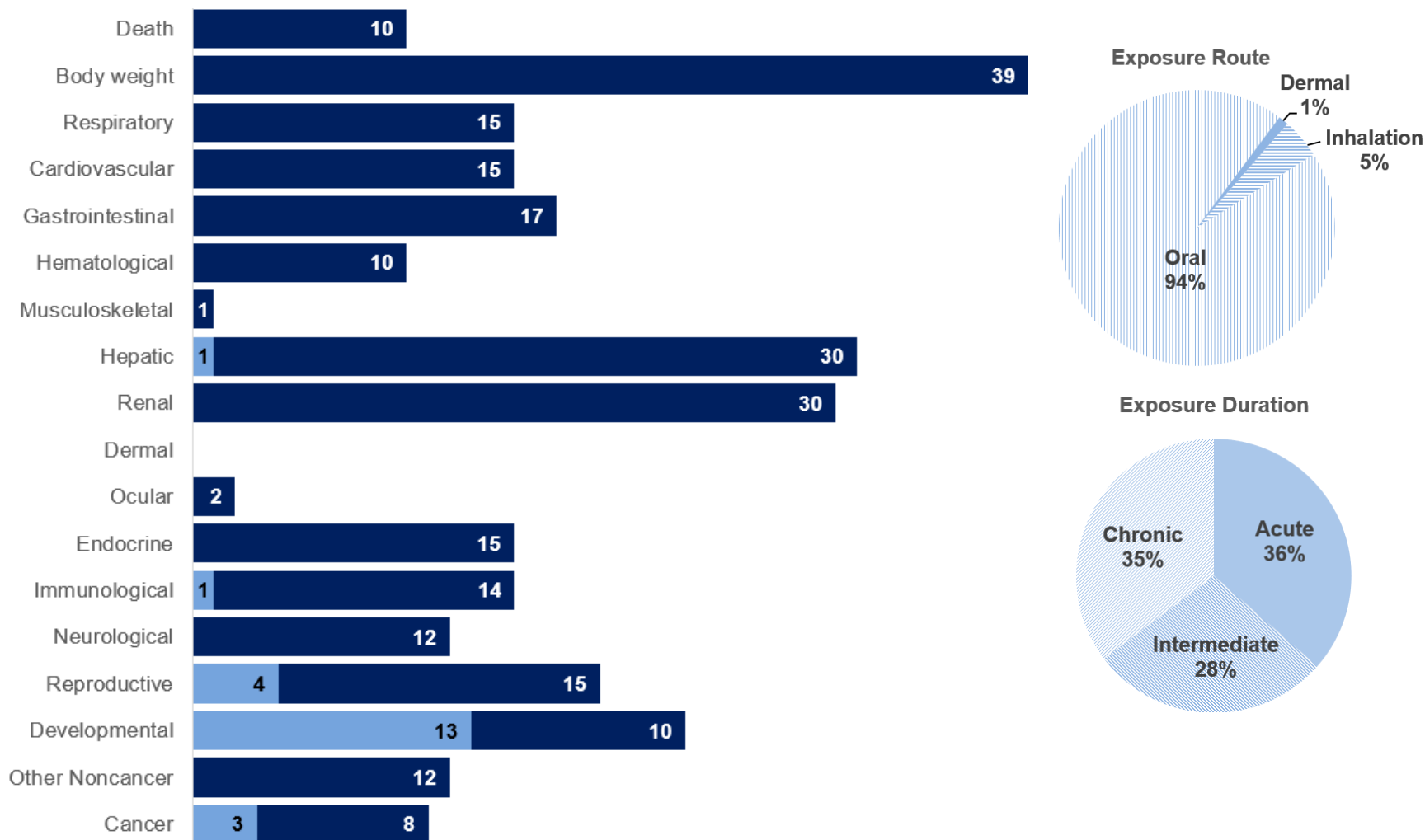
The human and animal studies suggest several sensitive targets of bromodichloromethane toxicity:

- **Hepatic Endpoints:** Hepatic effects are a presumed health effect for humans based on limited evidence in humans and strong evidence in mice following acute inhalation exposure and in rats and mice following acute, intermediate, and chronic oral exposure. The liver effects include increases in serum enzymes, increases in liver weight, hepatocellular degeneration, and bile duct damage.
- **Developmental Endpoints.** Developmental effects are a presumed health effect for humans based on strong evidence from acute and intermediate oral exposures in rats. The most sensitive developmental endpoint was full-litter resorption in rats acutely administered bromodichloromethane via gavage. Inconsistent results have been observed in epidemiology studies, with some studies finding decreases in birth weight and increased risk of small for gestational age, and other studies not finding developmental effects.
- **Renal Endpoints:** Renal effects are a suspected health effect for humans based on moderate evidence in rats and mice following inhalation and oral exposure. The main effect observed was renal tubular degeneration; high acute oral doses also reported increases in blood urea nitrogen, urinary glucose, and urinary protein levels.
- **Immune Endpoints.** Immunological effects are a suspected health effect for humans based on moderate evidence in rats following acute and intermediate oral exposure. Decreased immune responses to stimulants were observed in rats.
- **Reproductive Endpoints.** Data are inadequate to conclude whether reproductive effects will occur in humans. Inconsistent results have been observed in animal studies examining potential reproductive endpoints, with some studies reporting effects (alterations in reproductive hormone levels and decreases in sperm velocity) and others reporting no effects (no alterations in histopathology, no changes in sperm motility, and no alterations in fertility in a 2-generation rat study).
- **Other Endpoints.** Alterations in body weight and gastrointestinal, hematological, ocular, endocrine, and neurological effects have also been observed in inhalation and/or oral exposure studies in laboratory animals; however, these do not appear to be sensitive targets of bromodichloromethane toxicity.

2. HEALTH EFFECTS

Figure 2-1. Overview of the Number of Studies Examining Bromodichloromethane Health Effects

Most studies examined the potential body weight, hepatic, and renal effects of bromodichloromethane
 Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 84 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
Bove et al. 2007 Case-control study of residents living in Monroe County, New York; 128 cases and 253 controls	Exposure: Mean and median BDCM in sampled tap water were 8.72 and 8.48 µg/L. Logistic regression adjustments: alcohol consumption, beta carotene, total calories	Cancer effects: No association between BDCM concentrations in water samples and the risk of rectal cancer (OR 1.15, 95% CI 1.00–1.32).
Burch et al. 2015 Cross-sectional study of 2,781 1999–2006 NHANES adult participants (average age of 40 years, 53% women)	Exposure: Median BDCM in blood was 1.5 pg/mL (range of 0.2–86 pg/mL); median BDCM level in tap water was 4 µg/L (range of 0.03–52 µg/L). Logistic regression adjustments: age, race, smoking, body mass index, alcohol consumption, self-reported high blood pressure, diastolic blood pressure, total cholesterol, albumin, C-reactive protein	Hepatic effects: No association between blood BDCM levels above the median and the risk of elevated alanine aminotransferase levels were found (OR 1.01; 95% CI 0.67–1.51). No significant correlation (p=0.429) between blood BDCM levels and alanine aminotransferase activity.
Cao et al. 2016 Retrospective cohort study of 1,184 pregnant women in China	Exposure: Geometric mean BDCM levels in blood during late pregnancy was 1.5 ng/L (95% CI 1.4–1.6). Logistic regression adjustments: prenatal BMI, weight gain during pregnancy, infant's gender, parity, study city, maternal age, gestational age, education, birth length, SGA, household income	Developmental effects: BDCM was inversely associated with birth length. The estimated mean decrease was 0.15 cm (95% CI -0.29 to -0.01) for the highest (>4.8 ng/L) vs. lowest (<0.5 ng/L) exposure group (p=0.04 for trend). No association with birth weight or gestational age (p=0.18 and 0.93, respectively, for trend).
Chen et al. 2019 Longitudinal study of 451 mother-neonate pairs in China	Exposure: maternal blood BDCM measured in early pregnancy; mean of 1.1 ng/L Statistical analysis adjustments: gestational age, infant's sex, maternal age, pre-pregnancy BMI, maternal education, secondhand smoking, alcohol consumption	Developmental effects: Inverse association between maternal BDCM levels and neonatal neurological assessment test scores (measured at 3 days of age) in male and female infants combined (β -0.47, 95%CI -0.89 to -0.05) and males only (β -0.88, 95%CI -1.52 to -0.24); no associations in females only (β -0.11, 95%CI -0.66–0.44).

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
Danileviciute et al. 2012 Nested case-control study of 682 pregnant women in Lithuania	Exposure: Internal dose of trihalomethane ($\mu\text{g}/\text{day}$) estimated from daily water ingestion, showering, and bathing recollection data; daily uptake range of 0.0001–0.34 $\mu\text{g}/\text{day}$. Logistic regression adjustments: marital status, square gestational age, parity, maternal education, maternal and paternal smoking, alcohol consumption, BMI, blood pressure, ethnic group, pregnancy history, infant gender, birth year	Developmental effects: BDCM intake (entire pregnancy or individual trimesters) was not associated with low birth weight (OR 1.26, 95% CI 0.58–2.72) or SGA (OR 1.31, 95% CI 0.82–2.09). Non-conjugator phenotype for glutathione S-transferase increased risk for low birth weight, but not significantly.
Dodds and King 2001 Retrospective cohort study of 49,842 women in Canada	Exposure: BDCM in municipal water; concentration range categorized by quartile: - Q1: <5 $\mu\text{g}/\text{L}$ - Q2: 5–9 $\mu\text{g}/\text{L}$ - Q3: 10–19 $\mu\text{g}/\text{L}$ - Q4: ≥ 20 $\mu\text{g}/\text{L}$ Logistic regression adjustments: maternal age, parity, maternal smoking, neighborhood family income	Developmental effects: BDCM concentrations ≥ 20 $\mu\text{g}/\text{L}$ were associated with increased risk of neural tube defects based on 10 cases; the relative risk (RR) was 2.5 (95% CI 1.2–5.1). The risk for cardiovascular anomalies at BDCM ≥ 20 $\mu\text{g}/\text{L}$ was decreased (RR 0.3, 95% CI 0.2–0.7); there was no association between BDCM and risk of cleft defects (RR 0.6, 95% CI 0.2–1.9) at ≥ 20 $\mu\text{g}/\text{L}$.
Grazuleviciene et al. 2013 Prospective cohort study of 3,074 women in Lithuania	Exposure: Internal dose of trihalomethanes ($\mu\text{g}/\text{day}$) estimated from daily water ingestion, showering, and bathing recollection data during the first trimester of pregnancy. BDCM intake categorized by tertiles: - T1: 0.000–0.013 $\mu\text{g}/\text{day}$ - T2: 0.013–0.051 $\mu\text{g}/\text{day}$ - T3: 0.051–0.436 $\mu\text{g}/\text{day}$ Logistic regression adjustments: age, BMI, chronic disease, alcohol consumption, fetus number, previous premature birth, infant sex	Developmental effects: Exposure to BDCM during the first month of pregnancy increased the risk of congenital heart anomalies (OR 2.16, 95% CI, 1.05–4.46 for T3). No association during second (OR 1.54, 95% CI 0.78–3.04) or third (OR 1.32, 95% CI 0.68–2.56) month of pregnancy or during the first trimester as a whole (OR 1.82, 95% CI 0.89–3.69).

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
		<p>No association with congenital musculoskeletal or urogenital anomalies were found. The ORs for the T3 groups:</p> <p>Musculoskeletal anomalies</p> <ul style="list-style-type: none"> first month OR 0.73, 95% CI 0.29–1.84 second month OR 0.92, 95% CI 0.39–2.17 third month OR 1.70, 95% CI 0.78–3.71 first trimester OR 1.29, 95% CI 0.57–2.92 <p>Urogenital anomalies</p> <ul style="list-style-type: none"> first month OR 2.27, 95% CI 0.69–7.43 second month OR 1.81, 95% CI 0.66–4.96 third month OR 1.85, 95% CI 0.68–5.07 first trimester OR 2.87, 95% CI 0.92–8.99
<p>Hoffman et al. 2008</p> <p>Cross-sectional study of 2,766 pregnant women from three U.S. communities</p>	<p>Exposure: Average residential BDCM concentration in community with moderate levels of chlorinated disinfection byproducts:</p> <ul style="list-style-type: none"> - T1: 8.2–11.8 µg/L - T2: 11.9–14.1 µg/L - T3: 14.2–28.5 µg/L <p>Average residential BDCM concentration in community with moderate levels of brominated disinfection byproducts:</p> <ul style="list-style-type: none"> - T1: 15.8–20.1 µg/L - T2: 20.2–22.9 µg/L - T3: 23–29.2 µg/L <p>Bayesian adjustments: other disinfection byproducts, maternal age, race/ethnicity, income, education, employment status, pre-pregnancy BMI, parity, caffeine intake</p>	<p>Developmental effects: No association between average residential BDCM concentration and risk of SGA in the community with moderate levels of chlorinated disinfection byproducts (OR 1.5, 95% CI 0.6–3.7 for T3) or moderate levels of brominated disinfection byproducts (OR 0.9, 95% CI 0.4–2.4 for T3).</p>

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
<p>Iszatt et al. 2011</p> <p>Case-control study of 468 cases with hypospadias and 485 controls in England</p>	<p>Exposure: Trihalomethanes intake based on estimates of individual water consumption and use. BDCM intake categorized by quartiles:</p> <ul style="list-style-type: none"> - Q1: 0 µg/day - Q2: >0–1.0 µg/day - Q3: 2–5 µg/day - Q4: 6–50 µg/day <p>Logistic regression adjustments: family income, birth weight, folate supplement use during pregnancy, maternal smoking during weeks 6 through 18 of pregnancy, maternal occupational exposure to phthalates</p>	<p>Developmental effects: After adjustment, intake of ≥6 µg/day BDCM was associated with an increased risk of hypospadias (OR 1.65, 95% CI 1.02–2.69). However, there was no dose-response relationship (p=0.13 for trend).</p> <p>Concentration of BDCM in water was not associated with hypospadias for OR 1.05 (95% CI 0.65–1.68) for Q4. However, elevated risk of hypospadias was associated with consumption of cold tap water at home, total water, bottled water, and total fluid suggesting other factors may have influenced the risk.</p>
<p>Jones et al. 2019</p> <p>Prospective cohort study of 15,53 women reporting public water source for >10 years and participating in the Iowa Woman's Health Study</p>	<p>Exposure: BDCM in municipal water; concentration range categorized by quartile:</p> <ul style="list-style-type: none"> - Q1: <0.25 µg/L - Q2: 0.25–1.16 µg/L - Q3: 1.17–3.78 µg/L - Q4: >3.78 µg/L <p>Statistical analysis adjustments: age, physical activity, smoking status, NO₃-N level</p>	<p>Cancer effects: Association between BDCM concentration in municipal water and risk of rectal cancer in Q2 (HR 1.76, 95%CI 1.10–2.84), Q3 (HR 1.99, 95%CI 1.22–3.25), and Q4 (HR 1.87, 95%CI 1.17–3.00).</p> <p>No association between BDCM concentration in municipal water and the risk of colon cancer (Q4 HR 1.16, 95%CI 0.94–1.45).</p>
<p>King et al. 2000</p> <p>Retrospective cohort study of 49,756 women in Canada</p>	<p>Exposure: BDCM in municipal water; concentration range categorized by quartile:</p> <ul style="list-style-type: none"> - Q1: <5 µg/L - Q2: 5–9 µg/L - Q3: 10–19 µg/L - Q4: ≥20 µg/L <p>Logistic regression adjustments: maternal age, parity, maternal smoking, infant's sex, neighborhood family income</p>	<p>Developmental effects: Exposure to ≥20 µg/L BDCM almost doubled the risk of stillbirth (RR 1.98, 95% CI, 1.23–3.49).</p> <p>Analysis of continuous data showed a 29% increase in risk for stillbirth with each 10 µg/L BDCM (95% CI 1.10–1.53).</p> <p>Risk of unexplained stillbirth was not associated with BDCM (Q4 RR 1.35, 95% CI 0.57–3.19) but risk of stillbirth caused by asphyxia was increased 32% per 10 µg/L BDCM (95% 1.00–1.74).</p>

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Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
<p>MacLehose et al. 2008</p> <p>Prospective cohort study of 1,315 women in three metropolitan areas</p>	<p>Exposure: Brominated disinfection byproducts measured in water samples were used to estimate four exposure metrics: tap water concentration, amount ingested through drinking, quantity that reached the bloodstream through inhalation and dermal exposure while showering or bathing, and integrated measure of the amount in the bloodstream through ingestion and showering/bathing.</p> <p>Statistical analysis adjustments: maternal age, race, ethnicity, education, marital status, income, smoking, alcohol use, caffeine consumption, BMI, age at menarche, employment status, diabetes, vitamin use, and total water consumption (total ounces of tap water plus bottled water)</p>	<p>Reproductive effects: For the ingested metric, an association between time to pregnancy and BDCM levels were found; the OR at highest concentration (≥ 12.8 $\mu\text{g}/\text{day}$) was 1.5 (95% CI 1.2–1.9); this would be indicative of a shorter time to pregnancy.</p> <p>No associations between time to pregnancy and BDCM exposure were found for the other three metrics; the adjusted ORs in the highest exposure groups were 1.1 (95% CI 0.9–1.4), 1.1 (95% CI 0.9–1.3), and 1.1 (0.9–1.4) for the tap water, showering/bathing, and integrated exposure metrics, respectively.</p>
<p>Min and Min 2016</p> <p>Cross-sectional study of 933 1999–2004 NHANES adult participants; not diagnosed with cancer and 19 died from cancer</p>	<p>Exposure: Blood bromodichloromethane levels:</p> <ul style="list-style-type: none"> - T1: <1.00 $\mu\text{g}/\text{L}$ - T2: 1.00–2.70 $\mu\text{g}/\text{L}$ - T3: >2.71 $\mu\text{g}/\text{L}$ <p>Statistical analysis adjustments: age, sex, race/ethnicity, education family income, smoking status, alcohol consumption status, moderate physical activity, BMI, total cholesterol, hypertension, diabetes</p>	<p>Cancer effects: No association between total cancer mortality and BDCM levels ($p=0.0869$).</p>

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
<p>Rivera-Núñez and Wright 2013</p> <p>Retrospective cohort study of 672,120 live births in the United States</p>	<p>Exposure: BDCM in public water systems during the second and third trimesters. Mean BDCM concentration by trimester: 6 µg/L in second trimester and 6.1 µg/L in 3rd trimester.</p> <p>Logistic regression adjustments: maternal age, race/ethnicity, education, smoking, parity, adequacy of prenatal care, prenatal source of payment, income, marital status, maternal medical and reproductive health factors, season, sum of four trihalomethanes, sum of five haloacetic acids</p>	<p>Developmental effects: BDCM in 3rd trimester associated with reductions in mean birth weight (49–63 g) in unadjusted models, but there was no dose-response relationship; associations remained in adjusted models but the magnitudes of reductions were considerably lower.</p> <p>3rd trimester BDCM was not associated with increased SGA (OR 0.91, 95% CI 0.83–1.00).</p> <p>2nd trimester BDCM was not associated with increased preterm delivery (OR 1.09, 95% CI 0.97–1.23).</p>
<p>Rivera-Núñez et al. 2018</p> <p>Case control study of 2,460 stillbirth cases and 24,600 controls; mothers lived in a Massachusetts town with complete public water source and disinfection type data</p>	<p>Exposure: BDCM in public water systems during the second trimester. Mean BDCM concentration was 6.4 µg/L. BDCM concentration categorized into tertiles:</p> <ul style="list-style-type: none"> - T1: ≤4.1 µg/L - T2: >4.1–7.2 µg/L - T3: >7.2–49.5 µg/L <p>Statistical analysis adjustments: maternal race, education, marital status, source of water, sum of four trihalomethanes, sum of five haloacetic acids</p>	<p>Developmental effects: No associations between BDCM and all causes of stillbirths.</p> <p>Associations between BDCM and unexplained stillbirths for T2 (OR 1.78, 95%CI 1.20–2.63) and T3 (OR 1.51, 95%CI 1.01–2.27).</p>
<p>Summerhayes et al. 2012</p> <p>Retrospective cohort study of 314,982 births in Australia</p>	<p>Exposure: BDCM in water distributed by public utility company. BDCM concentration range for third trimester categorized by deciles:</p> <ul style="list-style-type: none"> - D1: 2.95–9.78 µg/L - D10: 21.96–52.55 µg/L <p>Logistic binomial adjustments: infant's sex, year of birth, season of birth, duration of pregnancy at first prenatal care visit, maternal smoking during pregnancy, maternal age, indigenous mother, maternal country of birth, previous pregnancy, preexisting diabetes, preexisting hypertension, gestational diabetes, preeclampsia, socioeconomic status</p>	<p>Developmental effects: SGA associated with interquartile range increase in 3rd trimester BDCM of 5 µg/L (RR 1.02, 95% CI, 1.01–1.04).</p> <p>3rd trimester analysis by deciles showed associations only for D9 (19.05–21.96 µg/L) (RR 1.06, 95% CI, 1.00–1.12) and D10 (RR 1.10, 95% CI, 1.04–1.16).</p> <p>In general, larger associations were seen in nonsmokers than in smokers.</p>

2. HEALTH EFFECTS

Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
Vlaanderen et al. 2017 Experimental study of 29 men and 30 women swimming in a chlorinated pool for 40 minutes	Exposure: Concentration of BDCM in exhaled breath after swimming was 2.2 µg/m ³ . Statistical analysis adjustments: sex, age, BMI	Immunological effects: Inverse associations between BDCM in exhaled breath and serum levels of C-X-C motif chemokine 10, C-C motif chemokine 22, C-reactive protein, and vascular endothelial growth factor. Association between exhaled breath BDCM and interleukin-1rA levels.
Waller et al. 1998 Prospective cohort study of 5,144 pregnant women in California	Exposure: BDCM levels in water distributed by public utility companies and reported intakes (glasses cold water and hot water per day) at 8 weeks of gestation. High personal exposure to BDCM was defined as drinking ≥5 glasses of cold tap water per day and first trimester BDCM water level of ≥18 µg/L. Logistic regression model adjustments: gestational age at interview, maternal age, history of pregnancy loss, maternal race, employment during pregnancy, cigarette smoking	Developmental effects: Association between high personal exposure to BDCM and spontaneous abortion, OR of 2.0 (95% CI 1.2–3.5). The OR adjusted for exposure to other trihalomethanes (chloroform, bromoform, chlorodibromomethane) was 3.0 (95% CI 1.4–6.6)
Windham et al. 2003 Prospective cohort study of 401 women	Exposure: Estimated BDCM levels based on reported daily water consumption, number and duration of showers taken per week, and average levels of BDCM in tap water; estimated BDCM exposure levels were not reported Statistical analysis adjustments: Age, race, BMI, income, pregnancy history, caffeine and alcohol consumption, smoking	Reproductive effects: Decrease in the length of the menstrual cycle with increasing exposures; the adjusted OR was -0.74 (95% CI -1.5 to -0.02) for the highest quartile of exposure (≥16 µg/L). Decrease in follicular phase length observed (-0.80, 95% CI -1.5 to -0.08) for the highest quartile of exposure.
Wright et al. 2004 Retrospective cohort study of 196,000 births in the United States	Exposure: BDCM in public water systems and private wells during the third trimester Linear and logistic regression adjustments: diabetes, median household income, infant sex, adequacy of prenatal care, maternal race, maternal education, maternal cigarette smoking, maternal age, parity, previous infant	Developmental effects: Exposure to >5 µg/L BDCM was associated with reductions in birth weight (12 g) and longer gestational age (0.5–0.6 days). Association between BDCM and risk of SGA; OR 1.1 (95% CI 1.07–1.14) for subjects with BDCM levels of >5–13 µg/L and OR 1.15, (95% CI 1.08–1.22) for subjects with BDCM levels of 14–46 µg/L.

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Table 2-1. Health Effects in Humans Exposed to Bromodichloromethane (BDCM)

Reference and study population	Exposure	Outcomes
	weighing $\geq 4,000$ g, previous preterm delivery, maternal medical history	Inverse association for preterm delivery; OR 0.89 (95% CI 0.85–1.10) for >5 –13 $\mu\text{g/L}$ and OR 0.92 (95% CI 0.85–0.99) for 14–46 $\mu\text{g/L}$.
Wright et al. 2017 Case-control study of 904 infants born with nonchromosomal congenital anomalies of the heart and circulatory system and 9,040 matched controls	Exposure: Public water supply BDCM levels, mean concentration 6.85 $\mu\text{g/L}$. Conditional logistic regression adjustments: type of water sources and treatment, health index, infant birth weight, town-level income, number of prenatal visits, maternal reproductive risk factors	Developmental effects: No associations between maternal BDCM exposure and risk of all cardiovascular defects, conotruncal heart defects, transposition of the great arteries, tetralogy of Fallot, arterial septal defects, ventricular septal defects, or pulmonary stenosis.
Zeng et al. 2013 Cross-sectional study of 401 men in China seeking semen examinations	Exposure: Mean and median blood BDCM levels were 1.98 and 1.69 ng/L . Statistical analysis adjustments: age, BMI, abstinence time, alcohol use, smoking status	Reproductive effect: No dose-related correlations between blood bromodichloromethane levels and sperm concentration (p for trend=0.61), sperm count (p for trend=0.44), or sperm motility (p for trend=0.76). No association between blood BDCM levels and serum testosterone levels were found ($p=0.70$).

BDCM = bromodichloromethane; BMI = body mass index; CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; SGA = small for gestational age

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Table 2-2. Levels of Significant Exposure to Bromodichloromethane – Inhalation

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Mouse (C57BL/6) 6 M	6 hours/day 7 days/week 1 week	1, 10, 30, 100, 150	LE, BW, OW, HP	Death Bd wt Hepatic Renal Ocular Other noncancer (urinary bladder)	10 10 1 10 150	30 30 10 30	30	2/6, 1/6, 3/6 deaths in wild type strain at 30, 100, and 150 ppm, respectively Decreased body weight gain Centrilobular hepatocellular degeneration at ≥30 ppm and hepatocellular necrosis at ≥100 ppm Tubular degeneration and nephrosis Mild eye irritation
Torti et al. 2001									
2	Mouse (FVB/N) 6 M	6 hours/day 7 days/week 1 week	1, 10, 30, 100, 150	LE, BW, OW, HP	Death Bd wt Hepatic Renal Other noncancer (urinary bladder)	100 1 1 150	10 10	30	2/6, 4/6, 6/6 deaths at 30, 100, and 150 ppm, respectively Centrilobular hepatocellular degeneration at ≥10 ppm and hepatocellular necrosis at ≥100 ppm Tubular degeneration and nephrosis
Torti et al. 2001									

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Bromodichloromethane – Inhalation

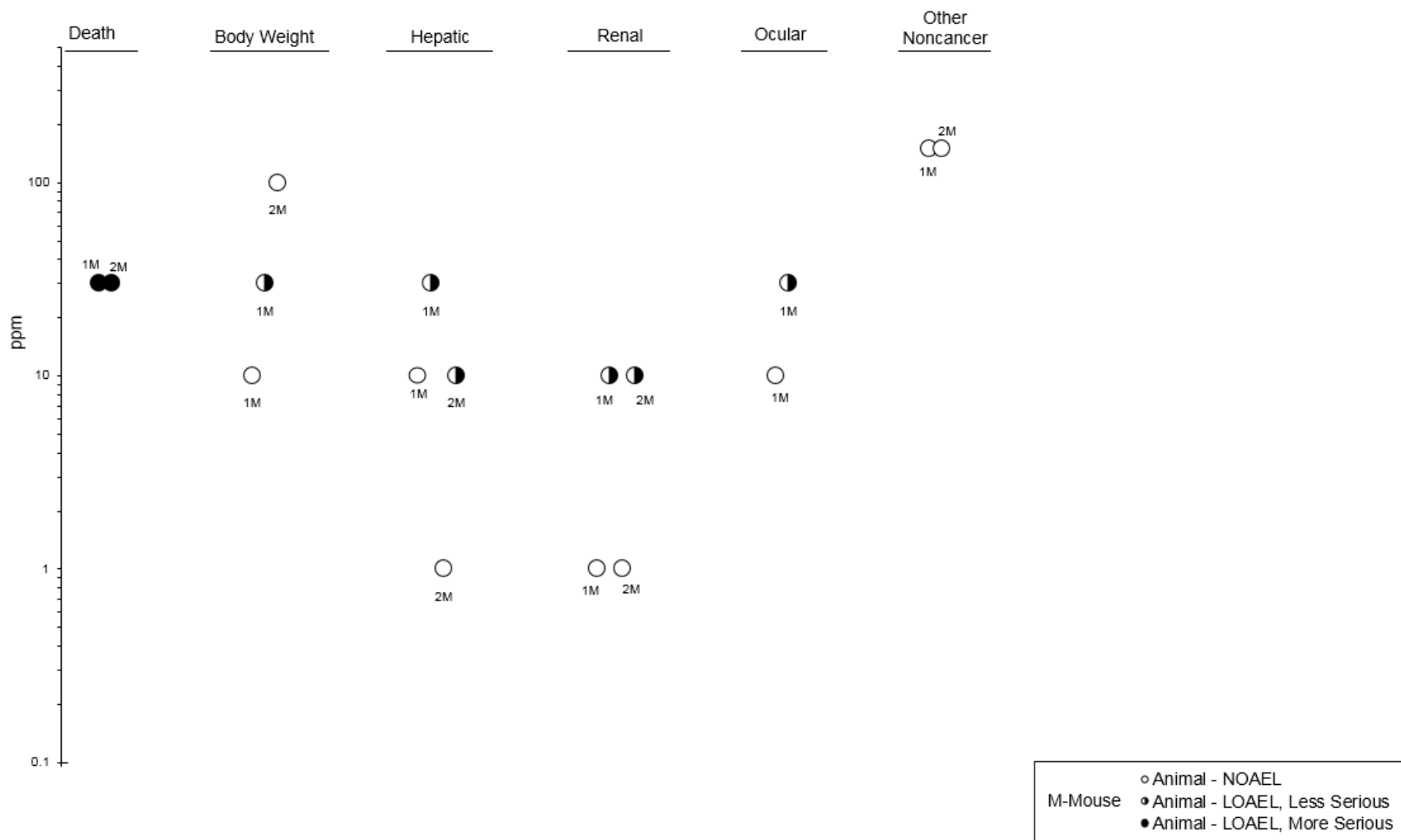
Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
3	Mouse (C57BL/6) 6 NS	6 hours/day 7 days/week 3 weeks	0, 0.3, 1, 3, 10, 30	LE, BW, OW, HP	Bd wt Hepatic Renal Other noncancer (urinary bladder)	30 30 3 30	10	30	Centrilobular hepatocellular degeneration was observed at ≥10 ppm in heterozygous strains Tubular degeneration; investigators provided severity scores but did not provide incidence data
Torti et al. 2001									
4	Mouse (FVB/N) 6 NS	6 hours/day 7 days/week 3 weeks	0, 0.3, 1, 3, 10, 30	LE, BW, OW, HP	Death Bd wt Hepatic Renal Other noncancer (urinary bladder)	30 30 3 30	10	30	4/6 deaths in wild-type strain Tubular degeneration at ≥10 ppm; investigators provided severity scores for these lesions but did not provide incidence data
Torti et al. 2001									

^aThe number corresponds to entries in Figure 2-2.

BW or Bd wt = body weight; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight

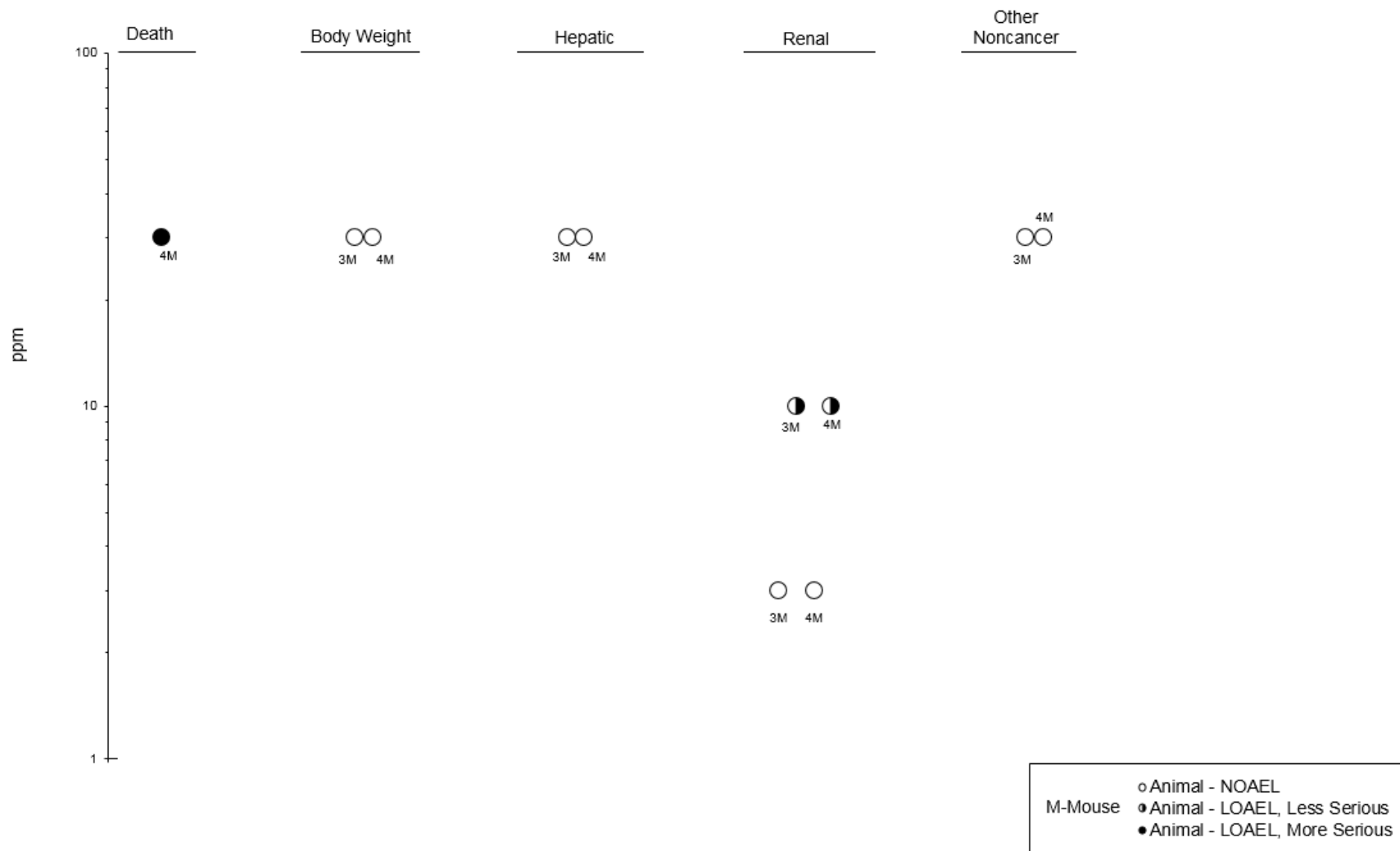
2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Bromodichloromethane – Inhalation
 Acute (≤ 14 days)



2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Bromodichloromethane – Inhalation
Intermediate (15-364 days)



2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (F344) 14 F	GDs 6–10 (GW)	0, 75	CS, BW, OF, DX	Bd wt Develop		75		Body weight on GD 20 reduced 35% 62% full-litter resorption rate
Bielmeier et al. 2001									
2	Rat (F344) 10–11 F	GDs 8 or 9; or 9 (GW)	0, 75, 100	CS, DX	Repro Develop		75		Reduced serum progesterone 64% full-litter resorptions
Bielmeier et al. 2001									
3	Rat (Sprague-Dawley) 13 F	GDs 6–10 (GW)	0, 75, 100	CS, BW, OF, DX	Develop	100			Full-litter resorption rate was 0%; no information was provided regarding pup weight
Bielmeier et al. 2001									
4	Rat (F344) 10–13 F	GDs 6–10, GDs 6–15, or GDs 11–15 (GW)	0, 75	CS, DX	Develop			75	Full-litter resorption in rats dosed on GDs 6–10 and 6–15
Bielmeier et al. 2001									
5	Rat (F344) 9–13 F	GDs 6–10 (GW)	0, 75, 100	CS, OF, DX	Repro Develop		75		Decreased serum progesterone and luteinizing hormone on GD 10 Full-litter resorptions (80%) on GDs 6–10
Bielmeier et al. 2004									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Rat (F344) NS-F	GDs 6–10 (GW)	0, 100	CS, OF, BI	Repro		100		Significant reductions in serum progesterone and luteinizing hormone on GD 10
Bielmeier et al. 2007									
7	Rat (Sprague-Dawley) 10 M, 10 F	Once (GO)	390, 546, 765, 1,071, 1,500	CS, LE	Death			916 M 969 F	LD ₅₀ values
Chu et al. 1980									
8	Rat (Sprague-Dawley) 10 M, 10 F	Once (GO)	390, 546, 765, 1,071, 1,500	CS, LE	Bd wt	546 M	765 M		Decreases in body weight gain were in males at 765 mg/kg (36% of controls) and 1,071 mg/kg (45%); no alterations were observed in females
					Hemato		390 F		Decreases in hematocrit and red blood cell count in females at ≥390 mg/kg and hemoglobin level at ≥546 mg/kg
					Other noncancer (blood glucose)	1,500			
Chu et al. 1982									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
9	Rat (F344) 6 F	5 days (GW)	0, 75, 150, 300	IX	Immuno		75		<p>Decreased response to the T-cell stimulant, phytohemagglutinin (PHA), in mesenteric lymph node lymphocytes at 75 mg/kg/day</p> <p>Decreased response to concanavalin A (Con A) in mesenteric lymph node lymphocytes at 150 mg/kg/day</p> <p>Decreased response to Con A and PHA in the splenic lymphocytes and to <i>S. typhimurium</i> in the mesenteric lymph node lymphocytes at 300 mg/kg/day</p> <p>Impaired humoral immunity (response to sheep red blood cells) at 300 mg/kg/day</p>

French et al. 1999

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
10	Rat (Fischer 344) 12 M	Once (G)	0, 20.5, 30.7, 41.0, 81.9, 122.9, 163.8, 245.7	BW, BC, OW	Bd wt Hepatic	245.7 163.8	245.7		Increases in ALT (239%), AST (130%), and sorbitol dehydrogenase (378%); significant increases at 81.9, 122.9, and 163.8 mg/kg, but were not considered biologically significant
Keegan et al. 1998									
11	Rat (Fischer 344) 6 M	Once (GW)	0, 200, 400	BW, BC, OW, HP	Bd wt Hepatic Renal	400 200 200	400	400	Vacuolar degeneration and necrosis and alterations in serum enzyme levels Tubule degeneration 24 and 48 hours post-exposure and tubule necrosis 48 hours post-exposure, increases in urinary glucose and protein levels and decreases in urinary pH and osmolarity; urinary pH and osmolarity decreased at 200 mg/kg
					Other noncancer (blood glucose)	400			
Lilly et al. 1994									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
12	Rat (Fischer 344) 6 M	Once (GO)	0, 200, 400	BW, BC, OW, HP	Bd wt	400			
					Hepatic	200	400	Vacuolar degeneration and necrosis and alterations in serum enzyme levels	
					Renal	200	400	Tubule degeneration 24 and 48 hours post-exposure and tubule necrosis 48-hours post-exposure, increases in urinary glucose and protein levels and decreases in urinary pH and osmolarity; urinary pH and osmolarity were also decreased at 200 mg/kg	
					Other noncancer (blood glucose)	400			
Lilly et al. 1994									
13	Rat (Fischer 344) 6 M	Once (GW)	0, 200, 400	BW, BC, OW, HP	Bd wt	200	400		12% decrease in body weight
					Hepatic	200	400	Minimal centrilobular necrosis and mild vacuolar degeneration	
					Renal		200	Mild to marked proximal tubule necrosis	
					Other noncancer (blood glucose)	400			
Lilly et al. 1996									
Note: Animals were killed 48-hours post exposure.									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
14	Rat (Fischer 344) 10 M	Once (GW)	0, 122.8, 163.8, 245.7, 327.7, 491.5	BW, BC, UR, OW	Bd wt	327.7	491.5		13% decrease in body weight 48 hours post-exposure
Lilly et al. 1997									
15	Rat (F344) 12–14 F	GDs 6–15 (GO), (GW)	0, 25, 50, 75	CS, BW, MX, DX, OF	Bd wt Develop		25	50	Decreased weight gain on GDs 6–8 at 25 mg/kg/day; weight loss at 50 mg/kg/day
						25 ^b		50	Full-litter resorptions; no alterations in gestation length, postnatal viability, or pup weight on PND 1 or 6 in surviving litters BMDL ₀₅ of 7.15 mg/kg/day
Narotsky et al. 1997									
16	Rat (F344/N) 5 M, 5 F	Once (GO)	0, 150, 300, 600, 1,250, 2,500	LE, CS	Death			600	Deaths occurred in 2/5 males and 1/5 females at 600 mg/kg and in all males and females at 1,250 or 2,500 mg/kg
NTP 1987									
17	Rat (F344/N) 5 M, 5 F	14 days (GO)	0, 38, 75, 150, 300, 600	LE, CS, BW	Bd wt	150	300	600	21% decrease in terminal body weights in males at 300 mg/kg/day and weight loss or no weight gain in males and females at 600 mg/kg/day
NTP 1987									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
18	Rat (Sprague-Dawley) 15 F	GDs 6–15 (GO)	0, 50, 100, 200	CS, BW, HP, MX, DX	Bd wt	100	200		Maternal body weight gain reduced by 38%
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Musc/skel	200			
					Hepatic	200			
					Renal	200			
					Endocr	200			
					Immuno	200			
					Neuro	200			
Repro	200								
				Develop	100	200		Delayed ossification of the sternebrae	
Ruddick et al. 1983									
19	Rat (Fischer 344) 6 F	5 days (GW)	0, 75, 150, 300	BW, BC, OW, HP	Death			300	2/6 rats died on day 5 16.8% decrease in body weight Hepatocellular vacuolar degeneration
					Bd wt	150	300		
					Hepatic	75	150		

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	75	150		Tubule vacuolar degeneration and tubular degeneration at ≥ 150 mg/kg/day; tubular necrosis and 8- and 12-fold increases in serum creatinine and urea nitrogen at 300 mg/kg/day
Thornton-Manning et al. 1994									
20	Mouse (ICR) 6 M	Once (GW)	Not reported	NX	Neuro		524		ED ₅₀ on the screen test was 524 mg/kg
Balster and Borzelleca 1982									
21	Mouse (ICR) 8 M	14 days (GW)	0, 1.2, 11.6	NX	Neuro	11.6			No significant alteration in performance on a swimming endurance test
Balster and Borzelleca 1982									
22	Mouse (ICR Swiss) NR, M,F	Once (GW)	500–4,000	CS, LE	Death			450 M 900 F	LD ₅₀ values
Bowman et al. 1978									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
23	Mouse (CD-1) 10 M	14 days (GO)	0, 37, 74, 148	CS, BW, BC, HP	Bd wt	148			
					Hepatic	37	74	Centrilobular pallor at ≥ 74 mg/kg/day, focal inflammation at 148 mg/kg/day	
					Renal	74	148		Intratubular mineralization, epithelial hyperplasia, and cytomegaly
Condie et al. 1983									
24	Mouse (C57BL/6) 6 F	14 days (W)	0, 10, 37, 62	IX	Immuno	62			No alterations in the response to T-lymphocyte or B-lymphocyte stimulants
French et al. 1999									
25	Mouse (CD-1) 8–9 M,F	14 day (GW)	0, 50, 125, 250	BW, HE, BC, OW, IX	Bd wt	125	250		20–22% decrease in body weight gain
					Hemato	50	125	Decreases in fibrinogen at 125 (females only) and 250 mg/kg/day	
					Hepatic	125	250	Increases in (>800%) in ALT and AST	
					Renal	125	250	41% increase in serum urea nitrogen levels	
				Immuno	125	250		Alterations in humoral immunity (decreases in antibody forming cells and hemagglutination)	

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain)	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Other noncancer (blood glucose)	125	250		30% decrease in blood glucose levels in males
Munson et al. 1982									
26	Mouse (B6C3F1)	Once (GO) 5 M, 5 F	0, 150, 300, 600, 1,250, 2,500	CS, LE	Death			600	100 and 40% mortality in males and females at 600 mg/kg; 100% mortality in males and females at 1,250 and 2,500 mg/kg
NTP 1987									
27	Mouse (B6C3F1)	14 days (GO) 5 M, 5 F	0, 19, 38, 75, 150, 300	CS, LE, BW	Death			150	100% mortality in males at 150 and 300 mg/kg; no deaths related to BDCM exposure in females
NTP 1987									
28	Mouse (C57BL/6 J)	5 days (GW) 6 F	0, 75, 150	BW, BC, OW, HP	Bd wt Hepatic Renal	150 150 150			
Thornton-Manning et al. 1994									
INTERMEDIATE EXPOSURE									
29	Rat (Wistar)	1 month (F) 7 M	0, 20, 60, 180	BW, OW, HE, BC, HP	Bd wt Resp Cardio Gastro Hemato Hepatic	60 180 180 180 180 60	180		19% decrease in body weight gain Decrease in absolute liver weight, vacuolization, swelling, and necrosis

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	180			
					Endocr	180			
Aida et al. 1989									
Note: BDCM was microencapsulated and added to the diet.									
30	Rat (Wistar) 7 M	1 month (GO)	0, 20, 60, 180	BW, OW, HE, BC, HP	Bd wt	60	180		15% decrease in body weight gain
					Resp	180			
					Cardio	180			
					Gastro	180			
					Hemato	180			
					Hepatic	20	60		Increases in relative liver weight at 180 mg/kg/day and vacuolization at ≥60 mg/kg/day
					Renal	180			
					Endocr	180			
Aida et al. 1989									
31	Rat (Wistar) 6 M, 6 F	6 months (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (32%) and females (24%)
					Resp	138.0			
					Cardio	138.0			
					Gastro	138.0			
					Hemato	138.0			

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Hepatic		6.1		Increases in absolute and relative weights in males at ≥ 6.1 mg/kg/day and in females at ≥ 31.7 mg/kg/day, fatty generation at $\geq 6.1/8.0$ mg/kg/day, bile duct proliferation and cholangiofibrosis at 138.0/168.4 mg/kg/day, and granulomas in females at ≥ 31.7 mg/kg/day
					Renal	138.0			
					Endocr	138.0			
					Neuro	138.0			
					Repro	138.0			
					Other noncancer (blood glucose)	6.1	25.5		Decreased blood glucose levels at $\geq 25.5/31.7$ mg/kg/day
Aida et al. 1992									
Note: BDCM was microencapsulated and added to the diet.									
32	Rat (Sprague-Dawley) 25 F	GDs 6–21 (W)	0, 2.2, 18.4, 45.0, 82.0	CS, BW, MX, DX	Develop	45	82		Minor ossification delays
Christian et al. 2001a									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
33	Rat (Sprague-Dawley) 30 F	GDs 6–21 (W)	0, 4.1–12.6, 11.6–40.2, 29.5–109	CS, BW, RX, MX, DX, HP	Repro	51.7			No alterations in reproductive function in a 2-generation study
					Develop	94.5			14% decrease in pup's body weight on PND 22, which was likely due to taste aversion.
Christian et al. 2001b									
34	Rat (Sprague-Dawley) 10 M	28 days (W)	0, 0.52, 5.2, 45	CS, HE, BC,HP	Bd wt	45			
					Hemato	45			
					Hepatic	45			
					Renal	45			
Chu et al. 1982									
35	Rat (F344) 6 M	26 weeks (W)	0, 5, 49	IX	Immuno	5	49		Decreased response to Con A in splenic lymphocytes
French et al. 1999									
36	Rat (Eker) 8 M, 8 F	4 or 10 months (W)	M: 0, 3.5, 35.0 F: 0, 6.5, 48.0	CS, OW, HP	Bd wt	35.0			
					Gastro	35.0			
					Hepatic	3.5	35.0		Increases in the incidence of centrilobular swelling and clear cell foci
Hooth et al. 2002									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
37	Rat (F344) 6 M	5 days/week 4 weeks (GO) or (GW)	0, 100	OW, HP	Renal	100			
Lipsky et al. 1993									
38	Rat (F344) 5 M	5 days/week 4 weeks (GO)	0, 50, 100	BW, UR, BC, OW, HP	Bd wt Renal	100 100			Decreases in urine pH and increases in formic acid excretion; minimal to slight cytoplasmic vacuolation in cortical tubules of 2/5 rats exposed to 100 mg/kg
Lock et al. 2004									
39	Rat (Eker) 8 M, 8 F	10 months (W)	0, 6.5, 48.0	CS, OW, HP	Gastro Other noncancer (urinary bladder)		6.5		Increase in aberrant crypt foci in colon
McDorman et al. 2003									
40	Rat (Fisher 344) 12 M, 12 F	6 months (W)	M: 0, 9.1, 27.3, 72.9 F: 0, 9.0, 26.9, 71.7	NX, HP	Neuro	71.7			No biologically relevant alterations in FOB tests or histopathological examination of the brain, spinal cord, hindlimb nerves, or optic nerve
Moser et al. 2007									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
41	Rat (F344/N) 10 M, 10 F	5 days/week 13 weeks (GO)	0, 19, 38, 75, 150, 300	CS, BW, HP	Death			300	5/10 males and 2/10 females died
					Bd wt	75	150	300	Decreases in body weight gain (30 and 12% less than controls) at 150 mg/kg, decrease in body weight gain of 32% in females at 300 mg/kg, no weight gain in males at 300 mg/kg
					Resp	300			
					Cardio	300			
					Gastro	300			
					Hepatic	150 F	300 F		Centrilobular degeneration, mild bile duct hyperplasia, and enlarged hepatocytes (females only)
					Renal	150	300		Degeneration of the proximal tubular epithelial cells
					Endocr	300			
					Immuno	150	300		Lymphoid atrophy of the thymus, spleen, and lymph nodes in males; this may have been secondary to the marked decrease in body weight gain
					Repro	150	300		Mild to moderate atrophy of the seminal vesicles and/or prostate at 300 mg/kg

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
42	Rat (F344/N) 10 M	22 days (W)	0, 6, 12, 20, 38, 71	CS, WI, BW, OW, HE, BC, HP	Bd wt	20	38		12 and 17% decrease in body weight gain at 38 and 71 mg/kg/day; this is likely secondary to the decrease in water consumption
					Resp	71			
					Cardio	71			
					Gastro	71			
					Hemato	71			
					Hepatic	71			
					Renal	71			
					Endocr	71			
					Immuno	71			
					Neuro	71			
					Repro	71			
NTP 2006									
43	Mouse (ICR) 16 M	30 days (GW)	0, 100	NX	Neuro	100			No alterations in performance on a passive avoidance learning test
Balster and Borzelleca 1982									
44	Mouse (ICR) 6–13 M	60 days (GW)	0, 100, 400	NX	Neuro		100		Alterations in operant behavior
Balster and Borzelleca 1982									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
45	Mouse (ICR) 6–8 M	90 days (GW)	0, 1.2 11.6	NX	Neuro	11.6			No dose-related alterations on two tests of motor performance or a test of exploratory behavior
Balster and Borzelleca 1982									
46	Mouse (C57BL/6) 6 F	16 days (GW)	0, 50, 125, 250	IX	Immuno	250			No alterations in the response to T-lymphocyte or B-lymphocyte stimulants
French et al. 1999									
47	Mouse (B6C3F1) 6 M	5 days/week 4 weeks (GO)	0, 25, 50	BW, UR, BC, OW, HP	Bd wt Renal	50 50			
Lock et al. 2004									
48	Mouse (B6C3F1) 10 M, 10 F	5 days/week 13 weeks (GO)	M: 0, 6.25, 12.5, 25, 50, 100 F: 0, 25, 50, 100, 200, 400	CS, BW, HP	Bd wt Resp Cardio Gastro Hepatic Renal Endocr	100 M 400 F 100 M 400 F 100 M 400 F 100 M 400 F 50 M 400 F 100 M 400 F	200 F 100 M		Enlarged centrilobular hepatocytes and microgranulomas Focal necrosis of the proximal renal tubular epithelium

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
NTP 1987									
49	Mouse (B6C3F1) 10 M	22 days (W)	0, 6, 10, 16, 29, 51	CS, WI, BW, OW, HE, BC, HP	Bd wt Resp Cardio Gastro Hemato Hepatic Renal Endocr Immuno Neuro Repro	51 51 51 51 51 51 51 51 51 51 51			
NTP 2006									
50	Rabbit (New Zealand white) 25 F	GDs 6–29 (W)	0, 1.4, 13.4, 35.6, 55.3	CS, BW, MX, DX	Develop	55.3			
Christian et al. 2001a									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt Resp Cardio Gastro Hemato Hepatic	25.5 138.0 138.0 138.0 138.0	138.0	6.1 ^c	Decreased body weight gain in males (23–25%) and females (31–39%) Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure and at ≥31.7 mg/kg/day after 18 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, bile duct proliferation at 31.7 (females only) and 138.0/168.4 mg/kg/day only after 12 months of exposure; cholangiofibrosis at 138.0/168.4 mg/kg/day; and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure BMDL ₁₀ of 0.78 mg/kg/day

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	138.0			
					Endocr	138.0			
					Neuro	138.0			
					Repro	138.0			
					Other noncancer (blood glucose)	31.7	168.4		Increase blood glucose levels in males only
					Cancer				No increases in tumor incidence
Aida et al. 1992									
Note: BDCM was microencapsulated and added to the diet.									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Bd wt Resp Cardio Gastro Hepatic Renal Endocr Cancer	36.3 36.3 36.3 36.3 36.3 20.6 36.3	36.3		Renal tubular cell hyperplasia No increases in the incidence of tubular cell adenoma or carcinoma
George et al. 2002									
53	Rat (F344) 7 M	52 weeks (W)	0, 22, 39	RX, HP	Repro	22	39		Decreases in sperm velocity from the cauda epididymidis; no changes in sperm motility
Klinefelter et al. 1995									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
54	Rat (F344/N) 50 M, 50 F	5 days/week 2 years (GO)	0, 50, 100	CS, WI, BW, OW, HP	Bd wt	50	100		Decreases in body weight gain; terminal weights 12 and 21% lower in males and females
					Resp	100			
					Cardio	100			
					Gastro	100			
					Hepatic		50		Fatty metamorphosis; increases in clear cell change at ≥50 mg/kg, eosinophilic cytoplasmic change, and focal cell change in females at 100 mg/kg
					Renal	50	100		Tubular epithelial cell cytomegaly in males at ≥50 mg/kg; increased incidence in nephrosis in females at 100 mg/kg
					Endocr	100			
					Immuno	100			
					Repro	100			
					Cancer			50	Adenocarcinomas in the large intestine in males at 50 mg/kg and males and females at 100 mg/kg; renal tubular cell adenocarcinoma at 100 mg/kg

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
55	Rat (F344/N) 50 M	2 years (W)	0, 6, 12, 25	CS, WI, BW, OW, HP	Bd wt Resp Cardio Gastro Hepatic Renal Endocr Immuno Repro Cancer	25 25 25 25 25 25 25 25 25			No increases in malignant tumors
NTP 2006									
56	Rat (Wistar) 58 M, 58 F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Bd wt Hepatic Cancer		90 M 190 F 90M 190 F		Decreased body weight (approximately 30%) in males and females Increased incidence of hepatic adenofibrosis Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
57	Mouse (B6C3F1) 78 M	104 weeks (W)	0, 8.1, 27.2, 43.3	CS, BW, FI, BC, OW, HP	Bd wt Gastro Hepatic Renal Endocr Cancer	43.3 43.3 43.3 43.3 43.3			No increases in the incidence of hepatocellular adenomas or carcinomas
George et al. 2002									
58	Mouse (B6C3F1) 50 M, 50 F	5 days/week 2 years (GO)	M: 0, 25, 50 F: 0, 75, 150	CS, BW, HP	Death Bd wt Resp Cardio Gastro Hepatic	 50 M 75 F 50 M 150 F 50 M 150 F 25 M 150 F	 150 F 50M	75 F	Decreased survival in females administered 75 or 150 mg/kg; the incidences of non-accidental deaths were 24/50, 37/50, and 35/50 in the 0, 75, and 150 mg/kg groups 25% lower body weights than controls in females Hepatic fatty metamorphosis

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	150 F	25 M		Renal cytomegaly
					Endocr	25 M	50 M 75 F		Thyroid follicular cell hyperplasia
					Immuno	50 M 150 F			
					Repro	50 M 150 F			
					Cancer			50 M 75 F	Renal tubular adenomas or adenocarcinomas in males at 50 mg/kg, hepatocellular adenomas or adenoma or carcinomas in females at ≥75 mg/kg
NTP 1987									
59	Mouse (B6C3F1) 50 F	2 years (W)	0, 9, 18, 36	CS, WI, BW, OW, HP	Bd wt Resp Cardio Gastro Hepatic Renal Endocr Immuno	36 36 36 36 36 36 36 36			

2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less	Serious	Effect
							serious	LOAEL	
					Repro	36			
					Cancer				No significant increases in neoplastic lesions

NTP 2006

^aThe number corresponds to entries in Figure 2-3.

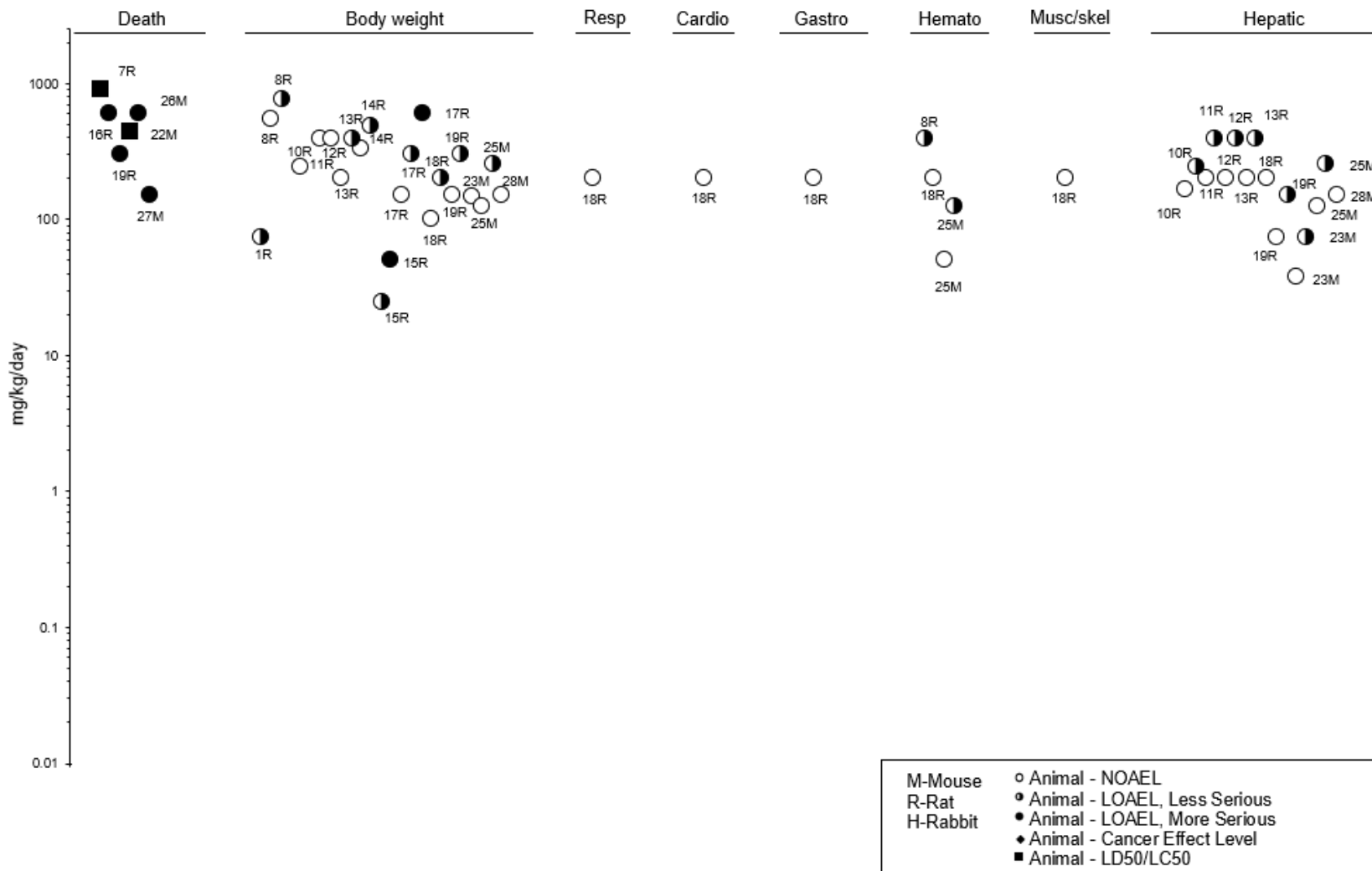
^bUsed to derive an acute-duration oral minimal risk level (MRL) of 0.07 mg/kg/day based on the BMDL₀₅ of 7.15 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

^cUsed to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL₁₀ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = biochemistry; BDCM = bromodichloromethane; BI = biochemical changes; BW or Bdw = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; ED₅₀ = dose resulting in a 50% response; Endocr = endocrine; (F) = exposure in feed; F = female(s); FI = food intake; FX = fetal toxicity; G = gavage, neat; Gastro = gastrointestinal; GD = gestation day; GO = gavage in oil vehicle; GW = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD₅₀ = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no observed-adverse-effect level; NR = not reported; NS = not specified; NX = neurotoxicity; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; UR = urinalysis; W = water

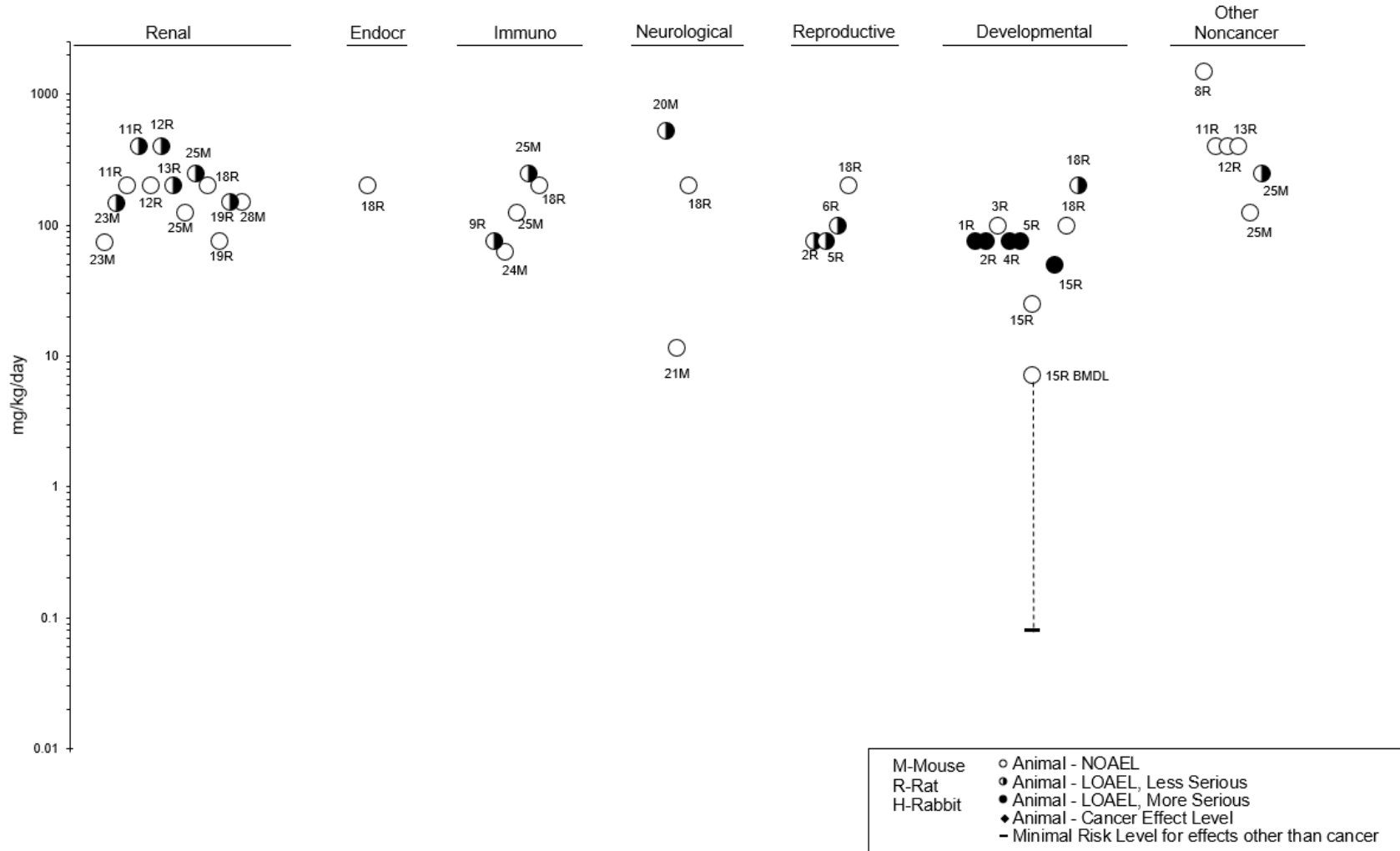
2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral
Acute (≤14 days)**



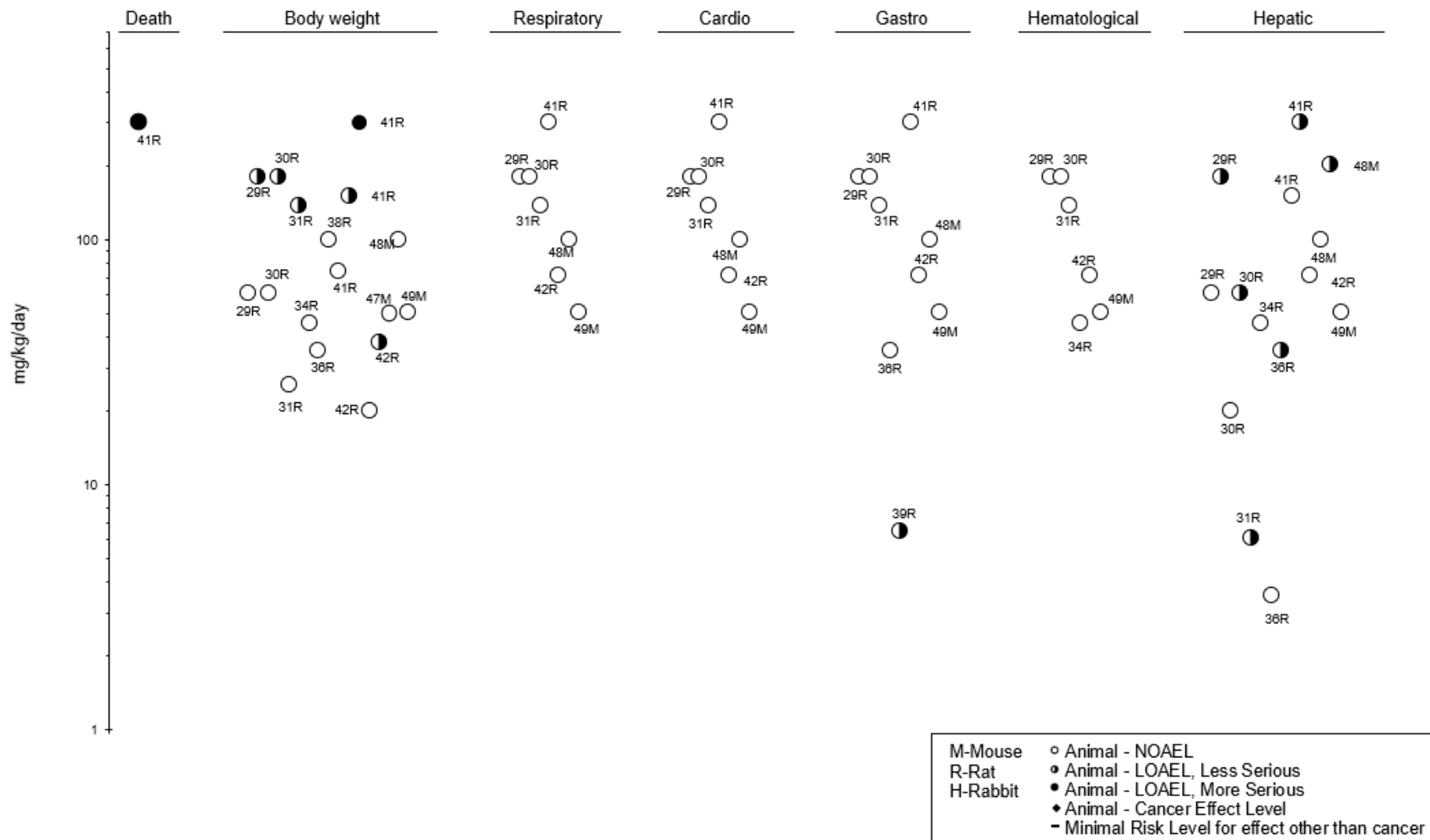
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral Acute (≤14 days)



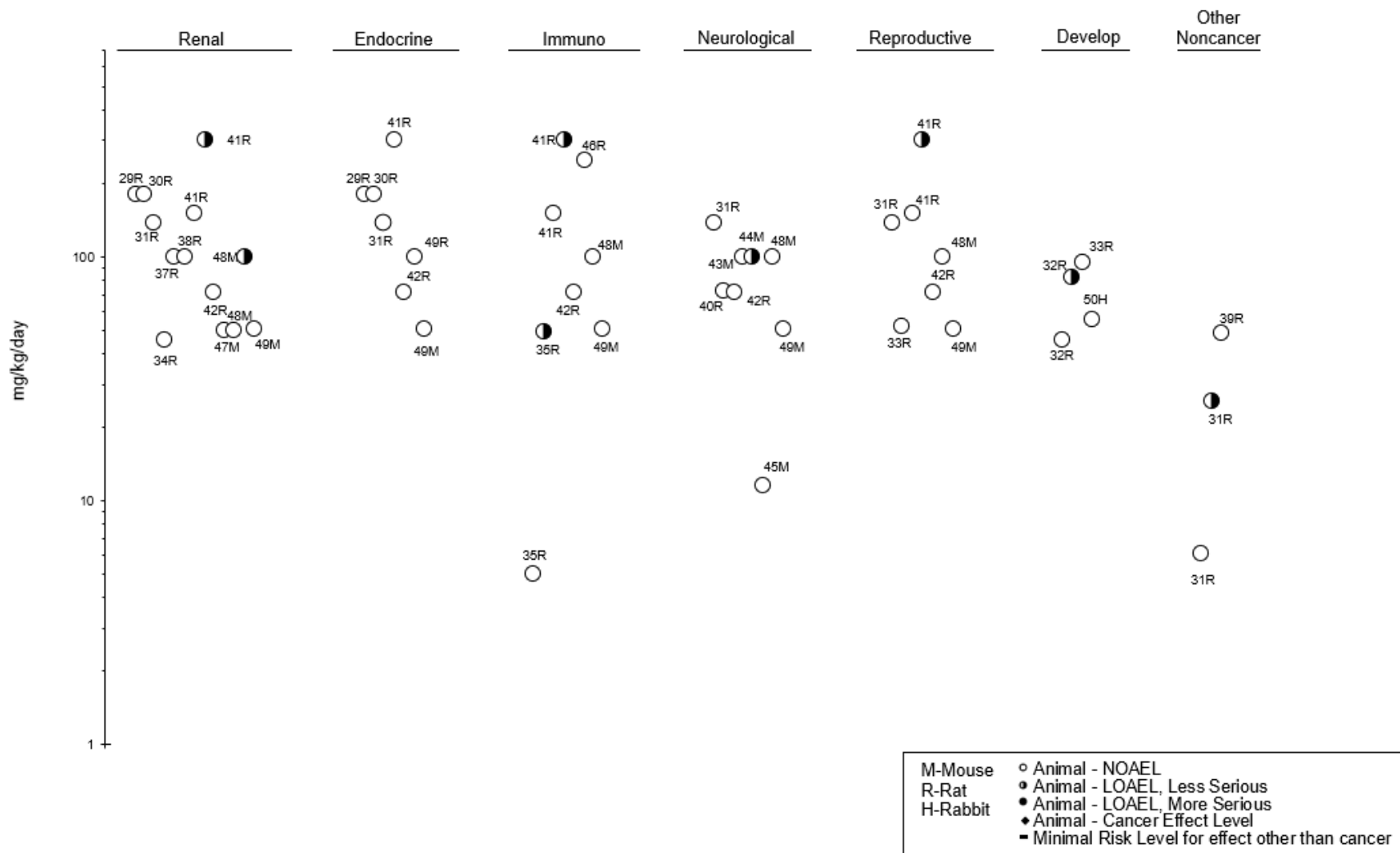
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral Intermediate (15-364 days)



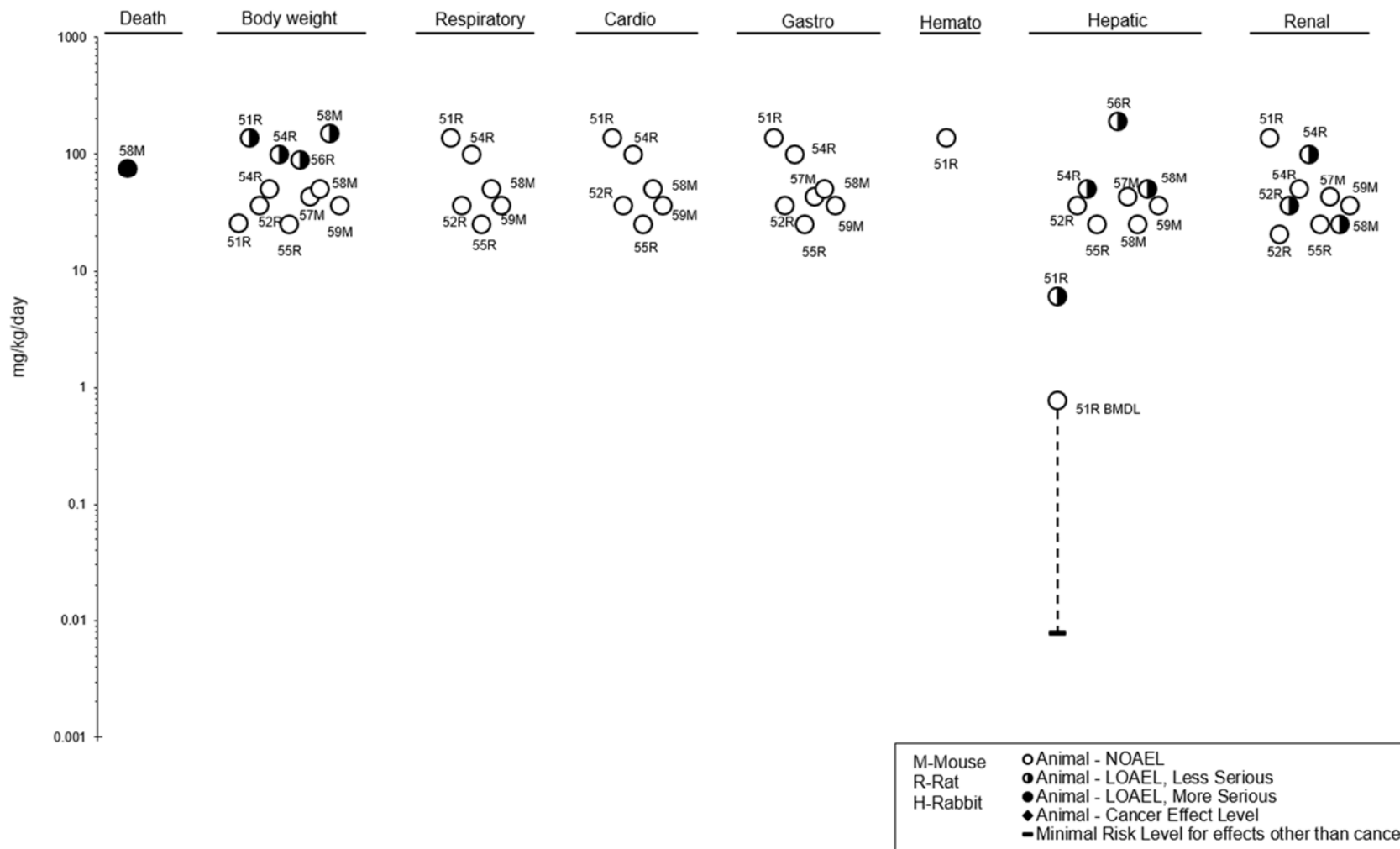
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral Intermediate (15-364 days)



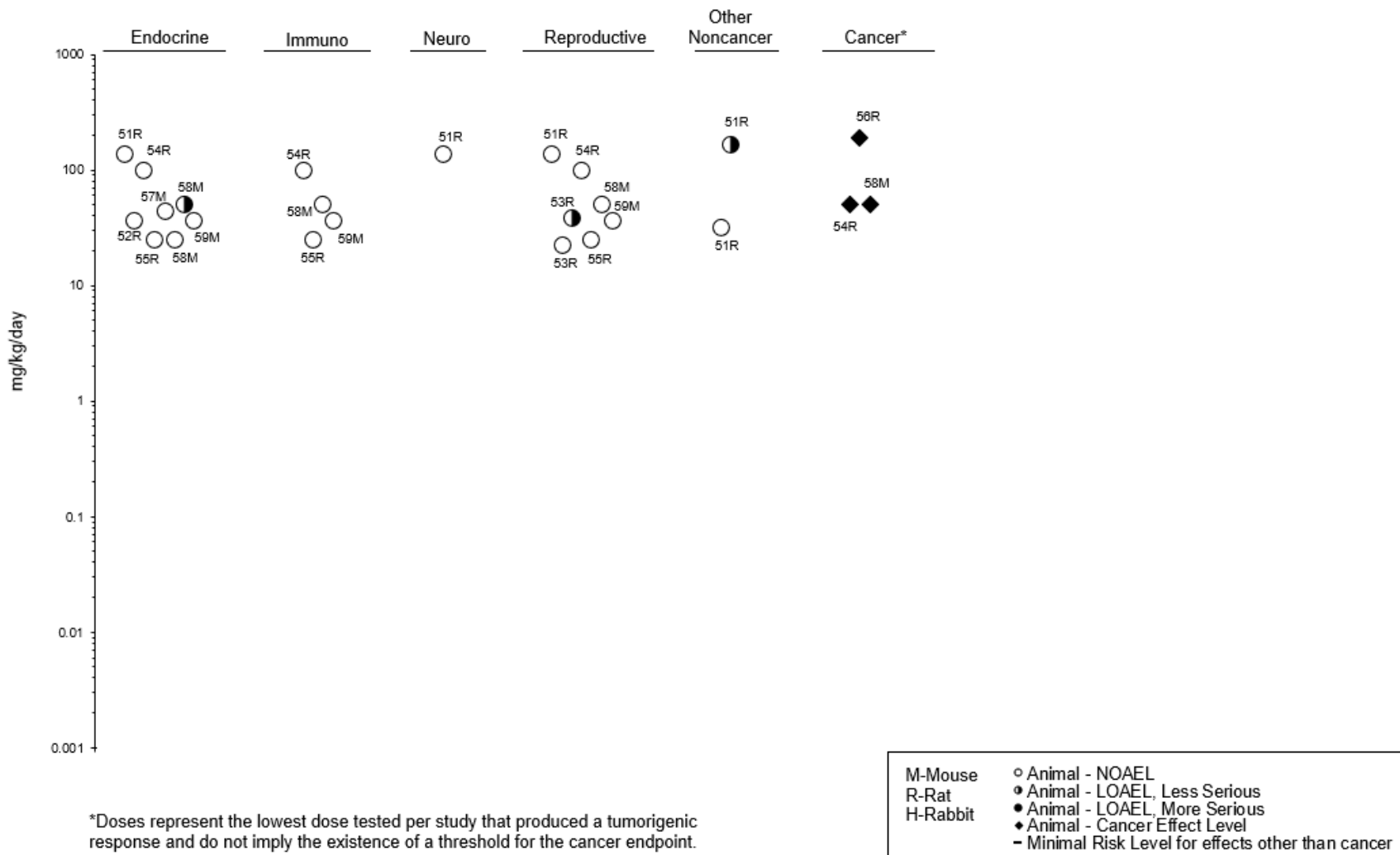
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral
Chronic (≥365 days)



2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral
Chronic (≥365 days)**



2. HEALTH EFFECTS

2.2 DEATH

Deaths have been reported in laboratory animals following acute or intermediate inhalation exposure and acute, intermediate, and chronic oral exposure. Increases in mortality were observed in two strains of mice exposed to 30 ppm bromodichloromethane vapor for 1 week (Torti et al. 2001). Deaths were also observed at 30 ppm in a similar 3-week study, but only in one of the two mouse strains tested (Torti et al. 2001).

Oral LD₅₀ values of 916 and 969 mg/kg were calculated in male and female rats (Chu et al. 1980). Deaths were also noted in rats receiving a single dose of 600 mg/kg (NTP 1987), but not in rats dosed for 14 days with 600 mg/kg/day (NTP 1987). However, another study reported 33% mortality in rats administered 300 mg/kg/day for 5 days (Thornton-Manning et al. 1994). The differences between the two studies may be due to the gavage vehicle used, oil in the NTP study versus an aqueous solution in the Thornton-Manning study. In contrast to the lack of sex differences observed in rats, male mice appear to be more sensitive to the lethal effect of bromodichloromethane than female mice. LD₅₀ values of 450 and 900 mg/kg were calculated in males and female mice, respectively (Bowman et al. 1978). NTP (1987) reported 100% mortality in male mice administered 600 mg/kg once or 150 mg/kg/day for 14 days; in females, 40% mortality occurred at 600 mg/kg and no deaths occurred at 150 or 300 mg/kg/day in the repeated exposure study.

Most intermediate- and chronic-duration studies did not test lethal doses. NTP (1987) reported increases in mortality in male and female rats administered 300 mg/kg for 13 weeks. No deaths were observed in studies testing lower doses in rats or mice (Aida et al. 1989, 1992; Chu et al. 1982; Hooth et al. 2002; Lock et al. 2004; McDorman et al. 2003; NTP 2006) or in female mice administered 400 mg/kg (NTP 1987). No deaths were noted in rats administered \leq 190 mg/kg/day for chronic durations (Aida et al. 1992; George et al. 2002; NTP 1987, 2006; Tumasonis et al. 1985). In mice, decreases in survival were observed in female mice administered 75 or 150 mg/kg for 2 years (NTP 1987); no deaths were observed in mice chronically exposed to lower doses (George et al. 2002; NTP 2006).

2.3 BODY WEIGHT

No human studies have evaluated the effect of bromodichloromethane exposure on body weights. In general, alterations in body weight do not appear to be a sensitive indicator of bromodichloromethane toxicity in laboratory animals. In C57BL/6 mice, inhalation exposure to \geq 30 ppm for 1 week resulted in decreases in body weight gain (Torti et al. 2001); increases in mortality were also observed at these

2. HEALTH EFFECTS

concentrations. No alterations in body weight gain were observed when the mice were exposed for 3 weeks or in another mouse strain exposed for 1 or 3 weeks (Torti et al. 2001).

Several acute-duration oral studies have reported decreases in body weight gain in rats administered doses ≥ 300 mg/kg (Chu et al. 1982; Lilly et al. 1996, 1997; NTP 1987; Thornton-Manning et al. 1994); other rat studies utilizing doses ≤ 400 mg/kg, did not find body weight alterations (Keegan et al. 1998; Lilly et al. 1994). Two mouse studies evaluated body weight, one found a significant decrease at 250 mg/kg (Munson et al. 1982), and the other reported no effect at 148 mg/kg (Condie et al. 1983). Several studies have reported decreases in maternal weight gain following acute-duration oral exposure to ≥ 25 mg/kg (Bielmeier et al. 2001; Narotsky et al. 1997; Ruddick et al. 1983).

In intermediate-duration oral studies, 12–30% decreases in body weight gain were observed in rats administered 138–180 mg/kg bromodichloromethane (Aida et al. 1989, 1992; NTP 1987). A 12–17% decrease was also observed in rats exposed to 38 mg/kg/day bromodichloromethane in drinking water; however, significant decreases in water consumption were also observed at this dose level and the decrease in body weight is likely to be secondary to the decreased water intake (NTP 2006). No alterations in body weight were observed in rats administered 35 or 45 mg/kg (Chu et al. 1982; Lock et al. 2004) or in mice administered 50–400 mg/kg (Lock et al. 2004; NTP 1987, 2006). Decreases in body weight were also observed in rats and mice following chronic-duration exposure to ≥ 90 mg/kg/day (Aida et al. 1992; NTP 1987; Tumasonis et al. 1985), but not at lower doses (George et al. 2002; NTP 2006).

2.4 RESPIRATORY

The respiratory tract has not been examined in the available inhalation exposure studies in mice (Torti et al. 2001). No respiratory effects have been reported in animal oral exposure studies (Aida et al. 1989, 1992; George et al. 2002; NTP 1987, 2006; Ruddick et al. 1983).

2.5 CARDIOVASCULAR

No human studies have evaluated the cardiotoxicity of bromodichloromethane. No histological alterations were observed in the hearts of rats and mice orally administered bromodichloromethane at doses as high as 200 mg/kg/day (Ruddick et al. 1983), 400 mg/kg/day (Aida et al. 1989, 1992; NTP 1987, 2006), or 138 mg/kg/day (Aida et al. 1992; George et al. 2002; NTP 1987, 2006) for acute-, intermediate-, or chronic-durations, respectively.

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2.6 GASTROINTESTINAL

No human studies have evaluated the gastrointestinal toxicity of bromodichloromethane. No non-neoplastic alterations have been observed in the gastrointestinal tract in most acute- (Ruddick et al. 1983), intermediate- (Aida et al. 1989, 1992; Hooth et al. 2002; NTP 1987, 2006), or chronic-duration (Aida et al. 1992; George et al. 2002; NTP 1987, 2006) oral studies in rats and mice. The NOAEL values for each duration category are 200, 400, and 138 mg/kg/day, respectively. McDorman et al. (2003) found an increase in the number of Eker rats having aberrant crypt foci in the colon following a 10-month exposure to 6.5 or 48.0 mg/kg/day in bromodichloromethane in drinking water. However, there were no significant increases in the total number of aberrant crypt foci, mean per colon, total number of crypts with aberrant foci, or distribution of aberrant foci in the different regions of the colon. The investigators considered aberrant crypt foci to be a preneoplastic lesion.

2.7 HEMATOLOGICAL

No studies examining hematological indices in humans were identified. Erythrocyte counts and hematocrit were significantly reduced in male rats 14 days after administration of a single dose of ≥ 390 mg/kg, and hemoglobin was significantly reduced in males and females at ≥ 546 mg/kg (Chu et al. 1982). No other acute (Munson et al. 1982; Ruddick et al. 1983), intermediate (Aida et al. 1989, 1992; Chu et al. 1982; NTP 2006), or chronic (Aida et al. 1992) oral studies reported erythrocyte or hemoglobin alterations, although the doses tested were lower than those in the Chu et al. (1982) acute study. The only other hematological alteration observed was a decrease in fibrinogen levels in female mice administered 125 mg/kg/day and male and female mice administered 250 mg/kg/day for 14 days (Munson et al. 1982).

2.8 MUSCULOSKELETAL

No studies evaluated the potential of bromodichloromethane to induce musculoskeletal alterations in humans. No histological alterations were observed in skeletal muscle of pregnant rats administered 200 mg/kg/day bromodichloromethane on GDs 6–15 (Ruddick et al. 1983). No longer-term studies examining musculoskeletal endpoints were identified.

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2.9 HEPATIC

Information on the hepatotoxicity of bromodichloromethane in humans is limited to a study which utilized NHANES data and did not find an association between bromodichloromethane blood levels and aspartate aminotransferase levels (Burch et al. 2015); this study is described in greater detail in Table 2-1. Animal studies provide strong evidence of the hepatotoxicity of bromodichloromethane. Based on a systematic review of the human and animal data, it is concluded that the liver is a presumed target of bromodichloromethane in humans (see Appendix C for additional information). The available animal data for bromodichloromethane and animal studies for two related compounds (bromoform and dibromochloromethane) (ATSDR 2005) provide evidence that oral exposure to bromodichloromethane results in an accumulation of fat in the liver as evidenced by increases in liver weight, centrilobular swelling, vacuolization, and fatty degeneration. Bromodichloromethane also appears to damage the bile duct. The animal studies also demonstrate vehicle-specific differences in hepatotoxicity, with greater toxicity associated with oil vehicles than aqueous vehicles.

A single dose of bromodichloromethane administered via gavage resulted in liver damage at doses as low as 74 mg/kg (Condie et al. 1983). At this dose, centrilobular pallor was observed in mice. At ≥ 81.9 mg/kg, marked increases in alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase were observed in rats and mice (Condie et al. 1983; Keegan et al. 1998; Lilly et al. 1994, 1996). At 400 mg/kg, mild centrilobular vacuolar degeneration and minimal centrilobular hepatocellular necrosis were observed in rats (Lilly et al. 1994, 1996). The toxicity of bromodichloromethane was greater when it was administered in a corn oil vehicle than when administered in an aqueous vehicle (Lilly et al. 1994). The magnitude of the increases in alanine aminotransferase and aspartate aminotransferase was greater for the corn oil vehicle, particularly 48 hours after administration when the enzyme levels were at least twice as high in the corn oil vehicle group compared to the aqueous vehicle group. Similarly, the incidences of hepatocellular necrosis 48 hours post-administration were 5/6 in the oil vehicle group and 2/6 in the aqueous vehicle group. Bromodichloromethane was more toxic following repeated acute exposure (5–14 days), with increases in alanine aminotransferase and aspartate aminotransferase observed at ≥ 250 mg/kg/day (Munson et al. 1982; Thornton-Manning et al. 1994) and centrilobular hepatocellular vacuolar degeneration at ≥ 150 mg/kg/day (Thornton-Manning et al. 1994).

Intermediate-duration studies have reported hepatic effects ranging from increases in liver weight to fatty degeneration. There is a considerable amount of overlap between the NOAEL and LOAEL values for hepatotoxicity between studies, which may be due to differences in study durations and/or administration

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route. Administration of bromodichloromethane via gavage with an oil vehicle resulted in vacuolization in rats exposed to ≥ 60 mg/kg/day for 1 month (Aida et al. 1989) and centrilobular degeneration in rats exposed to 300 mg/kg for 3 months (NTP 1987); the NOAELs for these studies were 20 and 150 mg/kg, respectively. Microencapsulating bromodichloromethane dissolved in oil and adding it to the diet resulted in hepatocellular vacuolization, swelling, and necrosis in rats exposed to 180 mg/kg/day for 1 month (Aida et al. 1989) and fatty degeneration in male rats exposed to ≥ 6.1 mg/kg/day for 6 months (LOAEL in females was 31.7 mg/kg/day) (Aida et al. 1992). Two studies administering bromodichloromethane in drinking water did not find increases in liver lesions at the highest doses tested, 45 mg/kg/day for 28 days (Chu et al. 1982) and 71 mg/kg/day for 22 days (NTP 2006). However, a third study identified a LOAEL of 35 mg/kg/day for centrilobular swelling in rats exposed to 35 mg/kg/day for 4 or 10 months (Hooth et al. 2002). The Aida et al. (1989) studies allow for a direct comparison between exposure routes since the gavage and dietary studies utilized the same rat strain (Wistar), dose levels, and exposure duration (1 month). The gavage study identified a lower LOAEL (60 mg/kg/day) for vacuolization than the dietary study (180 mg/kg/day). Enlarged hepatocytes with vacuolization were also observed in female mice administered via gavage ≥ 200 mg/kg bromodichloromethane in corn oil (NTP 1987); no liver effects were observed in a 13-week drinking water study in which mice were exposed to doses as high as 51 mg/kg/day (NTP 2006).

Eight studies have evaluated the chronic toxicity of bromodichloromethane in rats and mice (Aida et al. 1992; George et al. 2002; NTP 1987, 2006; Tumasonis et al. 1985). With the exception of the lifetime drinking water exposure study conducted by Tumasonis et al. (1985), the other studies involved a 2-year exposure to bromodichloromethane administered via gavage with a corn oil vehicle (NTP 1987), in drinking water (George et al. 2002; NTP 2006), or in the diet (Aida et al. 1992). The Aida et al. (1992) study identified the lowest LOAEL for hepatic effects; at ≥ 6.1 mg/kg/day, fatty degeneration was observed in the liver of male rats exposed for 12, 18, or 24 months; the LOAEL in the female rats was 31.7 mg/kg/day after 12 and 18 months and 8.0 mg/kg/day after 24 months of exposure. Fatty metamorphosis was observed in rats administered ≥ 50 mg/kg (lowest dose tested) for 2 years (NTP 1987). In drinking water studies, no histological alterations were observed in the liver of rats exposed to 56.3 mg/kg/day (George et al. 2002). NTP (2006) noted that minimal to mild liver inflammation of questionable significance was observed at 12 and 25 mg/kg/day; the biological relevance of the lesion was questioned since the lesion morphology is consistent with spontaneous inflammation observed in aging rats, which is considered to be due to bacterial showering from the intestinal tract. Tumasonis et al. (1985) reported an increase in the incidence of hepatic adenofibrosis in female rats exposed to 190 mg/kg/day. In a mouse gavage study, an increase in fatty metamorphosis was observed in males at

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50 mg/kg/day, but no lesions were observed in females at 150 mg/kg (NTP 1987). A drinking water study by George et al. (2002) did not find liver effects at the highest dose tested (43.3 mg/kg/day).

In addition to the hepatocellular effects noted in rats and mice, intermediate- and chronic-duration exposure has resulted in damage to the bile duct. Bile duct proliferation and cholangiofibrosis was observed in rats exposed to 138.0 (males)/168.4 (females) mg/kg/day for 6, 12, 18, and 24 months (Aida et al. 1992) and mild bile duct hyperplasia was observed in rats administered 300 mg/kg for 13 weeks (NTP 1987).

There are limited data on the mechanisms of bromodichloromethane hepatotoxicity. The available data suggest that its toxicity is due to the production of reactive intermediates. As reported by Thornton-Manning et al. (1994), pretreatment of rats with the cytochrome P450 inhibitor, 1-aminobenzotriazole, significantly reduced the hepatic toxicity of bromodichloromethane and pre-treatment with acetone, a CYP2E1 inducer, greatly increased its toxicity. Additionally, pretreatment with the glutathione synthesis inhibitor butathione sulfoxime (BSO) increased bromodichloromethane's toxicity (Gao et al. 1996). Similarly, adding glutathione to hepatic microsomes under anaerobic conditions decreased binding of [14C]bromodichloromethane to lipids (Gao et al. 1996). These data demonstrate a protective role of glutathione that is consistent with metabolism of bromodichloromethane to one or more reactive species.

2.10 RENAL

No studies have evaluated the renal toxicity of bromodichloromethane in humans. However, based on the available animal studies, the kidney is a suspected target in humans (see Appendix C for more information on the systematic review of these data).

In inhalation studies, renal tubular degeneration was observed in mice exposed to ≥ 10 ppm bromodichloromethane for 1 or 3 weeks (Torti et al. 2001); the NOAELs identified in these studies were 1 and 3 ppm, respectively. Increased incidence of nephrosis was also observed at 10 ppm in a 13-week study (Torti et al. 2001); the NOAEL was 3 ppm.

In single-dose oral studies, mild to marked renal tubule degeneration and minimal-to-moderate renal tubule necrosis were observed in rats following administration via gavage with corn oil or aqueous vehicles at 200 mg/kg (Lilly et al. 1996) and/or 400 mg/kg (Lilly et al. 1994). Increases in serum urea nitrogen, urinary glucose, and urinary protein levels were observed at 400 mg/kg/day (Lilly et al. 1994),

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and decreases in urinary pH and osmolarity were observed at ≥ 200 mg/kg (Lilly et al. 1994). Similarly, renal tubule degeneration and tubular regeneration were observed in rats administered ≥ 150 mg/kg/day for 5 days (Thornton-Manning et al. 1994), and tubular necrosis and increases in serum creatinine and urea nitrogen were observed at 300 mg/kg/day. The acute studies provide some suggestive evidence of species differences in that no renal effects have been observed in mice administered bromodichloromethane for 5 days at doses as high as 150 mg/kg/day (Thornton-Manning et al. 1994). Another study found intratubular mineralization and epithelial hyperplasia at 148 mg/kg/day in mice exposed for 14 days (Condie et al. 1983), but did not report tubular degeneration or regeneration.

Similar renal effects have been reported in rats and mice in intermediate- and chronic-duration studies. Degeneration of proximal tubular epithelial cells were observed in rats administered 300 mg/kg for 13 weeks (NTP 1987) and nephrosis was observed in rats (females only) administered 100 mg/kg for 2 years (NTP 1987). Another rat study reported renal tubular cell hyperplasia in rats exposed to 36.3 mg/kg/day for 2 years (George et al. 2002). Other intermediate and chronic studies did not find histological alterations in the kidneys at doses as high as 180 mg/kg/day (Aida et al. 1989, 1992; Chu et al. 1982; Lipsky et al. 1993; Lock et al. 2004; NTP 2006). As noted in NTP (2006), differences in the route of administrations (gavage versus feed versus water) and stability of the bromodichloromethane in water and feed may have accounted for the overlap between the NOAEL and LOAEL values. In mice, proximal tubular focal necrosis was observed in males administered 100 mg/kg for 13 weeks (NTP 1987), but no effects were observed in females at doses as high as 400 mg/kg. An increase in the incidence of renal tubular epithelial cell cytomegaly was also observed in mice at 25 mg/kg for 2 years (NTP 1987). No renal effects were observed in mice administered via gavage 50 mg/kg/day for 4 weeks (Lock et al. 2004) or exposed to 36 mg/kg/day in drinking water for 2 years (NTP 2006).

2.11 DERMAL

No human or animal studies have evaluated the dermal toxicity of bromodichloromethane.

2.12 OCULAR

No human studies examined potential ocular effects following inhalation, oral, or direct contact exposure to bromodichloromethane. Mild eye irritation was noted in mice exposed to ≥ 30 ppm bromodichloromethane vapors for 1 week (Torti et al. 2001); the investigators did not report incidence data. Eye irritation was not noted in a 3-week study conducted by this group.

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2.13 ENDOCRINE

In general, endocrine tissues do not seem to be a target of bromodichloromethane toxicity; see Section 2.16 for a discussion of alterations in reproductive hormone levels. Human studies evaluating endocrine endpoints following exposure to bromodichloromethane were not identified. No histological alterations were observed in rats following exposure to ≤ 200 mg/kg/day on GDs 6–15 (Ruddick et al. 1983), intermediate-duration exposure of rats to ≤ 300 mg/kg/day (Aida et al. 1989, 1992; NTP 1987, 2006) or mice to ≤ 400 mg/kg/day (NTP 1987, 2006), or chronic-duration exposure of rats to ≤ 138 mg/kg/day (Aida et al. 1992; NTP 1987, 2006). Thyroid follicular cell hyperplasia was observed in male mice administered via gavage 50 mg/kg or in females administered ≥ 75 mg/kg (NTP 1987); no endocrine effects were observed in mice exposed to ≤ 36 mg/kg/day in drinking water (NTP 2006).

2.14 IMMUNOLOGICAL

Immunotoxicity is a suspected health effect for humans based on a systematic review of several studies examining immunological endpoints in laboratory animals orally exposed to bromodichloromethane (see Appendix C for more information). Epidemiological data are limited to a study examining immune markers following a 40-minute swim in a chlorinated pool (Vlaanderen et al. 2017). Decreases in C-X-C motif chemokine 10, C-C motif chemokine 22, C-reactive protein, and vascular endothelial growth factor and increases in interleukin-1 α were associated with exhaled breath bromodichloromethane levels.

Acute exposures have resulted in decreased responses to humoral and cell-mediated immune stimulants in rats administered ≥ 75 mg/kg/day for 5 days (French et al. 1999) or mice administered 250 mg/kg/day for 14 days (Munson et al. 1982). Following a 26-week exposure to 49 mg/kg/day, an impaired response to the mitogen concanavalin A was observed in splenic lymphocytes, but there was no altered response in the lymph node lymphocytes or responses by either type of lymphocyte to other mitogens or to *Salmonella typhimurium* (French et al. 1999).

The available data provide some suggestive evidence that rats may be more sensitive to the immunotoxic effects of bromodichloromethane than mice. No alterations in immune function were observed in mice exposed to 62 mg/kg/day in drinking water for 14 days (French et al. 1999) or administered 125 mg/kg/day via gavage with an aqueous vehicle for 14 days (Munson et al. 1982) or 250 mg/kg/day for 16 days (French et al. 1999). These NOAELs are higher than LOAEL values in rats. Although

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bromodichloromethane results in impaired immune function, no histological alterations were observed in lymphoid tissues following acute (Ruddick et al. 1983), intermediate (NTP 1987, 2006), or chronic (NTP 1987, 2006) exposure; the lymphoid atrophy observed at 300 mg/kg in the NTP (1987) intermediate-duration rat study was likely secondary to a decrease in body weight rather than a direct effect on the lymphoid tissue.

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans exposed to bromodichloromethane. Balster and Borzelleca (1982) performed a series of tests in mice ≥ 24 hours after the last of a series of doses of bromodichloromethane. Exposure to doses of 1.2–11.6 mg/kg/day for 14–90 days had no effect on tests of coordination, strength, endurance, or exploratory activity, and 90-day exposure to 100 mg/kg/day did not affect passive avoidance learning. Exposure to 100 or 400 mg/kg/day for 60 days did result in an acute effect on operant behavior learning, but this change tended to diminish over the exposure period, suggesting that there was no progressive effect and that partial tolerance developed. One other study evaluating neurological function did not find alterations in performance on functional observational battery tests in rats exposed to 71.7 mg/kg/day for 6 months (Moser et al. 2007). No histological alterations in the brain and/or peripheral nerves were observed in rats or mice exposed to bromodichloromethane for acute (Ruddick et al. 1983), intermediate (Aida et al. 1992; Moser et al. 2007; NTP 1987, 2006), or chronic (Aida et al. 1992; NTP 1987, 2006) durations.

2.16 REPRODUCTIVE

In a systematic review of the available reproductive toxicity data for bromodichloromethane, it was determined that hazard identification for reproductive toxicity potential could not be classified due to the inconsistent results found in epidemiology and laboratory animal studies (see Appendix C for more information). A small number of human (Table 2-1) and laboratory animal (Table 2-2) studies evaluated the reproductive toxicity of bromodichloromethane; the studies examined potential effects on sperm parameters, menstrual cycle, fertility, hormone levels, and reproductive organ pathology. Three epidemiological studies examined reproductive endpoints associated with environmental exposure to bromodichloromethane. Interpretation of the study results is limited by the lack of confirming studies and potentially confounding exposure to other compounds, particularly other disinfection byproducts. Zeng et al. (2013) did not find a significant association between blood bromodichloromethane levels and sperm

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concentration, sperm count, or sperm motility in men. Associations between exposure to bromodichloromethane in drinking water and decreasing overall menstrual cycle length and follicular phase length specifically, as measured by urine estrogen and progesterone metabolite levels, were found in women participating in a reproductive health study (Windham et al. 2003). In a large prospective cohort study, a decreased time to pregnancy was associated with an estimate of the amount of bromodichloromethane ingested from tap water (MacLehose et al. 2008); however, no associations were found for other bromodichloromethane dose metrics. A fourth study examined possible interactions between CYP2E1, GSTZ1, and GSTT1 polymorphisms and bromodichloromethane levels in drinking water on sperm motility, sperm count, and sperm concentration (Yang et al. 2016). The only observed association was found in men with blood bromodichloromethane levels ≥ 1.70 $\mu\text{g/mL}$ and a CYP2E1 rs2031920 CC polymorphism.

Most studies evaluating the histopathology of the testes and uterus did not find alterations (Aida et al. 1992; NTP 1987, 2006; Ruddick et al. 1983). One study did find mild to moderate atrophy of the seminal vesicles and/or prostate in rats administered a lethal dose of 300 mg/kg for 13 weeks (NTP 1987). A 2-generation reproduction study in rats did not find any alterations in reproductive parameters at the highest dose tested (51.7 mg/kg/day) (Christian et al. 2001b). No alterations in the percentage of motile or progressively motile sperm were observed in rats exposed to doses of 39 mg/kg/day for 52 weeks (Klinefelter et al. 1995); however, the study did find significant decreases in sperm velocity at 39 mg/kg/day. A study in rats found a diminished responsiveness to luteinizing hormone when 75 mg/kg bromodichloromethane was administered on GDs 8–10 (Bielmeier et al. 2001, 2004, 2007).

2.17 DEVELOPMENTAL

The available human and animal studies provide evidence that developmental toxicity is a presumed health effect of bromodichloromethane in humans (see Appendix C for information on the systematic review).

A number of epidemiology studies have examined the association between exposure to trihalomethanes, bromodichloromethane among them, and developmental effects in humans (Table 2-1). Specific endpoints examined have included birth weight and length, small for gestational age (SGA), various birth defects, gestational age, preterm delivery, spontaneous abortion, stillbirth, and incidence of hypospadias. Overall, these studies provide limited evidence for an association between bromodichloromethane and developmental effects, possibly due to the main limitation of non-differential misclassification of

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individual exposure. In addition, the various studies have used different approaches to assess exposure, including blood levels of bromodichloromethane, bromodichloromethane in water supplied to the places of residence, and total dose (measured concentration of bromodichloromethane in water plus estimates of water ingestion combined with inhalation and dermal exposure through showering and bathing, and other activities). There is considerable uncertainty due to self-recollection of water use and due to spatial and seasonal variation of disinfection byproducts within a distribution system.

Mixed results have been reported in studies examining the potential effect of bromodichloromethane exposure and birth weight. Birth weight was not significantly associated with bromodichloromethane levels in blood during late pregnancy (median 2.5 ng/L) in a case-control study of pregnant women in China (Cao et al. 2016), with daily doses ≤ 0.34 μg bromodichloromethane/day during the entire pregnancy or individual trimesters in a nested-case-control study of pregnant women in Lithuania (Danileviciute et al. 2012), or with bromodichloromethane levels in water (Hoffman et al. 2008). In a retrospective cohort study of 196,000 live births in Massachusetts between 1995 and 1998, exposure to water containing ≥ 5 μg bromodichloromethane/L during the third trimester of pregnancy was associated with a reduction in birth weight of 12 g (Wright et al. 2004). A more recent study of the same population, that included evaluation of 672,120 live births, confirmed the earlier observations and reported that exposure to a mean concentration of 6.1 μg bromodichloromethane/L in water during the third trimester was associated with reductions in birth weight of 49–63 g in unadjusted models; the association remained significant in adjusted models, but the magnitude of the reductions in birth weight were considerably lower (Rivera-Núñez and Wright 2013).

Evaluations of small for gestational age (SGA) have also provided seemingly inconsistent results. SGA was not associated with exposure to bromodichloromethane assessed by measuring its concentration in blood (Cao et al. 2016), assessed as total intake via multi-route exposure (Danileviciute et al. 2012), or by average water concentration (Hoffman et al. 2008). In contrast, SGA was associated with third trimester bromodichloromethane water supply levels of ≥ 19 $\mu\text{g}/\text{L}$ in a retrospective cohort study of 341,982 live births in Australia (Summerhayes et al. 2012). In general, larger associations were seen in nonsmokers than in smokers, which the investigators attributed to the relatively large smoking effect on SGA possibly masking the effects of subtle risk factors such as trihalomethane exposure on SGA. An association between SGA and ≥ 5 μg bromodichloromethane/L in water during the third trimester was reported in the earlier study of women in Massachusetts (Wright et al. 2004); bromodichloromethane was also associated with longer gestational age (0.5–0.6 days) in this study. The most recent study of this population did not find an association after adjustments for confounding variables (Rivera-Núñez and Wright 2013);

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gestational age was not evaluated. In the two studies of women in Massachusetts, preterm delivery was not associated with bromodichloromethane levels in the water supply (Rivera-Núñez and Wright 2013; Wright et al. 2004).

Four studies evaluated associations between exposure to bromodichloromethane and risk of congenital anomalies. Mean bromodichloromethane levels in water during pregnancy were associated with an increase in risk of neural tube defects in a prospective cohort study of residents of Nova Scotia, Canada (Dodds and King 2001); no associations were found for cardiovascular defects or cleft defects. A study of women from Massachusetts did not find associations between bromodichloromethane water levels and the risk of cardiovascular defects (Wright et al. 2017). In a study of women from Lithuania, internal bromodichloromethane dose during the first month of pregnancy was associated with an increased risk of heart anomalies in comparisons of the third tertile (0.051–0.436 $\mu\text{g}/\text{day}$) versus the first tertile (0.000–0.013 $\mu\text{g}/\text{day}$) (Grazuleviciene et al. 2013); no associations were found for musculoskeletal or urogenital anomalies. An intake of ≥ 6 μg bromodichloromethane/day (combined estimates of water consumption, dishwashing, showering, and swimming during the first trimester) was associated with an increased risk of hypospadias in male offspring in a small case-control study in England (Iszatt et al. 2011); notably, the concentration of bromodichloromethane in water was not associated with hypospadias. However, elevated risk of hypospadias was associated with consumption of cold tap water at home, total water, bottled water, and total fluid (the concentrations of bromodichloromethane in water was not provided, but mean total trihalomethanes ranged from 15 to 51 $\mu\text{g}/\text{L}$).

As with other effects, mixed results have been found in studies examining the possible association between bromodichloromethane and the risk of stillbirth or spontaneous abortions. In a prospective cohort study of Canadian women, exposure to exposure to ≥ 20 μg bromodichloromethane/L in the water during pregnancy almost doubled the risk of stillbirth (King et al. 2000). Analysis of risk in a continuous representation showed a 29% increase in risk with each 10 μg bromodichloromethane/L. Risk of unexplained stillbirth was not associated with bromodichloromethane, but risk of stillbirth caused by asphyxia was increased 32% per 10 $\mu\text{g}/\text{L}$ bromodichloromethane. In contrast, a study of women living in Massachusetts did not find an association between bromodichloromethane levels in municipal water and all causes of stillbirths, but did find an association with unexplained stillbirths (Rivera-Núñez et al. (2018). A large prospective study of pregnant women in California found a doubling of the risk of spontaneous abortion among women with high personal exposure to bromodichloromethane in the tap water (Waller et al. 1998); the risk was further increased after adjustment for high exposure to other trihalomethanes.

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A study of 3-day-old infants found an inverse association between maternal blood bromodichloromethane levels and neonatal neurological assessment test scores (Chen et al. 2019); no other epidemiological studies evaluated potential neurodevelopmental effects.

Several studies provide information regarding the developmental effects of bromodichloromethane in laboratory animals following oral exposure. With the exception of one study in rabbits, all have been conducted in rats. The results of these studies indicate that: (1) F344 rats are considerably more susceptible than Sprague-Dawley rats, particularly for the endpoint of full-litter resorptions; (2) mode of administration of bromodichloromethane, gavage vs. drinking water, and the vehicle influence the toxicity; (3) bromodichloromethane is not teratogenic; and (4) effects occur in animals at exposure levels significantly higher than what humans normally encounter through residential or environmental exposures to bromodichloromethane.

The lowest LOAEL for developmental effects in animals was 50 mg/kg/day for full-litter resorptions in F344 rats dosed by gavage on GDs 6–15; no significant resorptions occurred at 25 mg/kg/day (Narotsky et al. 1997). A significantly higher resorption rate was reported when doses of 75 mg/kg/day were administered in an oil vehicle (83%) than when given in an aqueous vehicle (8%). The difference may have been due, at least in part, to a slower measured elimination rate of bromodichloromethane when administered in the oil vehicle compared to the aqueous vehicle. Comparative evaluation of F344 rats and Sprague-Dawley rats showed that full-litter resorptions occurred in the former at a rate of 62% (8/13) following dosing with 75 mg/kg/day, whereas the rate was 0% in the latter strain dosed with ≤ 100 mg/kg/day (Bielmeier et al. 2001). The investigators noted that it was not clear whether the difference in sensitivity was due to strain differences in reproductive physiology or toxicokinetics.

Studies in F344 rats indicate that the early gestation window as the most sensitive time period for bromodichloromethane-induced full-litter resorptions. Bielmeier et al. (2001) observed 75 and 50% full-litter resorption rates when rats were administered 75 mg/kg/day doses on GDs 6–10 and 6–15, respectively, while administration on GDs 11–15 resulted in 0% full-litter resorptions. It should be noted that in these studies, doses of bromodichloromethane that induced full-litter resorptions (≤ 100 mg/kg/day) also significantly reduced maternal body weight gain during gestation; however, there was no significant effect on pup viability or neonatal body weight in pregnancies with live litters sacrificed on postnatal day (PND) 6 (Bielmeier et al. 2004).

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Additional studies that examined a wide range of developmental endpoints in Sprague-Dawley rats and New Zealand white rabbits exposed during gestation to ≤ 200 mg/kg/day did not report full-litter resorptions (Christian et al. 2001a, 2001b; Ruddick et al. 1983).

Studies in rats reported minor delays in ossification of the forelimbs and hindlimbs following maternal doses of 82 mg/kg/day in drinking water on GDs 6–21 (Christian et al. 2001a) and of the sternbrae of fetuses from dams dosed with 200 mg/kg/day by gavage on GDs 6–15 (Ruddick et al. 1983). The respective NOAELs were 45 and 100 mg/kg/day. However, no developmental abnormalities were reported in fetuses from rabbits following maternal doses of ≤ 55.3 mg/kg/day in the drinking water on GDs 6–29 (Christian et al. 2001a). Other endpoints evaluated in these studies included number of corpora lutea, implantation sites, live and dead fetuses and early and late resorptions, fetal body weight, sex ratios, and external and soft tissue abnormalities; none were significantly affected by exposure to bromodichloromethane.

Bromodichloromethane was also tested in a 2-generation reproductive toxicity study in rats (Christian et al. 2001b). The most significant effect was a 14% reduction in body weight in pups from the F1 generation on PND 21; the maternal dose estimated by the investigators during lactation days 1–15 was 94.2 mg/kg/day. The decrease in pup body weight began when the pups started drinking water containing bromodichloromethane and there was a 20% decrease in water intake in this group which was attributed to taste aversion. Thus, the decrease in body weight was considered to be secondary to taste aversion and was not considered toxicologically relevant. Relative spleen weight was also significantly reduced in F1 pups on PND 21 (10–28%). Small but significant delays in preputial separation in F1 males and in vaginal patency in F1 females were reported. However, the differences lost significance when the effects were analyzed using body weight at weaning as covariate. Histological evaluation of unspecified tissues of weanling F1 or F2 pups did not show treatment-related alterations.

Support for the developmental toxicity of bromodichloromethane come from several *in vitro* studies. *In vitro* studies by Chen et al. (2003, 2004) provide some support for the association between bromodichloromethane exposure and increases in spontaneous abortion risks. These studies found bromodichloromethane-induced decreases in the secretion of chorionic gonadotrophin in cultured human placental trophoblasts. It is noted that trophoblasts are the sole source of chorionic gonadotrophin in humans and play a major role in maintenance of the conceptus. In porcine embryos, exposure to bromodichloromethane resulted in decreases in blastocyst rate and alterations in hormonal response (Pagé-Larivière et al. 2016). The study also found gene alterations that are consistent with cardiac anomalies.

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2.18 OTHER NONCANCER

The available studies in laboratory animals provide suggestive evidence that oral exposure to bromodichloromethane may result in a decrease in blood glucose levels. Decreases in blood glucose levels were observed in rats exposed to bromodichloromethane in the diet for 1, 6, or 18 months (Aida et al. 1989, 1992). However, these data are inconsistent and there is overlap between the NOAEL and LOAEL values. Following 6 months of exposure, the LOAEL was 25.5 (males)/31.7 (females) mg/kg/day and the NOAEL was 6.1/8.0 mg/kg/day; however, after 18 months, only females were affected and the NOAEL and LOAEL values were 31.7 and 168.4 mg/kg/day. This study (Aida et al. 1992) also reported significant increases in blood glucose levels in males exposed to 6.1 or 25.5 mg/kg/day, but not 138.0 mg/kg/day, for 12 months. Acute, single administration studies did not find significant alterations in blood glucose levels (Chu et al. 1982; Lilly et al. 1994, 1996).

No histological alterations were observed in the urinary bladder of rats exposed to 48.0 mg/kg/day bromodichloromethane for 10 months (McDorman et al. 2003).

2.19 CANCER

Information on the carcinogenicity of bromodichloromethane is limited to oral exposure studies in humans and animals. Numerous epidemiological studies indicate that there may be an association between ingestion of chlorinated drinking water (which typically contains bromodichloromethane) and increased risk of cancer in humans (e.g., Cantor et al. 1998; 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 bromodichloromethane or to one or more of the hundreds of other byproducts that are also present in chlorinated water. Three studies (Bove et al. 2007; Jones et al. 2019; Min and Min 2016) evaluated risk by individual trihalomethane. No associations were found between bromodichloromethane levels in public water supplies and rectal cancer risk (Bove et al. 2007) or between whole blood bromodichloromethane levels and total cancer deaths (Min and Min 2016). The third study (Jones et al. 2019) found an association between bromodichloromethane levels in municipal water and an increased risk of rectal cancer, but no association with colon cancer.

Several chronic oral studies in laboratory animals have examined the carcinogenic potential of bromodichloromethane. Gavage exposure studies have found significant increases in the incidence of neoplastic

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lesions in rats and mice. Administration of bromodichloromethane in corn oil for 2 years resulted in increases in the incidence of adenocarcinomas in the large intestine of male rats administered 50 mg/kg and male and female rats administered 100 mg/kg (NTP 1987). Increases in the incidences of renal tubular cell adenocarcinomas and/or combined incidence of adenoma and adenocarcinomas were observed in male and female rats at 100 mg/kg (NTP 1987) and in male mice administered 50 mg/kg (NTP 1987). In female mice, increases in the incidences of hepatocellular adenomas and/or carcinomas were observed at 75 and 150 mg/kg (NTP 1987). Tumasonis et al. (1985) also reported a significant increase in hepatic neoplastic nodules (no additional information was provided) in female rats exposed to 190 mg/kg/day bromodichloromethane in drinking water over a lifetime. Increases in the incidence of skin squamous cell papilloma and/or carcinoma were observed in male rats administered 50 mg/kg, but not at 100 mg/kg or in females at either dose (NTP 1987). Drinking water studies testing lower doses (≤ 36.3 mg/kg/day in rats and ≤ 43.3 mg/kg/day in mice) did not find dose-related increases in neoplastic lesions (George et al. 2002; NTP 2006); one study (George et al. 2002) found a significant increase in hepatocellular adenomas and carcinomas in male rats exposed to 3.9 mg/kg/day, but not in groups exposed to 20.6 or 36.3 mg/kg/day. Another study did not find significant increases in neoplastic lesions in male and female rats exposed to doses as high as 138.0 or 168.4 mg/kg/day, respectively, bromodichloromethane microencapsulated and added to the diet (Aida et al. 1992).

NTP (2006) explored possible differences in organ dosimetry between drinking water or dietary administration and gavage administration using physiologically based pharmacokinetic (PBPK) modeling to predict neoplasm incidences in the kidney and large intestine in rats exposed to bromodichloromethane in drinking water. Given the water concentrations used, the model predicted kidney cancer rates of $<1\%$, which is consistent with the empirical incidence of 0/50 in the NTP (2006) drinking water study, suggesting that the difference between the 1987 and 2006 studies was due to organ dosimetry. However, predicted incidences of large intestine neoplasms (3.5–10% depending on the dose metric used) were higher than the observed incidences (2% at 12 mg/kg/day and 0% at 6 and 25 mg/kg/day). NTP (2006) noted that the difference in large intestine tumors between the studies may have also been due to differences in fiber content of the diet used in each study (higher fiber content in the 2006 study compared to the 1987 study).

NTP, EPA, and IARC have classified bromodichloromethane as reasonably anticipated to be a human carcinogen (NTP 2016), a probable human carcinogen (Group B2) (IRIS 2002), or possibly carcinogenic to humans (Group 2B) (IARC 2016), respectively. The cancer classifications are based on inadequate data in humans and sufficient evidence in animal studies.

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2.20 GENOTOXICITY

This section is divided into two subsections. The first subsection discusses the results of *in vitro* and *in vivo* studies evaluating the genotoxicity of bromodichloromethane. The second subsection presents the results of *in vivo* studies evaluating epigenetic DNA alterations.

Genotoxicity. Bromodichloromethane has displayed mixed results for genotoxic activity in a variety of *in vivo* and *in vitro* tests with organisms ranging from bacteria to humans. As summarized in Table 2-4, bromodichloromethane produced mixed results in gene mutation studies using *Salmonella typhimurium* (Mortelmans et al. 1986; NTP 1987; Simmon et al. 1977; Sofuni et al. 1996; Varma et al. 1988; Zeiger 1990). Negative results were reported with and without metabolic activation in three studies (Mortelmans et al. 1986; NTP 1987; Zeiger 1990). Varma et al. (1988) reported positive results with metabolic activation in two strains and with or without activation in another two strains; Simmon et al. (1977) also reported an increase in gene mutations when tested with metabolic activation, but only when the assay was performed under a desiccator. Inconclusive results were reported by Sofuni et al. (1996), as only one study out of three produced an increased mutation frequency in the presence of activation only. A weakly positive result was reported in *Saccharomyces cerevisiae* in the absence of metabolic activation only (Nestmann and Lee 1985). Positive results for gene mutations were also found in mouse lymphoma cells with metabolic activation (McGregor et al. 1988; NTP 1987).

Table 2-4. Genotoxicity of Bromodichloromethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With Activation	Without Activation	
<i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	NTP 1987
<i>S. typhimurium</i> (strains not reported)	Gene mutation	(+) ^a	–	Sofuni et al. 1996
<i>S. typhimurium</i> (TA1535, TA1537)	Gene mutation	+	+	Varma et al. 1988
<i>S. typhimurium</i> (TA98, TA100)	Gene mutation	+	–	Varma et al. 1988
<i>S. typhimurium</i> (strains not reported)	Gene mutation	–	–	Zeiger 1990
<i>S. typhimurium</i> (TA100)	Gene mutation	No data	+ ^b	Simmon et al. 1977
<i>S. typhimurium</i> (TA97, TA98, TA100, TA1535, TA1537)	Gene mutation	No data	-	Mortelmans et al. 1986

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Table 2-4. Genotoxicity of Bromodichloromethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With	Without	
<i>Saccharomyces cerevisiae</i> (XVI85-14C reversion; D7 gene conversion)	Gene mutation	–	(+)	Nestmann and Lee 1985
Mouse lymphoma	Gene mutation	+	–	NTP 1987
Mouse lymphoma	Gene mutation	+	–	McGregor et al. 1988
Human hepatoma (HepG2) cells	DNA damage (OTM)	No data	+	Zhang et al. 2012
Human lymphoblastic leukemia cells (CCRF-CEM)	DNA damage (single strand breaks)	No data	+	Geter et al. 2004
Rat primary hepatocytes	DNA damage (single strand breaks)	No data	–	Geter et al. 2004
Human primary kidney cells	DNA damage (single strand breaks)	No data	+	Robbiano et al. 2004
Rat primary kidney cells	DNA damage (single strand breaks)	No data	+	Robbiano et al. 2004
Human primary kidney cells	Micronucleus test	No data	+	Robbiano et al. 2004
Rat primary kidney cells	Micronucleus test	No data	+	Robbiano et al. 2004
CHL cells	Chromosomal aberrations	+	–	Ishidate et al. 1988
CHL cells	Chromosomal aberrations	+	(+)	Matsuoka et al. 1996
CHO cells	Chromosomal aberrations, sister chromatid exchange	–	–	NTP 1987
CHO cells	Chromosomal aberrations, sister chromatid exchange	–	–	Anderson et al. 1990
Rat erythroblastic leukemia cells	Sister chromatid exchanges	–	+	Fujie et al. 1993
Human lymphocytes	Sister chromatid exchange	NA	–	Morimoto and Koizumi 1983; Tucker et al. 1993

^aResults were only positive in assays conducted by one of three laboratories.

^bResults were positive when assay was conducted in a desiccator; results were negative when tested in standard assay.

+ = positive results; (+) = weakly positive results; – = negative results; BDCM = bromodichloromethane; CHO = Chinese hamster ovary; CHL = Chinese hamster lung; NA = not applicable; OTM = olive tail moment

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DNA damage was observed in human cell lines (Geter et al. 2004; Zhang et al. 2012), rat hepatocytes (Geter et al. 2004), and human and rat kidney cells (Robbiano et al. 2004), all tested without metabolic activation. A toxicogenomic genotoxicity assay using *S. cerevisiae* provided evidence of DNA damage (Lan et al. 2018). Inconsistent results have been found in clastogenicity assays. Increases in micronuclei formation were observed in human and rat kidney cells (Robbiano et al. 2004). Four studies found negative results for chromosomal aberrations and/or sister chromatid exchanges (Anderson et al. 1990; Morimoto and Koizumi 1983; NTP 1987; Tucker et al. 1993). However, other studies have found positive results for chromosomal aberrations (Ishidate et al. 1988; Matsuoka et al. 1996) or sister chromatid exchanges (Fujie et al. 1993).

The *in vivo* genotoxicity of bromodichloromethane has been evaluated in humans, rats, and mice (Table 2-5). In a human study, a 1 µg/m³ increase in bromodichloromethane levels in expired air was associated with an increase in frequency of micronucleated peripheral blood lymphocytes; however, bromodichloromethane only accounted for 10% of the increase in micronuclei formation (Kogevinas et al. 2010). No significant associations were found for micronuclei formation in exfoliated urothelial cells (assessed 2 weeks postexposure), DNA damage in peripheral blood lymphocytes, or reverse mutations in a urine mutagenicity assay (Kogevinas et al. 2010).

Table 2-5. Genotoxicity of Bromodichloromethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Human (urine samples evaluated in <i>Salmonella</i> assay)	Reverse mutations (Ames assay)	–	Kogevinas et al. 2010
Human (peripheral blood lymphocytes; whole-body exposure in indoor pool)	DNA damage (comet assay)	–	Kogevinas et al. 2010
Rat (single gavage dose of 0.3 or 0.6 mM/kg in deionized water or 0.25% emulphor; 0.6–2.4 g/L in drinking water for 2 or 5 weeks)	DNA damage (single strand breaks)	–	Geter et al. 2004
Rat (single gavage dose of 1.5 mmol/kg in 4% emulphor)	DNA damage (single strand breaks)	–	Potter et al. 1996
Rat (single gavage dose of 458 mg/kg)	DNA damage in kidney cells (single strand breaks)	+	Robbiano et al. 2004
Rat (single gavage dose of 135 or 450 mg/kg in methylcellulose)	Unscheduled DNA synthesis in liver cells	–	Stocker et al. 1997
Human (peripheral blood lymphocytes; whole-body exposure in indoor pool)	Micronucleus test	+	Kogevinas et al. 2010

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Table 2-5. Genotoxicity of Bromodichloromethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Human (exfoliated urothelial cells; whole-body exposure in indoor pool)	Micronucleus test	–	Kogevinas et al. 2010
Rat (single gavage dose of 458 mg/kg)	Micronucleus test in kidney cells	+	Robbiano et al. 2004
Mouse (inhalation exposure to 1–150 ppm 6 hour/day for 7 days or 0.5–30 ppm 6 hours/day, 7 days/week for 3 weeks)	Micronucleus test in bone marrow and peripheral blood	(+)	Torti et al. 2002
Rat (bone marrow; intraperitoneal)	Chromosomal aberrations	+	Fujie et al. 1990
Rat (bone marrow; gavage in water)	Chromosomal aberrations	(+)	Fujie et al. 1990
Mouse (50 or 100 mg/kg/day via gavage in corn oil for 4 days)	Sister chromatid exchange in bone marrow cells	+	Morimoto and Koizumi 1983; Tucker et al. 1993

– = negative result; + = positive result; (+) = weakly positive results

Inconsistent results have been found in studies examining the potential of bromodichloromethane to cause DNA damage. Although Robbiano et al. (2004) found a significant increase in single strand breaks in kidney cells of rats administered a single dose of bromodichloromethane; studies by Geter et al. (2004) and Potter et al. (1996) did not find increases in kidney, liver, or duodenum epithelial cells of rats following single dose or repeated oral exposure. No increases in unscheduled DNA activity were observed in the livers of rats administered a single gavage dose of bromodichloromethane (Stocker et al. 1997). In general, positive results have been observed in several studies evaluating bromodichloromethane-induced clastogenic alterations. A weak induction of micronuclei was observed in mature red blood cells of mice exposed to 15 ppm bromodichloromethane vapor for 13 weeks (Torti et al. 2002). A significant increase in micronuclei in bone marrow cells was also observed in mice exposed to 100 ppm for 1 week, but the increase was not statistically significant at the next highest concentration (150 ppm); no significant increases in bone marrow nuclei were observed following a 3-week exposure to ≤ 15 ppm (Torti et al. 2002). Significant increases in micronuclei formation were also observed in kidney cells of rats administered via gavage 458 mg/kg bromodichloromethane (Robbiano et al. 2004). A dose-related increase in the frequency of chromosomal aberrations was observed in bone marrow cells of rats administered bromodichloromethane via intraperitoneal injection (Fujie et al. 1990); a weakly positive result was also reported in this study for rats receiving bromodichloromethane via gavage for 5 days. Increases in the frequency of sister chromatic exchanges were observed in mice administered bromodichloromethane for 4 days (Morimoto and Koizumi 1983). Although there are inconsistencies in the

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findings, overall the available data provide suggestive evidence that bromodichloromethane has the potential to damage DNA and chromosomes.

Epigenetic DNA Alterations. Two studies evaluated the potential of bromodichloromethane to induce epigenetic DNA alterations. A study of pregnant women found no associations between maternal blood bromodichloromethane levels (measured in late pregnancy) and DNA methylation in Alu and long interspersed nucleotide element-1 repetitive elements in cord blood after adjustments for prenatal body mass index (BMI), infant sex, passive smoking, and marital status (Yang et al. 2017). A second study (Tao et al. 2005) found significant reductions in DNA methylation in renal cells of mice administered bromodichloromethane via gavage in corn oil or in drinking water and rats administered bromodichloromethane via gavage (Tao et al. 2005). The decreases in DNA methylation were dose-related.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

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

- Bromodichloromethane is rapidly absorbed through the gastrointestinal tract and skin and is presumed to be rapidly absorbed through the respiratory tract.
- Absorbed bromodichloromethane is distributed throughout the body with the highest concentrations found in the fat, liver, lungs, and kidneys.
- The predominant pathway for bromodichloromethane metabolism is cytochrome P450 oxidation. Bromodichloromethane can also be metabolized via reduction to a dichloromethyl radical or glutathione conjugation catalyzed by glutathione transferase.
- Bromodichloromethane is rapidly excreted; the half-life following a single oral dose was 1.5–2.5 hours in rats and mice. The major route of excretion is expiration of the parent compound or carbon dioxide in exhaled air; smaller amounts of bromodichloromethane are excreted in the urine and feces.

3.1.1 Absorption

There are limited data on the bromodichloromethane absorption following inhalation exposure. Based on its physical-chemical properties and by analogy to another trihalomethane (chloroform) (ATSDR 1997), it is assumed that bromodichloromethane will be well absorbed.

Direct evidence of oral and dermal absorption of bromodichloromethane in humans comes from studies measuring blood levels of bromodichloromethane following ingestion or dermal exposure to bromodichloromethane (Leavens et al. 2007) or following ingestion, bathing, or showering with tap water containing trihalomethanes, including bromodichloromethane (Backer et al. 2000; Lynberg et al. 2001). Following oral exposure, bromodichloromethane is rapidly absorbed with peak blood levels of ¹³C-bromodichloromethane occurring 11 minutes after exposure (Leavens et al. 2007). Following a 1-hour dermal exposure, peak blood levels were observed at the end of the exposure, also suggesting that it is rapidly absorbed through the skin (Leavens et al. 2007).

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

Animal studies support the findings in humans that bromodichloromethane is rapidly absorbed following oral exposure (Aida et al. 1989; da Silva et al. 1999, 2000; Lilly et al. 1998; Mink et al. 1986; NTP 2006; Smith et al. 1985). In rats, peak blood levels were found 5–15 minutes (NTP 2006) or approximately 30 minutes (da Silva et al. 1999, 2000) after gavage administration. In contrast, a monkey study reported peak blood levels 4 hours after a gavage dose (Smith et al. 1985). Although studies have not quantified percent absorption, Mink et al. (1986) reported 62.7 and 92.7% recovery of radiolabeled bromodichloromethane in expired air, urine, and internal organs of rats and mice, respectively. Several animal studies found vehicle-specific differences in absorption rates. Mathews et al. (1990) found that 87–94% of radioactivity was excreted within 24 hours of single administration of 1–100 mg/kg bromodichloromethane. Lilly et al. (1998) and NTP (2006) found a more rapid initial uptake of bromodichloromethane dissolved in an aqueous solution than when it was dissolved in corn oil. Bromodichloromethane in olive oil administered via gavage was more rapidly absorbed than when the bromodichloromethane was dissolved in olive oil, microencapsulated, and added to the diet (Aida et al. 1989).

3.1.2 Distribution

Absorbed bromodichloromethane is distributed throughout the body. Six hours after a single intravenous administration of 10 mg/kg [¹⁴C]-bromodichloromethane in rats, the highest percentage of radioactivity is found in the fat, followed by muscle, liver, skin, blood, small intestine, and kidneys (Smith et al. 1985). In contrast, the highest percentage of radioactivity in rats after a single gavage dose is found in the stomach, followed by the liver, fat, muscle, small intestine, blood, skin, and kidney (Smith et al. 1985). Only a small amount of radioactivity was measured 24 hours after rats received a single gavage dose of 1, 10, or 100 mg/kg [¹⁴C]-bromodichloromethane. When tissue levels of radioactivity are compared based on tissue to blood ratios (see Table 3-1), the highest levels were found in the liver, kidney, stomach, small intestine, and large intestine (Mathews et al. 1990). Single administration studies found differences in the liver: blood ratios with the highest ratios present in rats administered 1 mg/kg as compared to 100 mg/kg. No evidence of bioaccumulation of radioactivity was observed in rats administered 10 or 100 mg/kg/day for 10 days. Mathews et al. (1990) examined the kidney and small intestines to examine the relative distribution between different regions. In the kidneys, 6–8 times higher levels of radioactivity were detected in the cortex, as compared to the medulla. No significant differences in radioactivity levels were found between the duodenum, jejunum, and ileum. Although no studies were located regarding distribution following inhalation or dermal exposure, it is expected to be similar to that of oral exposure based on the similarity of the distribution following intravenous and oral exposure (Smith et al. 1985).

Table 3-1. Tissue to Blood Ratios of Radioactivity 24-Hours After Gavage Administration of [¹⁴C]-Bromodichloromethane to Male Rats^a

	Single administration			10-Day administration	
	1 mg/kg	10 mg/kg	100 mg/kg	10 mg/kg/day	100 mg/kg/day
Adipose	0.83	0.42	0.68	1.01	1.99
Large intestine	3.33	2.30	2.89	1.74	3.03
Small intestine	3.71	2.91	2.45	1.91	3.18
Kidney	4.93	5.98	8.2	6.51	13.64
Liver	44.46	20.05	11.41	14.30	14.72
Muscle	2.38	1.99	1.56	0.59	1.14
Skin	1.28	0.94	0.90	1.23	2.21
Stomach	4.21	3.31	8.33	2.01	2.99

^aData from Mathews et al. (1990).

Batterman et al. (2002), Kenyon et al. (2016), and Lilly et al. (1997) determined partition coefficients for bromodichloromethane. In humans, blood:air, blood:urine, and milk:blood partition coefficients of 26.6, 4.13, and 1.26 were calculated (Batterman et al. 2002); Kenyon et al. (2016) estimated blood:air partition coefficients of 17.33 and 14.61 for male and female, respectively. A blood:air partition coefficient of 31.4 was calculated for rats (Lilly et al. 1997).

3.1.3 Metabolism

Three pathways have been identified for the metabolism of bromodichloromethane: (1) cytochrome P450 oxidation to phosgene (Allis and Zhao 2002; Allis et al. 2002; NTP 2006; Lilly et al. 1997; Mathews et al. 1990; Zhao and Allis 2002); (2) reduction to dichloromethyl radical (Lilly et al. 1997; Tomasi et al. 1985); and (3) glutathione conjugation (NTP 2006; Ross and Pegram 2003).

The predominant pathway is oxidation catalyzed by cytochrome P450. *In vivo* studies have identified four cytochrome P450 isozymes that are responsible for metabolizing bromodichloromethane in rats: CYP2E1, CYP2B1/2, CYP1A2, and CYP3A1 (Allis and Zhao 2002). Four isozymes are involved in humans: CYP2E1, CYP1A2, CYP2A6, and CYP3A4 (Allis and Zhao 2002). *In vitro* studies by these investigators showed that 90 and 60% of bromodichloromethane is metabolized by CYP2E1 in rats and humans, respectively; in humans, CYP3A4 accounts for most of the rest of the cytochrome metabolism. Oxidation of bromodichloromethane via CYP2E1 results in the formation of phosgene, which hydrolyzes to produce carbon dioxide (Allis and Zhao 2002; Lilly et al. 1997; Mathews et al. 1990). PBPK modeling

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estimates that following oral exposure to bromodichloromethane approximately 97% of the metabolism occurs in the liver; approximately 90% of total metabolism occurs on the first pass through the liver (NTP 2006). Cytochrome P450 oxidation accounts for 99% of the bromodichloromethane metabolism in the liver and 84–88% of the metabolism in the kidney and colon. Cytochrome P450 oxidation in the liver is also the primary metabolism pathway following inhalation exposure to bromodichloromethane (Allis et al. 2001). Several studies have shown that as the bromodichloromethane exposure level increases, the percentage of metabolism due to CYP2E1 decreases (Allis and Zhao 2002; Zhao and Allis 2002).

Although the metabolism of bromodichloromethane via glutathione conjugation catalyzed by glutathione transferase (GST) is quantitatively minor, the reactive metabolites formed may be toxicologically significant (Ross and Pegram 2003). In humans and rodents, the primary glutathione transferase isoform involved in bromodichloromethane metabolism is glutathione transferase theta 1-1 (GST T1-1) (Leavens et al. 2007; Ross and Pegram 2003). The GST T1-1 reactive metabolites are unstable, react with biomolecules near the site of generation, and have not been detected in circulation (Leavens et al. 2007). The reactive glutathione conjugates may result in the formation of DNA adducts (Ross and Pegram 2003).

Using PBPK modeling, NTP (2006) analyzed the relative contribution of cytochrome P450 and GST metabolism in the liver, kidney, and colon in rats following oral exposure to bromodichloromethane. The ratios of cytochrome P450/GST were 95, 6.9, and 6.0 in the liver, kidney, and colon following administration of 50 mg/kg. Following administration of 100 mg/kg, the ratios were 77, 7.1, and 5.3, respectively. The dose-related changes are likely due to first pass cytochrome P450 saturation in the liver and the higher levels of bromodichloromethane in the blood and availability to other tissues.

3.1.4 Excretion

The major route of excretion of bromodichloromethane in rats, mice, and monkeys is exhaled alveolar air, either as parent bromodichloromethane, or as volatile metabolites such as carbon dioxide (Mathews et al. 1990; Mink et al. 1986; Smith et al. 1985). Small amounts are excreted in the urine and feces. Twenty-four hours after a single exposure to 1, 10, or 100 mg/kg [¹⁴C]-bromodichloromethane, 71–82% of the radiolabel was expired as carbon dioxide, 3–5% as carbon monoxide, and 3–6% as expired volatiles (Mathews et al. 1990). Urinary and fecal excretion accounted for 4 and 0.7–3%, respectively, of the excreted radiolabel (Mathews et al. 1990). Similar excretion patterns were observed in another study of rats (Mink et al. 1986), a study in mice (Mink et al. 1986), and a study in monkeys (Smith et al. 1985).

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No route-specific differences in excretion patterns were observed in monkeys administered bromodichloromethane via gavage or intravenous injection (Smith et al. 1985).

The half-lives of bromodichloromethane in rats and mice following a single oral administration (100 mg/kg and 150, respectively) were estimated to be 1.5 and 2.5 hours, respectively (Mink et al. 1986), and the half-life in monkeys was 4–8 hours (Smith et al. 1985). This indicates that bromodichloromethane is effectively excreted and that tissue accumulation of bromodichloromethane is unlikely.

In a repeated-dose gavage study in rats (Mathews et al. 1990), the daily excretion of radiolabel (approximately 75%) did not change over the course of the 10-day administration of 10 mg/kg/day. However, administration of 100 mg/kg/day resulted in expiration of 30% of the radiolabel as carbon dioxide during the 8 hours after administration on day 1. On days 2–10, 60% of the label was expired as carbon dioxide.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Single species PBPK models have been developed for bromodichloromethane; however, a PBPK model that could be used to extrapolate from laboratory animals to humans for risk assessment has not been identified for this chemical. Kenyon et al. (2016) developed a human PBPK model that allows for the assessment of the contribution of multiple exposure routes (inhalation, oral, and dermal) to overall internal dose metrics for bromodichloromethane. The model predicts that dermal exposure and inhalation exposure during bathing will substantially contribute to the overall internal dose of bromodichloromethane. Lilly and associates developed a PBPK model in rats that allows predictions of tissue distribution and metabolism following inhalation (Lilly et al. 1997) or gavage administration with an oil or aqueous vehicle (Lilly et al. 1998). The model consists of five compartments (liver, kidney, fat, slowly

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perfused tissues, and rapidly perfused tissues) and assumes that 95% of bromodichloromethane metabolism occurs in the liver and the remaining 5% occurs in the kidney.

3.1.6 Animal-to-Human Extrapolations

No studies were identified that provide evidence to suggest differences in the toxicity or toxicokinetics of bromodichloromethane between humans and animals. There are limited human toxicology studies that do not allow for a comparison to rat and mouse toxicity studies. Some species differences have been noted between rats and mice, although the targets of toxicity appear to be similar. The available data suggest that the toxicity of bromodichloromethane is mediated by its reactive metabolites which are most likely formed by cytochrome P450 isoforms, particularly CYP2E1 (Allis and Zhao 2002; Lilly et al. 1997, 1998). CYP2E1 in rats is closely related to human CYP2E1 (Allis and Zhao 2002). Other P450 isoforms may also play an important role in bromodichloromethane metabolism at low concentrations; these isoforms differ in humans and rats (Allis and Zhao 2002; Zhao and Allis 2002); however, the contribution of other isoforms to the overall bromodichloromethane metabolism is not known.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to bromodichloromethane are discussed in Section 5.7, Populations with Potentially High Exposures.

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There are limited data on the toxicity of bromodichloromethane in children and the toxicity of bromodichloromethane is assumed to be similar to adults. As discussed in Section 2.16, gestational exposure to bromodichloromethane has resulted in full-litter resorption and delays in skeletal ossification in rats (Bielmeier et al. 2001; Christian et al. 2001a; Narotsky et al. 1997; Ruddick et al. 1983) and decreases in birth weight (Wright et al. 2004; Rivera-Núñez and Wright 2013) and increases in stillbirths or spontaneous abortions (King et al. 2000; Waller et al. 1998) in humans. No human or animal studies assessed the risks associated with childhood exposures. Animal data provide strong evidence that the liver is one of the critical targets of toxicity for bromodichloromethane (see Section 2.9 for details); mechanistic data suggest that a reactive metabolite is the causative agent. In rats (and humans), bromodichloromethane is primarily metabolized in the liver by the cytochrome P450 isoform CYP2E1 (Allis and Zhao 2002). As discussed in EPA (2005b), CYP2E1 levels rapidly increase during the first 24 hours after birth and the levels in children aged 1–10 years are similar to adults. A study evaluating human hepatic CYP2E1 expression during development found that CYP2E1 levels increased with age (Johnsrud et al. 2003). At 0–30 days of age, the median levels were approximately half that of infants 31–90 days of age and approximately 4 times lower than at age 91 days to 18 years. The lower levels of CYP2E1 may result in increased susceptibility of very young infants. Using the Kenyon et al. (2016) PBPK model, Kenyon et al. (2019) demonstrated that extrahepatic levels of bromodichloromethane were higher in neonates and infants, as compared to adults.

Persons with existing renal or hepatic disease might also be more susceptible, since these organs are adversely affected by exposure to bromodichloromethane. The elderly may represent an unusually susceptible population because they may have age-related deficiencies of liver and kidney function. They may also be frequently exposed to metabolism-influencing medications.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of

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exposure to bromodichloromethane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for bromodichloromethane from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by bromodichloromethane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Human studies have identified blood, alveolar air, and urine levels of bromodichloromethane as biomarkers of exposure. Since bromodichloromethane is rapidly excreted, these biomarkers assess recent exposure. A number of human studies have found associations between exposure to bromodichloromethane in tap water (Backer et al. 2000; Lynberg et al. 2001; Nuckols et al. 2005; Riederer et al. 2014; Rivera-Núñez et al. 2012) and blood bromodichloromethane levels. In 2015–2016, the geometric median blood bromodichloromethane level in the United States was below the detection limit of 6.00 pg/mL (CDC 2019); see Section 5.6 for a more detailed presentation of the NHANES biomonitoring data. Lynberg et al. (2001) reported that blood bromodichloromethane levels were approximately 1,000-fold lower than the bromodichloromethane level in a resident's tap water. Exposure to bromodichloromethane in tap water can occur via multiple routes of exposure from several daily activities including consumption of tap water, showering, and bathing. A study comparing the relative

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contribution of different activities found the highest levels of blood bromodichloromethane in subjects showering for 10 minutes, as compared to those bathing for 10 minutes or drinking 1 L of water in 10 minutes (Backer et al. 2000). A more detailed analysis of water use activity and bromodichloromethane blood levels found increases in blood levels associated with showering, bathing, and hand dish washing, but not with consumption of hot or cold beverages, clothes washing, or hand washing (Nuckols et al. 2005). Bromodichloromethane levels increased approximately 7–16-, 8.2–12-, or 3-fold after showering, bathing, or hand dish washing, respectively. Using NHANES 1999–2006 data, Riederer et al. (2014) examined predictors of blood bromodichloromethane levels. Water concentration was one of the major predictors of blood levels. Other factors that were negatively associated with blood bromodichloromethane levels included diabetes and eating cruciferous vegetables. Backer et al. (2000) examined the possible association of polymorphisms and bromodichloromethane blood levels. A significant association was found for the CYP2D6 *4/*4 enzyme variant (decreased metabolizing activity).

Studies of pool workers and swimmers report increases in bromodichloromethane levels in alveolar air (Aggazzotti et al. 1998; Caro and Gallego 2007, 2008; Lindstrom et al. 1997; Pleil and Lindstrom 1997). Alveolar air bromodichloromethane levels increased rapidly during the entire 1–2 hours exposure period (Caro and Gallego 2008). Alveolar air levels rapidly declined and returned to pre-exposure levels within 1 hour post-exposure (Aggazzotti et al. 1998; Caro and Gallego 2008). One study estimated a half-life of 26 minutes (Caro and Gallego 2008). Pleil and Lindstrom (1997) estimated a half-time of 0.45–0.63 minutes in blood based on alveolar elimination in swimmers exposed for 2 hours.

Studies in pool workers and swimmers have also established urinary bromodichloromethane as a biomarker of exposure (Caro and Gallego 2007, 2008). Urinary bromodichloromethane levels increased 1.8 times in workers at an indoor pool for 2 hours and 2.5 times in workers near the pool for 4 hours (Caro and Gallego 2007). Much higher increases in urinary bromodichloromethane were found in swimmers; a 3–4-fold increase in levels were observed following a 1-hour swim, suggesting that increased ventilation rate and dermal exposure increased the amount of bromodichloromethane absorbed. A half-time for bromodichloromethane in urine was estimated to be 45 minutes (Caro and Gallego 2008).

3.3.2 Biomarkers of Effect

There are no specific biomarkers to characterize the effects caused by bromodichloromethane. The available evidence suggests that the hepatotoxicity of bromodichloromethane is likely due to oxidative damage from reactive intermediates. Measurement of biomarkers of oxidative stress such as glutathione

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and oxidative response agents such as NrF2 could be indicative of liver toxicity. However, measurement of these agents would not be specific to bromodichloromethane.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Hewitt et al. (1983) reported that pretreatment of rats with an oral dose of acetone increased the hepatic and renal toxicity of an oral dose of bromodichloromethane given 18 hours later, as evidenced by increased relative liver weight, increased serum alanine aminotransferase and aspartate aminotransferase activities, increases in relative kidney weight, and increases in blood urea nitrogen levels, as compared to rats pretreated with water.

Several studies have examined toxicokinetic interactions between bromodichloromethane and other trihalomethanes and chloroacetic acids. The blood area under the curve (AUC) obtained in rats receiving a single gavage dose of 0.25 mmol/kg bromodichloromethane was significantly lower than the AUC when bromodichloromethane was administered with three other trihalomethanes (chloroform, dibromochloromethane, and bromoform, 0.25 mmol/kg of each compound); the AUC was 8.15 times higher when administered with other trihalomethanes (da Silva et al. 1999). The investigators suggested that this may be due to metabolic interactions between the compounds. Similar results were found when binary mixtures of trihalomethanes were tested (da Silva et al. 2000). Co-administration via intravenous injection of bromodichloromethane with trichloroacetic acid or monochloroacetic acid also resulted in higher blood bromodichloromethane levels (St. Pierre et al. 2003). *In vitro* studies demonstrated that the increases in bromodichloromethane blood levels were due to metabolic inhibition by other trihalomethanes or trichloroacetic acid (St. Pierre et al. 2005).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Bromodichloromethane is a trihalomethane with one bromide atom and two chloride atoms. It is a colorless liquid with relatively high vapor pressure and high water solubility. It was previously used as a halogenated fire retardant. Bromodichloromethane is a disinfection byproduct formed during the chlorination of waters.

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for bromodichloromethane.

Table 4-1. Chemical Identity of Bromodichloromethane

Characteristic	Information	Reference
Chemical name	Bromodichloromethane	HSDB 2012
Synonym(s) and registered trade name(s)	Dichlorobromomethane; BDCM; monobromodichloromethane; methane, bromodichloro-; Halon 1021	HSDB 2012; NIOSH 2015
Chemical formula	CHBrCl ₂	HSDB 2012
Chemical structure	$\begin{array}{c} \text{Br} \\ \\ \text{Cl}-\text{C}-\text{Cl} \\ \\ \text{H} \end{array}$	Haynes 2014
CAS Registry Number	75-27-4	HSDB 2012

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of bromodichloromethane.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Bromodichloromethane

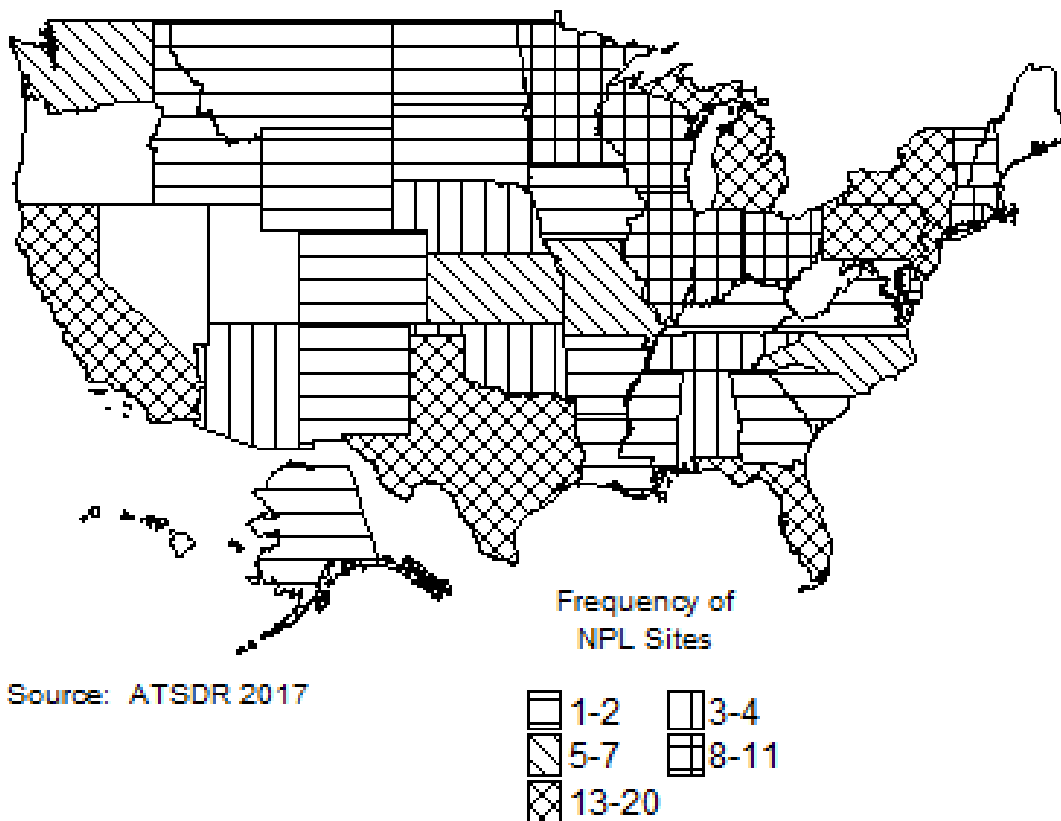
Property	Information	Reference
Molecular weight	163.829	Haynes 2014
Color	Colorless	O'Neil 2013
Physical state	Liquid	O'Neil 2013
Melting point	-56.0°C	Haynes 2014
Boiling point	90°C	Haynes 2014
Density:		Haynes 2014
at 20°C/4°C	1.980	
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Taste threshold	No data	
Solubility:		
Water	3,030 mg/L at 30°C	Yalkowsky et al. 2010
Organic solvent(s)	Very soluble in ethanol, acetone, and benzene; slightly soluble in carbon tetrachloride	Haynes 2014
Partition coefficients:		
Log K _{ow}	2.00	HSDB 2012
Log K _{oc}	1.8	Mabey et al. 1982
Vapor pressure		
at 20°C	50 mm Hg	HSDB 2012
Henry's law constant	2.12x10 ⁻³ at 25°C	EPA 1987
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	1 ppm=6.70 mg/m ³ 1 mg/m ³ =0.15 ppm	Verschueren 1977
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Bromodichloromethane has been identified in at least 238 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which bromodichloromethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 233 are located within the United States, 2 are located in the Virgin Islands, and 3 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Bromodichloromethane Contamination



- The most likely route of exposure for the general public to bromodichloromethane is through ingestion, inhalation, and dermal contact of chlorinated drinking water.
- A median bromodichloromethane intake of 2.8–4.2 $\mu\text{g}/\text{day}$ from drinking water has been estimated; inhalation and dermal exposure would add to this daily intake.

5. POTENTIAL FOR HUMAN EXPOSURE

- Bromodichloromethane is formed as a byproduct of water disinfection methods using chlorination. This is the primary source of bromodichloromethane in the environment.
- Its principal use is as a chemical intermediate for organic synthesis and as a chemical reagent.
- Volatilization is an important fate process. Bromodichloromethane evaporates from sources and enters the environment as a gas, which is slowly broken down in air. Residual bromodichloromethane may be broken down slowly by bacteria.
- In the atmosphere, bromodichloromethane is thought to undergo slow degradation through oxidative pathways, with a half-life of about 2–3 months.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL**5.2.1 Production**

The principal anthropogenic source of bromodichloromethane is its unintentional formation as a byproduct during the chlorination of water containing organic materials and bromide. It has been reported as the second most frequently detected trihalomethane, following chloroform, in drinking water (Bellar et al. 1974; EPA 2003; Krasner et al. 1989). Bromodichloromethane is formed when chlorine-based chemical disinfectants react with organic matter and bromide present in the system. The reaction is dependent on water quality and the treatment process used for disinfection. Factors such as organic matter concentration, bromide and chlorine concentration, temperature, pH, and contact time affect the production of byproducts during disinfection (WHO 2000).

Synthesis of bromodichloromethane can be achieved by treating a mixture of chloroform and bromoform with triethylbenzylammonium chloride and sodium hydroxide (IARC 1991). Bromodichloromethane is produced commercially by the reaction of dichloromethane with aluminum bromide.

No information is available in the TRI database on facilities that manufacture or process bromodichloromethane because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005a).

5.2.2 Import/Export

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

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5.2.3 Use

In the past, bromodichloromethane 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 (USGS 2006a). At present, the principal use of bromodichloromethane is as a chemical intermediate for organic synthesis and as a chemical laboratory reagent, particularly as a standard in the analysis of drinking water (IARC 1991; O'Neil 2013; Sittig 1985; Verschueren 1983). Bromodichloromethane is not listed as an ingredient in fire extinguishers or solvents as of April 2017, but it is listed as a possible colorant constituent in dyes and pigments as well as a polar organic compound in fragrances of consumer products; it may be used in pesticides or fracking practices, and it is a component of several water standard kits (Dionisio et al. 2015; EPA 2014a).

5.2.4 Disposal

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

Bromodichloromethane has been detected in the raw and treated waste water of numerous industries (EPA 1983), but no quantitative data on amounts of bromodichloromethane disposed of to the environment were located.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005a). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥ 10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to

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facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005a).

5.3.1 Air

There is no information on releases of bromodichloromethane to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005a).

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

Class et al. (1986) observed trace levels of bromodichloromethane, $0.7\text{--}6.7\text{ ng/m}^3$ (<1 ppt), and other bromomethanes in seawater and in the air above the ocean at several locations in the Atlantic between 1982 and 1985. The presence of bromodichloromethane was attributed to biosynthesis and release of bromodichloromethane by macroalgae (Class et al. 1986; Gschwend et al. 1985).

In 1978 through 1986, releases of bromodichloromethane from indoor and outdoor swimming pools were measured from the surface of the pool up to 2 m above the pool surface; air concentrations of bromodichloromethane ranged between 0.2 and $210\text{ }\mu\text{g/m}^3$ (IARC 1991).

5.3.2 Water

There is no information on releases of bromodichloromethane to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005a).

The principal source of bromodichloromethane in the environment is from chlorination of water. EPA (1980) estimated that >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

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may occur either indoors (e.g., while showering, washing, cooking, etc.) or outdoors after discharge of the water to the surface.

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

Releases of water containing bromodichloromethane that may enter groundwater include water use techniques such as the recharge of chlorinated waters for lawn and garden irrigation in commercial and residential areas, leaking swimming pools and water lines, leaking chlorinated water distribution and sewer pipes, and unintentional backflow of chlorinate water to supply wells (USGS 2003, 2006a).

5.3.3 Soil

There is no information on releases of bromodichloromethane to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005a).

Water use techniques such as the recharge of chlorinated public waters for lawn and garden irrigation in commercial and residential areas may contribute to bromodichloromethane in the soil environment (USGS 2006a).

Monitoring efforts during the summer and fall of 2008 at the Love Canal in Niagara Falls, New York identified bromodichloromethane as a contaminant in the soil/sediment/water samples (Hauser and Bromberg 1982).

Hoekstra et al. (1998) detected bromodichloromethane at concentrations ranging from 0.03 to 0.31 ng/L (0.0003–0.0031 µg/L) in soil-air samples taken from soil layers, at depths of 10–160 m below the surface, in a Douglas fir forest near Apeldoorn in the Netherlands. Bromodichloromethane was not detected in the ambient air samples taken 5–10 cm above the soil surface. Concentrations of bromodichloromethane in the soil layers were higher in the deeper layers reaching a maximum at a depth of 120 cm.

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5.4 ENVIRONMENTAL FATE**5.4.1 Transport and Partitioning**

Air. Because of the relatively high vapor pressure of bromodichloromethane (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 bromodichloromethane in the environment is estimated to exist in air (EPA 1980).

Bromodichloromethane 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 bromodichloromethane removed from air in this way is likely returned to air through volatilization.

Water. Volatilization from surface waters depends on factors such as turbulence and temperature. A measured Henry's Law constant for bromodichloromethane of 2.12×10^{-3} at 25°C indicates that volatilization from water is an important fate process. 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 bromodichloromethane applied to a soil column in the laboratory escaped by volatilization. A fate study in a waste water treatment wetland near Phoenix, Arizona, receiving chlorinated municipal wastewaters, resulted in 83% removal of bromodichloromethane. Volatilization was indicated as the primary removal process, with an atmospheric flux of 2.47 g/day/ha (Keefe et al. 2004).

Bromodichloromethane is moderately soluble in water (3,030 mg/L). Significant transport of bromodichloromethane can occur in water, especially in groundwater where volatilization is restricted. This transport pathway may be important at waste sites or other locations where bromodichloromethane spills lead to groundwater contamination.

Sediment and Soil. An estimated log K_{oc} value of 1.8 (Mabey et al. 1982) indicates that bromodichloromethane is expected to possess high mobility in soil surfaces and has the potential to leach into groundwater. Bromodichloromethane applied to the surface of a sandy soil (92% sand, 5.9% silt, 2.1% clay, <0.1% organic carbon) in a packed column experiment quickly percolated to the bottom of the column (140 cm) when eluted with water (Wilson et al. 1981). Roughly 48% of the initially applied amount was collected in column effluent and about 54% was shown to volatilize from the column.

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Other Media. The moderate solubility and low log K_{ow} indicate that bioaccumulation of bromodichloromethane by fish or other aquatic species is likely to be minor, but no estimate of a bioaccumulation factor in aquatic species was located.

5.4.2 Transformation and Degradation

Air. Pathways responsible for bromodichloromethane degradation in the atmosphere are not well studied, but likely involve oxidative reaction with hydroxyl radicals or singlet oxygen (EPA 1980; Mabey et al. 1982). Bromodichloromethane does not contain chromophores that will absorb light at wavelengths >290 nm, and therefore, direct photochemical decomposition is not likely to be significant (EPA 1980). The typical atmospheric lifetime of bromodichloromethane has been estimated to be 2–3 months (EPA 1980). This relatively persistent tropospheric half-life of bromodichloromethane suggests that a small percentage of the bromodichloromethane present in air will eventually diffuse into the stratosphere where it will be destroyed by photolysis. In addition, long-range global transport is possible.

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

Biodegradation in aqueous media may be significant in some cases. For example, Tabak et al. (1981) reported 35% loss of the test substance in a static test after 7 days of incubation in a medium inoculated with sewage at 25°C. Repeated culturing lead to increased losses, up to 59% after 28 days, indicating gradual adaptation of the degradative microbes. Tabak et al. (1981) also examined the volatilization of bromodichloromethane after 10 days at 25°C. The study resulted in 8% loss of test substance due to volatilization, indicating that biodegradation is the prominent degradation process for bromodichloromethane (Tabak et al. 1981).

Under anaerobic aquatic conditions where volatilization cannot occur, biodegradation may be the predominant mechanism for degradation of bromodichloromethane. In a continuous-flow biofilm reactor with a settled sewage inoculum and three zones (aerobic, denitrifying, and sulfate-reducing regions) bromodichloromethane achieved $>99\%$ transformation, coinciding with the onset of the sulfate-reducing zone in the column; concentrations were approximately 46 and <0.1 µg/L in the influent and effluent, respectively, after 120 days (Cobb and Bouwer 1991). Bouwer et al. (1981) and Bouwer and McCarty

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(1983a) studied the degradation of bromodichloromethane 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. Minimal to no degradation was observed by Bouwer et al. (1981) under aerobic conditions after a 6-week study using mixed methanogenic bacterial cultures in sterile and seeded conditions. Under anaerobic conditions, rapid degradation (>99% after 2 days) was observed by Bouwer and McCarty (1983a). Slow degradation under anaerobic conditions (50–70% 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).

Sediment and Soil. Biodegradation of bromodichloromethane 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.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to bromodichloromethane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of bromodichloromethane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on bromodichloromethane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-1 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. Bromodichloromethane has been detected in indoor and outdoor air, water sources, and in soil; an overview summary of the range of concentrations detected in environmental media is presented in Table 5-2.

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Table 5-1. Lowest Limit of Detection Based on Standards^a

Media	Detection Limit	Reference
Air	0.019 ppbv	EPA 1999
Drinking water	0.003 µg/L	EPA 1990
Surface water and groundwater	0.049 µg/L	USGS 1998
Soil	0.02 µg/L	EPA 2014d, 2002, 1996a, 1996b, 1996c
Sediment	0.02 µg/L	EPA 2014d, 2002, 1996a, 1996b, 1996c
Whole blood	0.29 ng/L; 0.36 ng/L	Bonin et al. 2005

^aDetection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-2. Summary of Environmental Levels of Bromodichloromethane

Media	Low	High	For more information
Outdoor air (ppbv)	0.00076	0.180	Table 5-6
Indoor air (ppbv)	0.01	0.49	Table 5-7
Surface water (ppb)	0.3	1.1	Table 5-9
Ground water (ppb)	0.02	23	Table 5-10
Drinking water (ppb)	Range of mean levels 1.0–20.3		Table 5-11
Food (ppb)	Trace	37	Tables 5-13 and 5-14
Soil	No monitoring data were located		

Detections of bromodichloromethane in air, water, and soil at NPL sites are summarized in Table 5-3.

Table 5-3. Bromodichloromethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of concentrations	NPL sites
Water (ppb)	6	8.01	7,560	100	64
Soil (ppb)	9.35	7.26	2,190	6	6
Air (ppbv)	0.10	0.13	228	3	3

^aConcentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

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5.5.1 Air

Data from the EPA Air Quality System (AQS) database were used to calculate the annual mean percentile distributions of bromodichloromethane from multiple monitoring locations across the nation for the years 2010–2018 (EPA 2019). The results of these data are summarized in Table 5-4. The AQS database is EPA's source of criteria air pollutant and hazardous air pollutant (HAP) monitoring data. Monitoring data for other years may be obtained directly from the EPA AQS website.

Table 5-4. Percentile Distribution of Annual Mean Bromodichloromethane Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States

Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2010	151	0.0089	0.010	0.033	0.10	0.47
2011	127	0.0079	0.012	0.029	0.099	0.47
2012	124	0.0072	0.010	0.050	0.075	0.23
2013	117	0.0095	0.0097	0.050	0.052	0.24
2014	116	0.0090	0.012	0.050	0.067	0.12
2015	52	0.0090	0.0090	0.050	0.11	0.23
2016	101	0.0000	0.0000	0.000328	0.0023	0.35
2017	87	0.0000	0.0000	0.0000	0.0020	0.12
2018	83	0.0000	0.0000	0.0005	0.0019	0.033

Source: EPA 2019

The 2012 and 2013 National Monitoring Program sponsored by the EPA compiled 24-hour air sample data from 64 and 66 monitoring sites, respectively, located in 26 states across the United States (EPA 2015a, 2014b). Samples from 34 sites were assessed for volatile organic compounds, including bromodichloromethane, in 2013 and samples from 30 sites were obtained for 2012. The percent of detections at each site ranged from about 0 to 15%, with the exception of the site in Northbrook, Illinois at which bromodichloromethane was detected in 93% of the 61 samples at that site in 2013 and 100% of the samples in 2012 (EPA 2015b, 2014c). The results of these data are summarized in Table 5-5.

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Table 5-5. Statistical Summary of Bromodichloromethane Concentrations from the 2012 and 2013 National Monitoring Program

Non detects ^a	Measured detects ^a	Measured detects <MDL	Minimum (ppbv) ^b	Maximum (ppbv)	Arithmetic mean (ppbv)	Median (ppbv)	25 th (ppbv)	75 th (ppb)	Standard deviation (ppbv)
2013									
1,728	155	113	0.005	8.36	0.009	0	0	0	0.205
2012									
1,350	116	NR	0.006	4.10	0.010	0	0	0	0.152

^aOut of 1,883 valid samples in 2013 and 1,466 valid samples in 2012.

^bExcludes zeros for non-detects.

MDL = method detection limit

Source: EPA 2014b, 2015a

Ambient air monitoring data for bromodichloromethane, including data for concentrations detected during water-related activities, are compiled in Tables 5-6, 5-7, and 5-8.

Table 5-6. Outdoor Air Monitoring Data for Bromodichloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Texas, North Carolina, Arkansas	Suburban, urban, source dominated	Not specified (1983 or earlier)	0.00076–0.180 ppbv	0.0011 ppbv	Not detected in two of the rural, remote sites monitored in Arkansas	Brodzinsky and Singh 1983
California	Urban, industrial	1982/1983		0.01–0.10 ppbv	Detected above 0.01 ppbv in 35% of the samples	Shikiya et al. 1984
Atlantic Ocean	Open ocean	1982/1984/1985	0.001–0.007 ppbv		Air samples at several locations; attributed to releases from macroalgae	Class et al. 1986
Texas, Louisiana, North Carolina, Arkansas	Suburban, urban, source dominated	Not specified (2005 or earlier)		0.74 µg/m ³ (0.11 ppbv)	Outdoor air	EPA 2005b
Germany	Surface air above swimming pools	1995–1999	0.03–2.0 µg/m ³ (0.0045–0.3 ppbv)	0.1–0.4 µg/m ³ (0.02–0.06 ppbv)	Measured 20 or 150 cm above the water surface of outdoor pools	WHO 2006

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Table 5-6. Outdoor Air Monitoring Data for Bromodichloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Surface air above swimming pools	1986	<0.1 µg/m ³ (<0.02 ppbv)	Not reported	Measured 200 cm above the water surface outdoor pools	WHO 2006

Table 5-7. Indoor Air Monitoring Data for Bromodichloromethane

Location(s)	Geographic type	Date(s)	Mean concentration	Notes	Reference
New Jersey	Suburban	Not specified (1999 or earlier)	0.38–0.75 µg/m ³ (0.056–0.11 ppbv)	Indoor air of 48 households	EPA 2005b
Southwestern United States	Urban living space air	August 1997	0.01–0.49 ppbv	Indoor air concentrations from 24-hour integrated samples 0.2–0.9 µg/m ³ (0.03–0.13 ppbv); air exchange rates in the home influenced concentrations	Kerger et al. 2005
Italy	Surface air above indoor swimming pools	1993–1998	17.4–20 µg/m ³ (2.61–3 ppbv)	Measured 20 cm above water surface of indoor pool	WHO 2006
Germany	Surface air above swimming pools	1995–1999	4.1–9.2 µg/m ³ (0.62–1.38 ppbv)	Measured 20 or 150 cm above the water surface of indoor pools	WHO 2006
United States	Surface air above swimming pools	1986	Range of <0.1–10 µg/m ³ (0.02–2 ppbv)	Measured 200 cm above the water surface of indoor pools	WHO 2006

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Table 5-8. Water-Related Activities and Indoor Air Monitoring Data for Bromodichloromethane

Activity	Range
Showering ^{a,b}	Prior: 0.3–20.9 µg/m ³ (0.04–3.12 ppbv)
	During: 33.1–141.5 µg/m ³ (4.94–21.1 ppbv)
	After: 14.8–96 µg/m ³ (2.21–14.3 ppbv)
Bathing ^{a,c}	Prior: 0.4–2.1 µg/m ³ (0.06–0.31 ppbv)
	During: 7.0–65.1 µg/m ³ (1.0–9.71 ppbv)
	After: 5.9–29.0 µg/m ³ (0.88–4.33 ppbv)

^aThe average concentration of bromodichloromethane in the household water samples was reported as 42.0 µg/L.

^bDurations of showers were 6.8–20 minutes; ventilated and non-ventilated scenarios were assessed.

^cDurations of bath were 6.8–20 minutes.

Source: Kerger et al. 2000

5.5.2 Water

Bromodichloromethane occurs in water primarily as a byproduct of the chlorination process used for disinfection, but it also can be found in surface waters from biosynthesis by macroalgae.

The concentration of bromodichloromethane 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 chlorination treatment practices (EPA 1985). The amount of bromodichloromethane tends to increase as a function of increasing organic content and bromide ion in the source water (Arguello et al. 1979; Bellar et al. 1974).

Concentrations of bromodichloromethane in swimming pool waters are affected by several factors including the frequency and number of swimmers in the pool, the chlorine dose used for disinfection, the bromide content, and the source water used (Kim et al. 2002).

Water monitoring data for bromodichloromethane are compiled in Tables 5-9, 5-10, 5-11, and 5-12.

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Table 5-9. Surface Water Monitoring Data for Bromodichloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
California, Utah, Florida	Monitoring sites	January–December 2012	Not detected–140 µg/L	Mean: 11.07 µg/L; median: 0.0 µg/L	EPA STORET data: Routine monitoring samples from: California Department of Water Resources; Hopland Band of Pomo Indians Tribal EPA; Dade Environmental Resource Management (Florida); Utah Department of Environmental Quality; water depths 0–1 m	WQP 2017
California, Utah, Florida	Monitoring sites	January–December 2013	Not detected–25.0 µg/L	Mean: 0.74 µg/L; median: 0.0 µg/L	EPA STORET data: Routine monitoring samples from: California Department of Water Resources; Hopland Band of Pomo Indians Tribal EPA; Dade Environmental Resource Management (Florida); Utah Department of Environmental Quality; water depths 0–1 m	WQP 2017
California; Utah, Florida	Monitoring sites	January–December 2014	Not detected–51.90 µg/L	Mean: 1.93 µg/L; median: 1.2 µg/L	EPA STORET data: Routine monitoring samples from: California Department of Water Resources; Hopland Band of Pomo Indians Tribal EPA; Dade Environmental Resource Management (Florida); Utah Department of Environmental Quality; water depths 0–12 m	WQP 2017

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Table 5-9. Surface Water Monitoring Data for Bromodichloromethane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
California; Minnesota	Monitoring sites	January–October 2015	Not detected– 13.00 µg/L	Mean: 1.99 µg/L; median: 0.0 µg/L	EPA STORET data: Routine monitoring samples from: California Department of Water Resources; Minnesota Pollution Control Agency-Ambient Surface Water; water depths 0–1 m	WQP 2017
Atlantic Ocean	Open ocean; African coast, West Africa, Porto Santo, Sao Miguel, Bermuda Islands, Tenerife	1982/1984/1985	0.0001– 0.001 µg/L (seawater); 0.0004 µg/L (rain)	Not reported	Surface water concentrations attributed to releases from macroalgae	Class et al. 1986
Gila River Phoenix, Arizona	River surface water	1997–1998	Not detected	Not reported		Rostad et al. 2000
The Rhine, Meuse, northern delta area, and Westerscheld	Surface water	1992–1997	<100 µg/L	Not reported		Miermans et al. 2000

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Table 5-10. Groundwater Monitoring Data for Bromodichloromethane

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
Salt Lake Valley, Utah	Well	1999	0.02–0.51 µg/L	Not reported	Detected in 17 of 30 wells sampled; attributed to the recharge of chlorinated public supply waters used to irrigate lawns and gardens in residential areas	USGS 2003
United States	Shallow groundwater	1996 and 2002	Trace: ≤0.2 µg/L	Not reported	Detected in 14% of samples; ≥0.2 in 1.7% of the samples	Squillace et al. 2004
United States	Domestic wells	1986–2001	0.2–7.0 µg/L	Not reported	Detected in 124 of 2,400 wells sampled	USGS 2006b
United States	Public wells	1986–2001	0.2–21 µg/L	Not reported	Detected in 46 of 1,095 wells sampled	USGS 2006b
United States	Untreated Ground and source water	1985–2002	0.02–23 µg/L	Not reported	Detected in 1–3% of the aquifers samples; 0.1–1.7% shallow groundwaters; more frequently detected in groundwater samples collected from urban areas as compared to agricultural areas	USGS 2006b
United States	Untreated Ground; public and domestic wells	1997–2007	0.08–0.09 µg/L (median values)	Not reported	10% (66 out of 631) of the public well samples; 1.7% (33 out of 1,861) of the domestic well samples; detected at a higher frequency in wells surrounded by urban areas compared with undeveloped, mixed, and agricultural surroundings	Carter et al. 2012
United States	Public wells	1993–2007		Not reported	Detected in 11% of the samples (932 wells)	USGS 2010b
United States	Principal aquifers	1991–2010	>0.2 µg/L	Not reported	0.93% frequency of detection of bromodichloromethane in 40 aquifers in the United States used for drinking water; 1.67% frequency of detection of bromodichloromethane in 22 aquifers beneath urban areas	USGS 2015
Taiwan	Groundwater	Not specified (2000 or prior)		Not reported	Detected in less than 5% of 214 sample taken at 30 industrial sites	Kuo 2000
Tampa Bay, Florida	Groundwater in an aquifer	October 2002–January 2003; August–September 2004	0.040 µg/L	Not reported	Detected 3 times in 30 source-water samples collected from 30 community water system wells during the first phase, concentration not reported; 1 time in 11 source-water samples collected during the second phase	USGS 2007

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Table 5-11. Drinking Water Monitoring Data for Bromodichloromethane

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Finished water	August 1973–February 1974	1.1–20.8 µg/L	Not reported	Sampling sites not reported	Bellar et al. 1974
Tampa Bay, Florida	Finished water	August–September of 2004	0.053–7.48 µg/L	Not reported	Detected in 10 of 10 finished water samples	USGS 2007
United States	Drinking water	2000–2004		1.0, 15.0, and 20.3 µg/L	Three locations were sampled weekly; it was found that all trihalomethanes were removed after heating the drinking water; faucet filters completely removed trihalomethanes and pitcher filters removed on average 40% of the trihalomethanes.	Savitz et al. 2006
India	Finished water	March 2009–June 2009		0.03–315 µg/L (median 12.40 µg/L)	Samples collected from water treatment plant endpoints at 11 locations	Basu et al. 2011
United States	Drinking/finished water	1991–2003		1.62 µg/L	Detected in 3 out of 34 tap water samples	FDA 2006
Italy	Italian tap water	Not specified (2005 or prior)	0.249 µg/L	Not reported	Not detected in Italian mineral water, contaminated mineral water, Italian superficial snow, or Antarctic superficial snow	Zoccolillo et al. 2005
Korea	Tap water	2009	Maximum 10.7 µg/L	6.1 µg/L (median 6.3 µg/L)	Detected in 100% of 770 tap water samples from six municipal water treatment plants using chlorination disinfection methods; highest concentrations were observed in the summer samples	Lee et al. 2013

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Table 5-11. Drinking Water Monitoring Data for Bromodichloromethane

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Drinking water	1988–1989	Seasonal medians 4.1–10 µg/L	Not reported	35 water utilities; 25 across the United States and 10 in California	Krasner et al. 1989
Canada	Drinking water	1976–1977	2.9 µg/L	Not reported	Reported concentration in winter samples from water supplies serving 38% of the population in 70 communities	WHO 2000
United States, Florida, Washington, Pennsylvania, Ohio, Michigan	Drinking water	1974–1986	Not detected– 73 µg/L	1–20 µg/L		Coleman et al. 1975; EPA 1979; Furlong and D'itri 1986; Symons et al. 1975

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Table 5-12. Swimming Pool Water Monitoring Data for Bromodichloromethane

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
Miami, Florida	Saltwater and freshwater swimming pools	Not specified (1980 or prior)		13–34 µg/L		Beech et al. 1980
Poland, Italy, United States, Germany, Hungary, and the United Kingdom	Swimming pools	1981–2002	<0.1–150 µg/L	1.3–22.6 µg/L		WHO 2006
Not reported	Laboratory study of pool water		7.9 µg/L	Not reported	Concentration in groundwater control 4.4 µg/L	Kim et al. 2002
Portugal	Indoor swimming pools	April–November 2011	1–21.5 µg/L	Not reported	Detected in 99% of the pool water samples	Silva et al. 2012
Not reported	Swimming pools	February–August 2008	Specific concentrations of bromodichloromethane were not reported, it was noted that its occurrence was sporadic compared with the other disinfection byproducts that appeared regularly in the samples	Not reported	Water was sampled 20–30 cm below pool surface	Weaver et al. 2009

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5.5.3 Sediment and Soil

Little information was located regarding concentrations of bromodichloromethane in ambient soils. Because of its volatility, it is likely that bromodichloromethane would be present only at low levels in most soils.

Bromodichloromethane was detected in <1% of 705 soil samples taken from 30 industrial sites investigated in Taiwan. Sites included chemical and petrochemical industrial districts, technology industrial parks, general industrial districts, metal processing areas, oil refinery plants, pesticide manufacturing facilities, and landfills. Samples were collected via purge-and-trap techniques using EPA method 5035 (Kuo 2000).

5.5.4 Other Media

Bromodichloromethane is not a common contaminant of food, occurring only in trace quantities in some samples (trace quantities are concentrations above the method detection limit but below the method quantification limit).

A market basket study conducted by the U.S. Food and Drug Administration (FDA) in 1991–2003 evaluated over 400 food products (FDA 2006). Bromodichloromethane was detected in about 10% of the foods, mostly at trace levels. Data are provided in Table 5-13.

Table 5-13. Bromodichloromethane Detections in Food from the U.S. Food and Drug Administration (FDA) 1991–2003 Market Basket Survey

Food	Number of detections	Number of samples	Mean concentration (ppb)
Processed American cheese	1	44	0.07
Boiled beef/pork frankfurters	4	44	0.39
Beef/pork bolognas	2	44	0.43
Salami lunch meats	1	44	0.09
Popcorn popped in oil	1	40	0.13
Raw/frozen strawberry samples	1	43	0.07
Regular carbonated colas	4	44	0.43
Diet carbonated colas	4	44	0.36
Plain milk chocolate candy bars	1	44	0.09

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Table 5-13. Bromodichloromethane Detections in Food from the U.S. Food and Drug Administration (FDA) 1991–2003 Market Basket Survey

Food	Number of detections	Number of samples	Mean concentration (ppb)
Light vanilla ice creams	3	44	0.16
Salted margarines	3	44	0.30
Salted butters	1	44	0.14
Baby food beef and gravy	1	44	0.07
Swiss cheeses	3	44	0.36
Cream cheese	1	44	0.09
Fast food chicken nuggets	3	44	0.23
Graham crackers	1	44	0.07
Fast food french fries	1	44	0.07
Fast food tacos with beef and cheese	1	44	0.09
Take out pizzas	1	44	0.11
Vanilla ice creams	5	44	0.34
Fruit sherbets	3	44	0.32
Fruit popsicles	6	44	0.50
Sour creams	4	44	0.30
Carbonated fruit drinks	3	44	0.43
Fast food chicken legs	1	4	0.75
Pan cooked catfish	1	4	0.75
Salted and roasted sunflower seeds	1	4	1.0
Bottled cranberry juice cocktails	1	4	1.75
Orange juices	1	4	0.75
Prepared potato salads	1	4	1.0
Prepared coleslaws	1	4	0.75
Fried eggs with added fat	1	40	0.33
Canned pork and bean samples	1	44	0.25
Creamy peanut butter	1	44	0.23
Homemade cornbread	1	44	0.30
Raw orange	1	44	0.32
Canned pineapple	1	44	0.32
Bottled apple juice	1	44	0.75
Fresh/frozen, boiled collards	1	44	0.32
Tomatoes	1	44	0.25
Green peppers	1	44	0.32
Fast food quarter-pound hamburgers on a bun	1	44	0.84

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Table 5-13. Bromodichloromethane Detections in Food from the U.S. Food and Drug Administration (FDA) 1991–2003 Market Basket Survey

Food	Number of detections	Number of samples	Mean concentration (ppb)
Creamy low calorie salad dressing	1	4	2.5

Source: FDA 2006

A 5-year study of 70 foods was conducted from 1996 to 2000 using purge-and-trap methods (Fleming-Jones and Smith 2003). Forty-one of the foods had at least one detection of a volatile organic compound over 100 ppb. Bromodichloromethane was detected in 10 of these 41 foods at concentrations ranging from 3 to 5 ppb, with the expectation of the highest concentration found in 1 sample of cooked hamburger at 37 ppb. Data are provided in Table 5-14.

Table 5-14. Bromodichloromethane in Food

Food	Number of detections	Concentration ppb
American cheese	1	3
Fruit-flavored sherbet	1	3
Popsicle	1	3
Fast food french fries	1	3
Fast food chicken nuggets	1	3
Carbonated cola	2	3
Sour cream	1	4
Beef frankfurters	2	4–5
Popcorn popped in oil	1	5
Cooked hamburger	1	37

Source: Fleming-Jones and Smith 2003

Hiatt and Pia (2004) screened 35 milk samples from eight grocery stores in Las Vegas, Nevada in January and February 2002. Concentrations of bromodichloromethane were 0.02–0.30 µg/L in whole milk, 0.03–0.37 µg/L in 2% milk, and 0.04–0.14 µg/L in 1% milk.

A market basket study of 39 food items detected bromodichloromethane in one dairy composite at 1.2 ppb and in butter at 7 ppb (Entz et al. 1982). A study of bromodichloromethane in food processing water and processed foods revealed no detectable levels except in ice cream at one processing plant (0.6–2.3 ppt) (Uhler and Diachenko 1987). Soft drinks have been found to contain bromodichloromethane

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(Abdel-Rahman 1982; Entz et al. 1982), but usually at concentrations (0.1–6 µg/L) below those found in municipal water supplies. Cooking foods in water containing bromodichloromethane is unlikely to lead to contamination, since bromodichloromethane would rapidly volatilize (Kool et al. 1981).

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

Bromodichloromethane has been detected in the milk of rats at a concentration of 0.38 µg/g after exposure to 112 mg/kg-day, but was not detected in placentas, amniotic fluid, or fetal tissue collected on GD 21, nor plasma collected from postpartum day 29 weanling pups, after similar exposures (EPA 2005b). Bromodichloromethane was detected in one fetus and in the placentas of rabbits exposed to 76 mg/kg/day, but it was not detected in placentas of rabbits exposed to approximately 32 mg/kg/day, nor in amniotic fluid or the remaining fetuses from rabbits exposed to doses of approximately 76 mg/kg/day (EPA 2005b).

5.6 GENERAL POPULATION EXPOSURE

The general population can be exposed to bromodichloromethane via ingestion and dermal contact of water containing this chemical and also by inhalation of bromodichloromethane that has volatilized into air. Exposure may occur when people are involved in water-related activities such as showering, bathing, swimming pool activities, and washing dishes in water containing bromodichloromethane. Occupational exposure may occur via inhalation and dermal contact for individuals who work at swimming pools (e.g., lifeguards).

No studies were located examining the exposures of children to bromodichloromethane. Exposure will likely occur through inhalation, dermal contact, and, ingestion of water containing bromodichloromethane. Exposures would be expected to vary depending on the amount of water consumed, the length of time a child spends doing water-related activities, and the quality of the water the child is exposed to.

The average exposures to bromodichloromethane for the general human population from surface water and groundwater systems have been estimated at 20 and 8.1 µg/person/day, respectively (EPA 2005b). The estimated exposure of the general human population to bromodichloromethane from ingesting drinking water containing bromodichloromethane, assuming a median bromodichloromethane

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concentration of 1.4–2.1 $\mu\text{g/L}$ (ppb) and a water intake for an adult of 2 L/day, would be 2.8–4.2 $\mu\text{g/day}$ (EPA 2005b). Exposure can also occur by inhalation of bromodichloromethane volatilized from chlorinated water (e.g., while showering, cooking, or swimming), and by dermal contact with such water. In 67% of breath samples, collected from 11 subjects in Texas and North Carolina, bromodichloromethane concentrations ranged from 0.12 to 4.36 $\mu\text{g/m}^3$ (EPA 2005b). Based on a chemical structure analogy to chloroform, an estimated dermal exposure to bromodichloromethane in a child swimming 2 hours/day in a saline pool would typically be 0.003 mg/day, with a maximum of 0.04 mg/day (Beech et al. 1980). Higher exposure levels might occur through ingestion of water contaminated with bromodichloromethane near a waste site, but available data suggest that this is not a common occurrence.

The updated Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2019) includes results from the assessment of bromodichloromethane levels in the National Health and Nutrition Examination Survey (NHANES) for blood samples from the U.S. general population surveyed during the years 2001–2016. As shown in Table 5-15, geometric mean bromodichloromethane levels were 2.21, 1.50, 1.41, 1.52, 1.61, and 1.34 pg/mL for the survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 respectively; in 2013–2014 and 2015–2016, geometric mean levels could not be calculated because the proportion of results below the limit of detection was too high to provide a valid result. The analytical method used for the analysis was gas chromatography with high-resolution mass spectrometry (Bonin et al. 2005). The limits of detection (LODs) for survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016 are 0.233, 0.62, 0.62, 0.62, 0.62, 0.62, 6.00, and 6.00 pg/mL, respectively.

After activities such as bathing, showering, or swimming in chlorinated water, median blood levels of bromodichloromethane increased over baseline levels, and then returned to baseline during the next 1–2 hours following the end of the activity (Ashley et al. 2005; Lourencetti et al. 2010; Silva et al. 2013).

Ashley et al. (2005) and Gordon et al. (2006) investigated human exposure to bromodichloromethane via dermal, ingestion, and inhalation pathways. Activities included drinking a hot and cold beverage, showering/bathing in hot water, drinking 0.5 L of tap water, washing and drying a load of laundry, washing hands, running a dishwasher, and opening and removing dishes from a dishwasher, washing clothes with chlorine bleach, washing dishes by hand, and staying in a room adjoining an operating shower. These activities led to approximately a 3–4-fold increase in bromodichloromethane levels in the blood of the seven subjects following showering, bathing, or hand washing. Dermal exposure was cited

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Table 5-15. Blood Bromodichloromethane Levels in the NHANES U.S. Population

	Survey years	Geometric mean (95% CI) (pg/mL)	Selected percentiles (95% confidence interval) (pg/mL)				Sample size
			50 th	75 th	90 th	95 th	
Total	2001–2002	2.21 (1.65–2.97)	2.30 (1.56–3.21)	4.63 (3.24–6.20)	8.45 (5.86–12.0)	12.0 (7.68–19.2)	785
	2003–2004	1.50 (1.20–1.86)	1.40 (1.10–1.90)	3.40 (2.60–4.20)	6.20 (5.30–7.00)	9.50 (7.00–12.0)	1,322
	2005–2006	1.41 (1.09–1.83)	1.30 (0.880–1.80)	3.00 (2.10–4.40)	6.30 (4.30–9.70)	10.0 (6.80–14.0)	3,139
	2007–2008	1.52 (1.24–1.86)	1.42 (1.05–1.90)	3.13 (2.50–4.20)	6.42 (4.70–8.30)	9.59 (7.05–14.6)	2,982
	2009–2010	1.61 (1.23–2.10)	1.44 (0.911–2.33)	3.84 (2.64–5.33)	7.89 (6.36–9.58)	12.0 (9.65–14.5)	3,275
	2011–2012	1.34 (1.07–1.67)	1.18 (0.817–1.66)	2.94 (2.07–3.92)	5.89 (4.32–8.29)	8.95 (6.35–13.5)	2,700
	2013–2014	*	<LOD	<LOD	7.00 (<LOD–8.00)	10.0 (8.00–11.0)	3,160
	2015–2016	*	<LOD	<LOD	9.00 (6.00–13.0)	13.0 (9.00–21.0)	3,077
Age group							
12–19 years	2005–2006	1.23 (0.954–1.58)	1.00 (0.620–1.60)	2.80 (1.70–4.10)	5.50 (4.10–7.20)	8.20 (6.20–12.0)	932
	2007–2008	1.49 (1.19–1.86)	1.26 (0.910–1.88)	3.10 (2.42–4.05)	6.20 (4.13–8.52)	9.02 (6.20–15.0)	482
	2009–2010	1.42 (0.912–2.34)	3.84 (2.65–5.82)	8.41 (5.45–12.7)	8.41 (5.45–12.7)	13.0 (8.78–18.0)	558
	2011–2012	*	0.956 (<LOD–1.21)	2.03 (1.51–3.00)	4.19 (3.06–6.62)	9.06 (6.49–13.7)	507
	2013–2014	*	<LOD	<LOD	<LOD	9.00 (6.00–10.0)	594
	2015–2016	*	<LOD	<LOD	6.00 (<LOD–10.0)	9.00 (<LOD–15.0)	543
20–59 years	2001–2002	2.21 (1.65–2.97)	2.30 (1.56–3.21)	4.63 (3.24–6.20)	8.45 (5.86–12.0)	12.0 (7.68–19.2)	785
	2003–2004	1.50 (1.20–1.86)	1.40 (1.10–1.90)	3.40 (2.60–4.20)	6.20 (5.30–7.00)	9.50 (7.00–12.0)	1,322
	2005–2006	1.45 (1.11–1.89)	1.30 (0.900–1.90)	3.10 (2.10–4.60)	6.40 (4.30–10.0)	11.0 (6.90–14.0)	1,537
	2007–2008	1.60 (1.28–2.01)	1.56 (1.13–2.04)	3.33 (2.61–4.43)	6.90 (4.94–9.29)	11.0 (7.39–15.6)	1,607
	2009–2010	1.67 (1.24–2.26)	1.53 (0.893–2.56)	4.07 (2.66–5.85)	8.47 (6.66–10.2)	13.0 (10.1–16.2)	1,797
	2011–2012 ^a	1.38 (1.09–1.075)	1.22 (0.862–1.82)	2.91 (2.08–3.88)	6.00 (4.35–8.62)	9.06 (6.49–13.7)	2,196
	2013–2014 ^a	*	<LOD	<LOD	7.00 (<LOD–9.00)	10.0 (8.00–12.0)	2,566
	2015–2016 ^a	*	<LOD	<LOD	9.00 (6.00–14.0)	15.0 (10.0–19.0)	2,534
≥60 years	2005–2006	1.43 (0.996–2.05)	1.40 (0.850–2.00)	3.20 (1.60–5.90)	6.50 (3.20–15.0)	9.70 (5.00–18.0)	670
	2007–2008	1.28 (1.07–1.53)	1.20 (0.870–1.59)	2.60 (1.90–3.41)	4.88 (3.67–6.50)	7.39 (5.70–8.80)	893
	2009–2010	1.41 (1.13–1.78)	1.33 (0.851–1.86)	3.25 (2.39–4.25)	6.07 (5.07–7.59)	8.42 (6.95–11.6)	920

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Table 5-15. Blood Bromodichloromethane Levels in the NHANES U.S. Population

	Survey years	Geometric mean (95% CI) (pg/mL)	Selected percentiles (95% confidence interval) (pg/mL)				Sample size
			50 th	75 th	90 th	95 th	
Sex							
Males	2001–2002	2.19 (1.60–3.00)	2.31 (1.63–3.21)	4.64 (3.21–6.08)	7.96 (5.74–15.3)	13.0 (6.93–20.5)	382
	2003–2004	1.48 (1.18–1.85)	1.40 (0.940–2.00)	3.40 (2.60–4.30)	6.60 (5.40–7.20)	11.0 (7.20–14.0)	650
	2005–2006	1.39 (1.07–1.80)	1.20 (0.830–1.70)	3.00 (2.00–4.30)	6.50 (4.30–10.0)	11.0 (6.80–16.0)	1,489
	2007–2008	1.52 (1.24–1.87)	1.50 (1.03–1.95)	3.23 (2.59–4.20)	6.72 (4.80–9.02)	11.0 (7.31–15.9)	1,487
	2009–2010	1.48 (1.18–1.85)	1.41 (0.861–2.23)	3.79 (2.46–5.62)	8.32 (6.36–10.6)	13.0 (10.1–17.2)	1,616
	2011–2012	1.33 (1.06–1.67)	1.17 (0.756–1.69)	2.91 (2.08–3.88)	5.92 (4.48–8.29)	9.17 (6.65–13.3)	1,363
	2013–2014	*	<LOD	<LOD	7.00 (<LOD–9.00)	10.0 (8.00–12.0)	1,523
	2015–2016	*	<LOD	<LOD	9.00 (6.00–14.0)	14.0 (9.00–21.0)	1,523
Females	2001–2002	2.24 (1.66–3.01)	2.28 (1.49–3.24)	4.63 (3.09–7.01)	8.62 (5.26–12.9)	11.1 (7.68–25.0)	403
	2003–2004	1.51 (1.21–1.90)	1.50 (1.10–1.90)	3.30 (2.50–4.20)	6.10 (4.69–7.30)	7.80 (6.40–12.0)	672
	2005–2006	1.44 (1.10–1.88)	1.30 (0.900–1.90)	3.10 (2.10–4.60)	6.20 (4.20–9.40)	9.40 (6.30–13.0)	1,650
	2007–2008	1.51 (1.22–1.87)	1.40 (1.01–1.92)	3.03(2.42–4.10)	6.20 (4.60–7.82)	8.31 (6.80–12.9)	1,495
	2009–2010	1.62 (1.24–2.16)	1.53 (0.946–2.46)	3.92 (2.79–5.19)	7.67 (6.22–9.28)	11.2 (8.99–13.9)	1,659
	2011–2012	1.35 (1.06–1.67)	1.22 (0.828–1.70)	2.94 (1.96–4.06)	5.87 (4.05–8.63)	8.63 (5.87–13.3)	1,337
	2013–2014	*	<LOD	<LOD	6.00 (<LOD–8.00)	9.00 (7.00–11.0)	1,637
	2015–2016	*	<LOD	<LOD	8.00 (<LOD–13.0)	13.0 (7.00–21.0)	1,554
Race/ethnicity							
Mexican Americans	2001–2002	3.28 (2.29–4.68)	3.32 (2.19–4.70)	6.81 (3.71–10.4)	10.8 (8.24–14.7)	14.7 (11.1–20.5)	227
	2003–2004	1.65 (1.15–2.38)	1.60 (0.820–2.80)	3.50 (2.60–4.90)	7.30 (4.50–10.0)	10.0 (7.30–11.0)	244
	2005–2006	1.95 (1.19–3.18)	1.90 (1.00–3.70)	4.40 (2.10–9.10)	9.10 (4.80–17.0)	14.0 (7.50–22.0)	771
	2007–2008	1.61 (1.27–2.03)	1.57 (1.08–2.20)	3.44 (2.42–4.50)	5.93 (4.70–8.15)	8.90 (6.80–13.2)	574
	2009–2010	2.19 (1.37–3.49)	2.18 (1.10–4.16)	5.50 (3.20–8.98)	11.3 (6.59–19.5)	16.2 (11.2–22.5)	667
	2011–2012	1.53 (1.16–2.04)	1.19 (0.761–2.16)	3.44 (2.41–5.20)	9.06 (5.21–15.4)	15.9 (6.55–40.0)	298
	2013–2014	*	<LOD	<LOD	<LOD	10.0 (<LOD–14.0)	500
	2015–2016	*	<LOD	<LOD	9.00 (7.00–12.0)	13.0(9.00–17.0)	552
Non-Hispanic blacks	2001–2002	2.32 (1.82–2.94)	2.50 (1.56–3.55)	4.57 (3.60–5.56)	8.69 (5.63–9.49)	10.0 (5.89–13.5)	130
	2003–2004	1.56 (1.15–2.13)	1.70 (1.10–2.20)	2.90 (2.15–3.80)	5.10 (3.80–6.60)	6.60 (4.90–13.0)	290
	2005–2006	1.74 (1.27–2.37)	1.70 (1.00–2.70)	3.80 (2.70–4.80)	6.40 (4.50–8.90)	8.70 (6.60–11.0)	817
	2007–2008	1.72 (1.42–2.08)	1.70 (1.30–2.21)	3.29 (2.80–4.01)	5.78 (4.70–7.30)	7.49 (6.03–9.70)	593
	2009–2010	1.97 (1.50–2.58)	1.99 (1.41–2.53)	3.76 (2.55–5.82)	7.70 (5.35–10.2)	10.5 (8.52–13.4)	579
	2011–2012	1.84 (1.09–3.12)	1.72 (0.734–3.80)	4.48 (2.11–8.95)	9.60 (5.03–15.2)	13.0 (8.47–22.3)	712
	2013–2014	*	<LOD	<LOD	7.00 (<LOD–10.0)	9.00 (8.00–11.0)	603
	2015–2016	*	<LOD	<LOD	7.00 (<LOD–13.0)	11.0 (6.00–18.0)	639

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Table 5-15. Blood Bromodichloromethane Levels in the NHANES U.S. Population

	Survey years	Geometric mean (95% CI) (pg/mL)	Selected percentiles (95% confidence interval) (pg/mL)				Sample size
			50 th	75 th	90 th	95 th	
Non-Hispanic whites	2001–2002	2.02 (1.42–2.87)	2.16 (1.36–3.09)	4.34 (2.92–6.01)	7.33 (4.72–15.3)	11.1 (6.01–26.1)	365
	2003–2004	1.42 (1.11–1.81)	1.30 (0.850–1.90)	3.30 (2.30–4.40)	6.20 (5.20–7.20)	9.80 (6.70–13.0)	684
	2005–2006	1.29 (0.989–1.67)	1.10 (0.710–1.70)	2.70 (1.80–4.10)	5.80 (4.00–8.60)	9.40 (6.20–14.0)	1,318
	2007–2008	1.45 (1.11–1.87)	1.32 (0.917–1.90)	3.03 (2.23–4.30)	6.50 (4.20–9.29)	9.59 (6.30–15.3)	1,347
	2009–2010	1.46 (1.06–2.02)	1.25 (0.673–2.30)	3.59 (2.22–5.37)	7.28 (5.51–9.28)	10.9 (8.50–14.3)	1,470
	2011–2012	1.18 (0.909–1.53)	1.03 (<LOD–1.51)	2.55 (1.65–3.42)	4.83 (3.26–6.95)	7.54 (4.79–12.6)	933
	2013–2014	*	<LOD	<LOD	7.00 (<LOD–10.0)	9.00 (8.00–11.0)	1,288
2015–2016	*	<LOD	<LOD	9.00 (<LOD–15.0)	14.0 (8.00–21.0)	999	
All Hispanics	2011–2012	1.70 (1.39–2.08)	1.52 (1.11–2.16)	3.66 (2.86–4.69)	8.08 (5.98–9.67)	12.9 (7.51–22.1)	587
	2013–2014	*	<LOD	<LOD	7.00 (<LOD–10.0)	11.0 (8.00–14.0)	798
	2015–2016	*	<LOD	<LOD	9.00 (7.00–12.0)	13.0 (9.00–17.0)	964
Asians	2011–2012	1.49 (1.20–1.84)	1.43 (0.998–1.96)	3.04 (2.39–4.11)	5.23 (4.63–6.51)	7.44 (5.99–9.64)	388
	2013–2014	*	<LOD	<LOD	9.00 (<LOD–12.0)	12.0 (9.00–15.0)	361
	2015–2016	*	<LOD	<LOD	9.00 (6.00–13.0)	14.0 (12.00–15.0)	349

^aValues for participants 20+ years of age.

*= geometric mean not calculated because the proportion of results below the limit of detection (0.62 in 2011–2012 and 6.00 pg/mL in 2013–2014 and 2015 and 2016) was too high to provide a valid result; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2019; https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf

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as the primary route of exposure during bathing, while inhalation played a stronger role during showering (Gordon et al. 2006).

Tables 5-16, 5-17, and 5-18 contain available human blood, breath, and urine concentrations of bromodichloromethane resulting from exposure to this substance via water-related activities.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The environmental medium most likely to be contaminated with bromodichloromethane 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. 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 bromodichloromethane 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 bromodichloromethane levels.

People working in chemical plants or laboratories where bromodichloromethane 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 bromodichloromethane, but this can only be evaluated on a case-by-case basis.

People working at and using chlorinated swimming pools (especially indoor pools), such as lifeguards, pool and/or water venue operators, and regular or professional/athletic swimmers, may be exposed to bromodichloromethane more often than the general population (Fantuzzi et al. 2001; Lindstrom et al. 1997).

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Table 5-16. Exposure and Blood Concentrations

Population and exposure scenario	Study date	Average media concentration	Average blood concentration before activity	Average blood concentration during activity	Average blood concentration after activity	Reference
100 subjects, ages 18–45; 10-minute controlled shower ^a	2004	70.9–74.3 µg/m ³ (shower air); 19.9 µg/L (shower water)	0.00225 µg/L (2.25 ng/L)	0.0648 µg/L (64.8 ng/L) (10 minutes after shower)	0.0326 µg/L (32.6 ng/L) (30 minutes after shower)	Silva et al. 2013
7 subjects, ages 21–30; hot water shower	Not reported	8.0–46.4 µg/L (tap water)	Not reported	25.5–95.2 ng/L (5 minutes after shower)	Not reported	Ashley et al. 2005
7 subjects, ages 21–30; hot water bath	Not reported	6.3–33.0 µg/L (tap water)	Not reported	26.0–64.7 ng/L (5 minutes after bath)	Not reported	Ashley et al. 2005
150 women; showering/bathing, bathing children, postshower/bathroom time, washing dishes by hand, and swimming in summer	Not reported	1.3–12.2 µg/L (water)	1.1–4.7 ng/L ^b			Rivera-Núñez et al. 2012
150 women; showering/bathing, bathing children, postshower/bathroom time, washing dishes by hand, and swimming in winter	Not reported	6.0–7.3 µg/L (water)	2.1–5.6 ng/L ^b			Rivera-Núñez et al. 2012
150 women; ingestion of water; showering/bathing, bathing children, postshower/bathroom time, washing dishes by hand, and swimming	Not reported	6.3–8.5 µg/L (yearly average water)		2.0–3.3 ng/L		Rivera-Núñez et al. 2012
150 women; non-ingestion of water; showering/bathing, bathing children, postshower/bathroom time, washing dishes by hand, and swimming	Not reported	6.3–8.5 µg/L (yearly average water)		2.3–2.6 ng/L		Rivera-Núñez et al. 2012
31 adult subjects; drinking tap water	Not reported	5.52 µg/L	2.6 pg/mL	3.8 pg/mL (10 minutes after drink)	2.8 pg/mL (60 minutes after drink)	Backer et al. 2000

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Table 5-16. Exposure and Blood Concentrations

Population and exposure scenario	Study date	Average media concentration	Average blood concentration before activity	Average blood concentration during activity	Average blood concentration after activity	Reference
31 adult subjects; bathing	Not reported	6.22 µg/L	2.3 pg/mL	17.0 pg/mL (10 minutes after bath)	9.9 pg/mL (30 minutes after bath)	Backer et al. 2000
31 adult subjects; showering	Not reported	6.27 µg/L	3.3 pg/mL	19.4 pg/mL (10 minutes after shower)	10.3 pg/mL (30 minutes after shower)	Backer et al. 2000
50 females; showering	1999	12.2–13.5 ppb (µg/L) (median house water concentrations)	6.2–6.8 ppb (µg/L)	Not reported	38–43 ppb (µg/L)	Lynberg et al. 2001

^a40°C shower temperature and a water flow rate between 5.6 and 6.7 L/minute; average concentration of bromodichloromethane in shower water.

^bAverage concentration throughout specified season.

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Table 5-17. Exposure and Breath (Alveolar Air) Concentrations

Population and exposure scenario	Average media concentration	Average breath concentration before activity	Average breath concentration during activity	Average breath concentration after activity	Reference
9 subjects ages 22–37; 10-minute controlled shower	1.9 µg/L (shower water) 1.1 µg/m ³ (shower air)	0.1 µg/m ³		1.3 µg/m ³	Lourencetti et al. 2010
11 subjects; 40-minute swim indoor pool	1.9 µg/L (pool water) 1.1 µg/m ³ (pool air)	0.1 µg/m ³		1.8 µg/m ³	Lourencetti et al. 2010
Swimmers exposed under training conditions for 2 hours using indoor pool	2.68 µg/m ³ (pool air)	Not reported; <2.68 µg/m ³	3–3.2 µg/m ³ (1 hour into activity); 4.5–5.5 µg/m ³ (2 hours into activity)	2 µg/m ³ (outside for 10 minutes); <1 µg/m ³ (outside for 55 minutes)	Lindstrom et al. 1997
32 subjects working at public indoor pools	2–5.3 µg/L (pool water); 8.7, 3.5, and 2.9 µg/m ³ (poolside, reception area, and engine room)		0.3–9.5 µg/m ³ (average concentrations during work day)		Fantuzzi et al. 2001

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-18. Exposure and Urine Concentrations

Population and exposure scenario	Average media concentration	Average urine concentration before activity	Average urine concentration at end of exposure	Average urine concentration postexposure	Reference
14 male and female indoor swimming pool workers ages 23–50; 2–4-hour work shifts	2.2 µg/L (2,200 ng/L) (pool water)	18–23 ng/L (mean 20 ng/L)	23.9 ng/L (2 hour shift) 26.9 ng/L (4 hour shift)		Caro and Gallego 2007
1 indoor swimming pool worker; 2-hour work shift	2.2 µg/L (2,200 ng/L) (pool water)	20 ng/L	40 ng/L	20 ng/L (120 minutes after exposure)	Caro and Gallego 2007
10 swimmers using indoor pool ages 23–50; 2 times/week 1 hour swimming	2.2 µg/L (2,200 ng/L) (pool water)	21.0 ng/L	70.4 ng/L (at the end of 1 hour)		Caro and Gallego 2007
1 swimmer using indoor pool; 2 times/week 1 hour swimming	2.2 µg/L (2,200 ng/L) (pool water)	20 ng/L	80 ng/L (at the end of 1 hour)	20 ng/L (180 minutes after exposure)	Caro and Gallego 2007

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 bromodichloromethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of bromodichloromethane.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal/ocular exposure of humans and animals to bromodichloromethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of bromodichloromethane. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, most of the data on the toxicity of bromodichloromethane come from oral studies in laboratory animals. The most commonly examined endpoints were body weight, liver, and kidneys. A small number of studies involving exposure to bromodichloromethane in tap water primarily examined developmental toxicity endpoints. The laboratory animal toxicity database consists of a small number of inhalation studies examining a couple of potential endpoints and no dermal exposure studies.

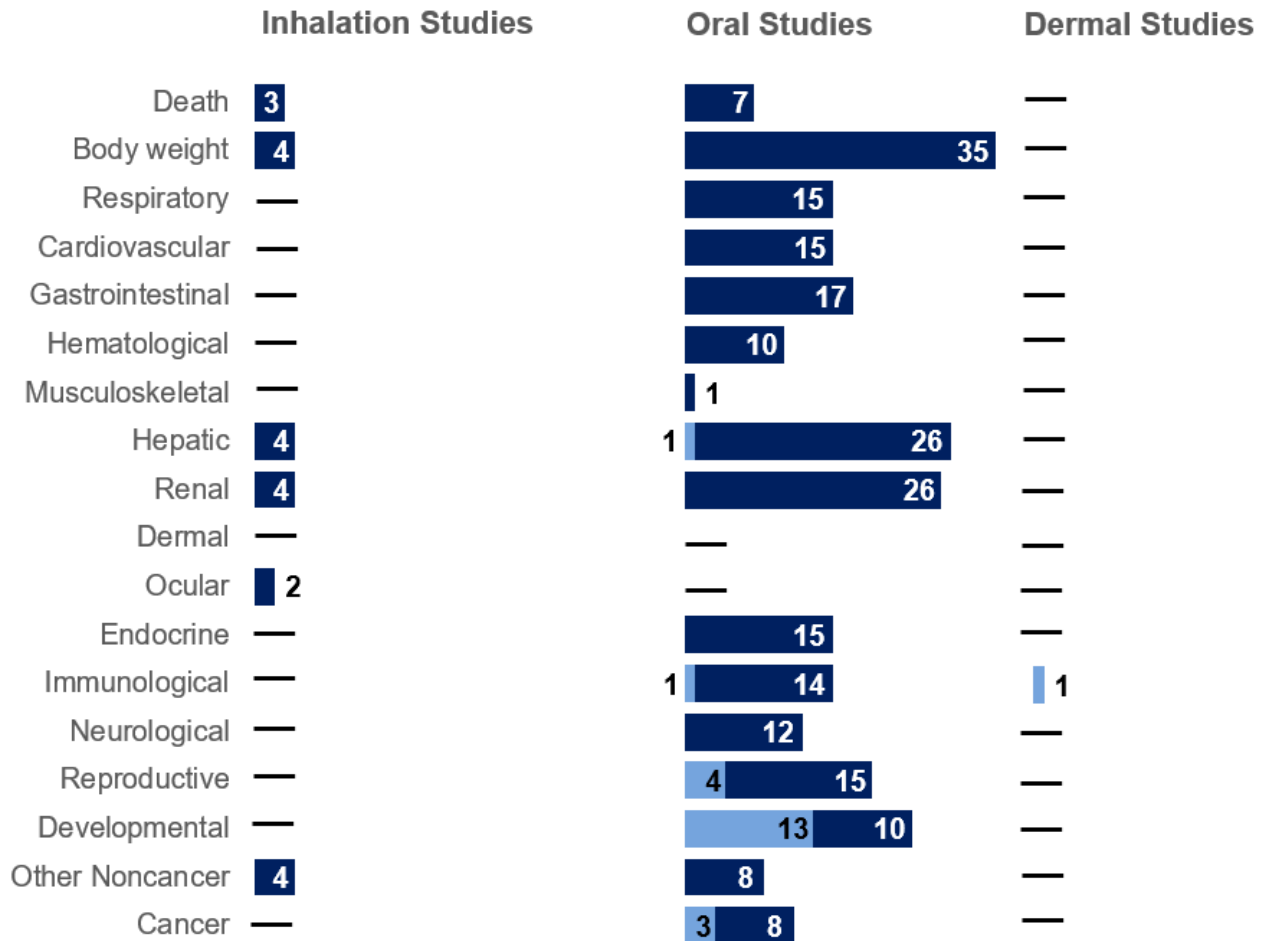
6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public

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Figure 6-1. Summary of Existing Health Effects Studies on Bromodichloromethane By Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; a total of 84 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The available acute inhalation database was not considered adequate for derivation of an MRL. Several limitations were identified, including the lack of examination of the respiratory tract, lack of reporting incidence data for the liver and kidney lesions, and lack of developmental toxicity studies, particularly since developmental toxicity is a sensitive endpoint following oral exposure. Additional inhalation toxicity studies are needed; these studies should include examination of suspected sensitive targets including the respiratory tract, kidney, and liver. Developmental toxicity studies are also needed to determine whether this is a more sensitive endpoint than liver or kidney toxicity.

Intermediate-Duration MRLs. The available intermediate inhalation database was not considered adequate for derivation of an MRL. The lowest LOAEL identified in the 3-week study conducted by Torti et al. (2001) was for renal toxicity. As with acute inhalation exposure, a number of limitations were identified in the database, including the lack of incidence data for the kidney lesions, lack of examination of the respiratory tract, lack of developmental toxicity data, and relatively short duration of the only intermediate-duration study. Additional studies involving at least 13 weeks of exposure and examination of a wide array of tissues and systems are needed to derive an inhalation MRL.

The database for intermediate-duration oral exposure was considered inadequate for derivation of an MRL. Although the existing database includes a number of adequate studies examining relevant endpoints, an MRL based on the lowest LOAEL (6.1 mg/kg/day) was lower than the MRL derived for chronic-duration oral exposure. Additional studies testing lower doses and with a larger number of animals per group would provide valuable information for deriving an intermediate-duration oral MRL.

Chronic-Duration MRLs. The lack of chronic-duration inhalation studies precluded derivation of a chronic MRL. Chronic toxicity studies examining a wide range of endpoints are needed to identify the most sensitive target and establish concentration-response relationships.

Health Effects. Toxicokinetic studies (Backer et al. 2000; Kenyon et al. 2016; Nuckols et al. 2005) provide evidence that inhalation and dermal exposure to bromodichloromethane are significant contributors to the blood bromodichloromethane levels. However, Torti et al. (2001) is the only available inhalation study in laboratory animals and no dermal exposure studies were identified. Inhalation and

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dermal exposure studies examining a wide range of potential endpoints are needed to identify whether the critical targets of toxicity for these routes differ from oral exposure targets and establish dose-response relationships. Oral toxicity studies in laboratory animals have administered bromodichloromethane via drinking water, gavage in oil, and feed. In humans, exposure via drinking water would be prominent oral exposure route. Studies are needed to investigate possible differences between various oral exposure subroutes; these data could provide insight into the applicability of dietary and gavage administration studies for assessing potential human toxicity of bromodichloromethane.

Hepatic. Oral exposure studies in laboratory animals have found considerable overlap in NOAEL and LOAEL values across studies, which are likely due to differences in oral route of exposure (i.e., gavage, drinking water, feed) and the vehicle used (Aida et al. 1989, 1992; Chu et al. 1982; Hooth et al. 2002; NTP 2006). Additional studies are needed to evaluate the relevance of each of these routes to humans exposed to bromodichloromethane in tap water.

Renal. Available oral exposure studies in laboratory animals suggest a higher toxicity associated with gavage administration than drinking water or feed exposure (Aida et al. 1989, 1992; Chu et al. 1982; Lipsky et al. 1993; Lock et al. 2004; NTP 1987, 2006). Additional studies are needed to explain these differences and evaluate whether the results of gavage studies are applicable to humans.

Reproductive. Human and animal studies provide suggestive evidence that the reproductive system of males and females are sensitive targets of bromodichloromethane toxicity (Bielmeier et al. 2001, 2004, 2007; Windham et al. 2003). However, the findings of many of the studies have not been confirmed and it is not known if the alterations would result in impaired reproductive function. Additional studies in animals examining reproductive endpoints in males and females would provide data useful for determining whether reproductive toxicity is an endpoint of concern for the general population.

Developmental. Studies in F344 rats (Bielmeier et al. 2001; Narotosky et al. 1997) have found increases in full-litter resorptions; however, this was not found when Sprague-Dawley rats were similarly exposed to the same or higher doses (Bielmeier et al. 2001) and was not observed in another developmental toxicity study (Christian et al. 2001a) or a 2-generation study (Christian et al. 2001b). Although this endpoint was used as the basis of the acute-duration oral MRL, additional research is needed to explain the strain difference and assess whether it is a relevant endpoint in humans.

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Epidemiology and Human Dosimetry Studies. A small number of epidemiology studies have evaluated the toxicity of bromodichloromethane in populations exposed to the compound in tap water using either bromodichloromethane levels in blood or tap water as exposure metrics (Bove et al. 2007; Burch et al. 2015; Cao et al. 2016; Danileviciute et al. 2012; Dodd and King 2001; Grazuleviciene et al. 2013; Hoffman et al. 2008; Iszatt et al. 2011; King et al. 2000; MacLehose et al. 2008; Rivera-Núñez and Wright 2013; Summerhayes et al. 2012; Waller et al. 1998; Wright et al. 2004; Zeng et al. 2013). A common limitation of these studies is the lack of control for the presence of other trihalomethanes and disinfection byproducts, many of which have similar toxic endpoints as bromodichloromethane. Additionally, epidemiology studies controlling confounding exposures and examining endpoints that have been shown to occur at low doses in laboratory animals (hepatic, renal, immunological, reproductive, and developmental) would be useful. *In vitro* studies (Chen et al. 2003, 2004) suggest an effect on trophoblasts; *in vivo* studies in nonhuman primates would provide additional information for the interpretation of the human studies finding increases in spontaneous abortions.

Biomarkers of Exposure and Effect. Levels of bromodichloromethane in alveolar air, urine, and blood have been used as biomarkers of exposure. Although increases in these levels are associated with exposure, additional research is needed to extrapolate biomarker levels to external exposure doses.

Absorption, Distribution, Metabolism, and Excretion. There are limited data on the toxicokinetic properties of bromodichloromethane following inhalation or dermal exposure; since these routes are major contributors to blood levels in populations using tap water containing bromodichloromethane, additional toxicokinetic data would be useful. Studies would also be useful evaluating potential metabolic saturation; these data would be useful for assessing the applicability of high-dose studies in laboratory animals to low-dose human exposure scenarios. A PBPK model that would allow extrapolation from animals to humans would decrease the uncertainties in MRL derivations.

Comparative Toxicokinetics. There are limited data available that allow for a comparison of the toxicokinetic properties across species. Since metabolites are responsible for the toxicity of bromodichloromethane, studies comparing metabolism in different animal species and humans could provide valuable information in extrapolating animal toxicity data to humans.

Children's Susceptibility. No studies have evaluated the toxicity of bromodichloromethane in children or young animals. Bromodichloromethane is primarily metabolized by CYP2E1, which is fully developed in children; it is not known if there would be toxicodynamic differences between children and

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adults that might influence susceptibility. Studies in young animals and/or children would be useful to address these concerns.

Physical and Chemical Properties. Further studies on these parameters do not appear to be essential.

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to bromodichloromethane.

Environmental Fate. Studies to obtain reliable quantitative rate values for the key fate processes of bromodichloromethane would be valuable. Of particular importance would be studies on the volatilization of bromodichloromethane from chlorinated drinking water, and on the atmospheric reactions of bromodichloromethane. 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.

Bioavailability from Environmental Media. Based on the physical properties of bromodichloromethane, it is not expected that bioavailability would vary widely between water, soil, food, and other media. Investigative studies on the relative bioavailability of bromodichloromethane in different environmental media would add to the understanding of this chemical's behavior.

Food Chain Bioaccumulation. Studies on bromodichloromethane uptake and retention by fish, plants, and other food sources would be helpful.

Exposure Levels in Environmental Media. Studies of bromodichloromethane levels in air (especially indoor air) in the vicinity of open bodies of chlorinated water, including water treatment plants, would be helpful. In view of the ready volatilization of bromodichloromethane from water, airborne levels in such locations might be significant.

Exposure Levels in Humans. Additional data on bromodichloromethane levels in air to estimate inhalation exposure in ambient air or the workplace would be beneficial. It would be helpful to know how rapidly bromodichloromethane would volatilize from a glass of water, a bathtub full of water, and a swimming pool, and what concentration would then be in the breathing zone of occupants of the house.

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Exposures of Children. Based on the concentrations of bromodichloromethane measured in water used for drinking and bathing, studies are needed to assess the inhalation, dermal, ocular, and oral exposures of children during water-related activities. Data on inhalation and dermal doses would especially be useful for in and around both indoor and outdoor swimming pools.

Analytical Methods. Since bromodichloromethane may be toxic to humans, very low levels in water, air, or other media may be of concern, so improvements in detection sensitivity would be valuable, especially in environmental media such as water and air.

6.3 ONGOING STUDIES

No ongoing studies were identified for bromodichloromethane.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding bromodichloromethane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for bromodichloromethane.

Table 7-1. Regulations and Guidelines Applicable to Bromodichloromethane

Agency	Description	Information	Reference
Air			
EPA	RfC	Not evaluated	IRIS 2002
	Subchronic p-RfC	0.02 mg/m ³ ^a	EPA 2009a
WHO	Air quality guidelines	Not listed	WHO 2010
Water & Food			
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	1 mg/L	
	10-Day health advisory (10-kg child)	0.6 mg/L	
	DWEL	0.1 mg/L	
	Lifetime health advisory	No data	
	10 ⁻⁴ Cancer risk	0.1 mg/L	
	National primary drinking water regulations		EPA 2009b
	MCL - Total trihalomethanes	0.080 mg/L	
	MCLG - Bromodichloromethane	0 mg/L	
	RfD	0.02 mg/kg/day ^b	IRIS 2002
Subchronic p-RfD	0.008 mg/kg/day ^c	EPA 2009a	
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value	0.06 mg/L (60 µg/L)	
	TDI	21.4 µg/kg body weight	
FDA	Substances Added to Food	Not listed ^d	FDA 2019
	Allowable level for disinfection byproducts in bottled water – Total trihalomethanes	0.080 mg/L	FDA 2017
Cancer			
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016
EPA	Carcinogenicity classification	B2 ^e	IRIS 2002

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Table 7-1. Regulations and Guidelines Applicable to Bromodichloromethane

Agency	Description	Information	Reference
IARC	Carcinogenicity classification	Group 2B ^f	IARC 1999
Occupational			
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2018a
	PEL (8-hour TWA) for shipyards and construction	No data	OSHA 2018b
	PEL (8-hour TWA) for construction	No data	OSHA 2018c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2018
Emergency Criteria			
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1 ^g	1.3 mg/m ³	
	PAC-2 ^g	14 mg/m ³	
	PAC-3 ^g	85 mg/m ³	

^aThe subchronic p-RfC is based on a NOAEL of 20 mg/m³ for kidney degeneration in mice.

^bThe RfD is based on a LOAEL of 17.9 mg/kg/day for renal cytomegaly in a chronic mouse gavage bioassay.

^cThe subchronic p-RfD is based on pregnancy loss in gavage-treated rats.

^dThe Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."

^eB2: probable human carcinogen.

^fGroup 2B: possibly carcinogenic to humans.

^gDefinitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor Extract Manufacturer's Association; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LOAEL = lowest-observed-adverse-effect level; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; PPRTV = provisional peer-reviewed toxicity value; p-RfC = provisional inhalation reference concentration; p-RfD = provisional oral reference dose; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TDI = tolerable daily intake; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥ 365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: The acute-duration inhalation database was not considered suitable for derivation of an MRL due to several data gaps: lack of examination of the respiratory tract, lack of incidence data in the only available inhalation study, and lack of developmental toxicity studies.

There are limited data on the acute inhalation toxicity of bromodichloromethane. Torti et al. (2001) reported hepatic, renal, body weight, and ocular effects in two strains of mice exposed to bromodichloromethane vapor 6 hours/day, 7 days/week for 1 week. The kidney was the most sensitive target, with tubular degeneration and nephrosis observed at ≥ 10 ppm; the NOAEL was 1 ppm. At 30 ppm, hepatocellular centrilobular degeneration and decreases in body weight gain were observed. Increases in mortality were observed at ≥ 30 ppm; the cause of death was not reported, but the investigators noted that animals exposed to 100 and 150 ppm were lethargic with labored breathing. There are several methodological and reporting deficiencies in the Torti et al. (2001) study that limit its usefulness for deriving an MRL. One limitation is the lack of examination of the respiratory tract, which could be a sensitive target of toxicity. Mild eye irritation was noted at 30 ppm, so it is possible that bromodichloromethane also resulted in respiratory tract irritation. Another limitation is the lack of reporting of incidence data for the liver and kidney lesions; only a description of the lesions was provided. Thus, there is some uncertainty in identifying NOAEL and LOAEL values for the study.

Acute-duration oral studies have found developmental toxicity to be a more sensitive target of toxicity than the kidney or liver. For example, increases in the incidence of full-litter resorptions were observed in rats administered ≥ 50 mg/kg/day during gestation (Narotsky et al. 1997); the lowest LOAEL for kidney effects in rats was 150 mg/kg/day with a NOAEL of 75 mg/kg/day (Thornton-Manning et al. 1994) and the lowest LOAEL for liver effects was 74 mg/kg/day with a NOAEL of 37 mg/kg/day (Condie et al. 1983). Although the causative agent (bromodichloromethane or a metabolite) of the litter resorptions is not known, there are no data to suggest that developmental effects will not be a sensitive endpoint following inhalation exposure.

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: The intermediate-duration inhalation database was not considered suitable for derivation of an MRL due to several data gaps: lack of incidence data for histological alterations, lack of examination of the respiratory tract, and relatively short duration of the only available intermediate-duration study (Torti et al. 2001), as well as the lack of developmental toxicity studies.

The intermediate-duration inhalation database for bromodichloromethane is limited to several mouse studies conducted by Torti et al. (2001). In two strains of mice, renal tubular degeneration was observed following exposure to 10 or 30 ppm 6 hours/day, 7 days/week for 3 weeks; the NOAEL was 3 ppm. No hepatic, body weight, or urinary bladder effects were observed in these studies at the highest concentration of 30 ppm. Minimal centrilobular hepatocellular degeneration was observed at 10 and 30 ppm in p53 heterogenous mouse strains (Torti et al. 2001). The kidney and liver lesions observed in the mice were described; however, no incidence data were provided Torti et al. (2001). Thus, there is some uncertainty in identifying NOAEL and LOAEL values for the study. Torti et al. (2001) also exposed the heterogenous mouse strains to ≤ 15 ppm bromodichloromethane for 13 weeks. The investigators noted minimal cortical scarring and tubular karyocytomegaly in the kidneys, but did not provide any additional information that would allow for identification of a LOAEL; no other effects were noted. This study in transgenic mice was not considered a suitable basis for an MRL. The Torti et al. (2001) studies did not include an examination of the respiratory tract; results from the acute-duration inhalation study by these investigators provide suggestive evidence (labored breathing at lethal concentrations and eye irritation at 30 ppm) that bromodichloromethane exposure may affect the respiratory tract. Intermediate and chronic oral studies (NTP 1987) also provide suggestive evidence that the renal toxicity of bromodichloromethane increases with exposure duration. Thus, a 3-week study may not be suitable for establishing an MRL for continuous exposure for up to 1 year.

Liver, kidney, immunological, neurological, and developmental effects have been observed in intermediate-duration oral studies (Aida et al. 1989, 1992; Balster and Borzelleca 1982; Christian et al. 2001a; French et al. 1999; NTP 1987). The available data suggest that the liver may be the most sensitive effect for oral exposure; however, based on the Torti et al. (2001) inhalation study, the kidney may be more sensitive than the liver following inhalation exposure. The LOAELs for kidney (71 mg/kg/day), immunological (49 mg/kg/day), and developmental (82 mg/kg/day) effects identified in intermediate-duration oral studies are similar. However, immunological and developmental toxicity have not been assessed in inhalation studies. Given these data gaps, there is considerable uncertainty in establishing an intermediate-duration inhalation MRL for bromodichloromethane at this time.

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified.

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.07 mg/kg/day
Critical Effect: Full-litter resorption
Reference: Narotsky et al. 1997
Point of Departure: BMDL₀₅ of 7.15 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 15
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.07 mg/kg/day was derived for bromodichloromethane based on an increased incidence of full-litter resorptions in rats administered bromodichloromethane via gavage on GDs 6–15 (Narotsky et al. 1997). The MRL is based on a BMDL₀₅ of 7.15 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of bromodichloromethane following acute, oral exposure; these studies examine a wide range of potential endpoints including liver and kidney effects (Condie et al. 1983; Keegan et al. 1998; Lilly et al. 1994, 1996; Munson et al. 1982; Ruddick et al. 1983; Thornton-Manning et al. 1994), immunotoxicity (French et al. 1999), reproductive toxicity (Bielmeier et al. 2001), and developmental toxicity (Bielmeier et al. 2001, 2004; Narotsky et al. 1997; Ruddick et al. 1983). The LOAELs for these studies range from 50 to 400 mg/kg/day; a summary of select LOAELs is presented in Table A-1 (studies identifying LOAELs for body weight effects were not included since this is not considered a primary effect of bromodichloromethane).

The available data suggest that developmental toxicity, particularly full-litter resorption, is the most sensitive endpoint following acute-duration oral exposure. In multiple studies conducted by Bielmeier et al. (2001) and Narotsky et al. (1997), full-litter resorptions have been observed at 50 mg/kg/day (8–17% resorptions) and ≥ 75 mg/kg/day (17–100% resorptions). Similar LOAELs (≥ 74 –75 mg/kg/day) were identified for liver and immunological effects. The liver effects consisted of centrilobular pallor, vacuolar degeneration and necrosis, and increases in liver enzymes (Condie et al. 1983; Keegan et al. 1998; Lilly et al. 1994, 1996; Munson et al. 1982; Thornton-Manning et al. 1994). Two studies demonstrated impaired immune responses in rats and mice administered ≥ 75 mg/kg/day (French et al. 1999; Munson et al. 1982). The kidney appears to be slightly less sensitive than other targets, with LOAEL values ranging from 148 to 400 mg/kg/day. The effects included tubular degeneration, hyperplasia, and necrosis, and increases in blood urea nitrogen levels (Condie et al. 1983; Lilly et al. 1994, 1996; Munson et al. 1982; Thornton-Manning et al. 1994).

APPENDIX A

Table A-1. Summary of Relevant LOAEL Values Following Acute Oral Exposure to Bromodichloromethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
F344 rat	GDs 6–15 (GW)	25	50	17% full-litter resorption	Narotsky et al. 1997
F344 rat	GDs 6–15 (GO)	25	50	8% full-litter resorption	Narotsky et al. 1997
F344 rat	GDs 6–10 (GW)	–	75 ^a	62% full-litter resorption	Bielmeier et al. 2001
F344 rat	GDs 8–9, or GD 0 (GW)	–	75 ^a	64% full-litter resorption	Bielmeier et al. 2001
F344 rat	GDs 6–10 or GDs 6–15 (GW)	–	75 ^a	75 or 50% full-litter resorption	Bielmeier et al. 2001
F344 rat	GDs 6–10 (GW)	–	75 ^a	80% full-litter resorption	Bielmeier et al. 2004
Sprague- Dawley rat	GDs 6–10 (GW)	100		0% full-litter resorption	Bielmeier et al. 2001
Sprague- Dawley rat	GDs 6–15 (GO)	100	200	Delayed ossification of sternebrae	Ruddick et al. 1983
Kidney effects					
CD-1 mouse	14 days (GO)	74	148	Intratubular mineralization, epithelial hyperplasia, and cytomegaly	Condie et al. 1983
Fischer 344 rat	5 days (GW)	75	150	Tubular vacuolar degeneration	Thornton-Manning et al. 1994
Fischer 344 rat	Once (GW)		200	Proximal tubule necrosis	Lilly et al. 1996
CD-1 mouse	14 days (GW)	125	250	Increased blood urea nitrogen levels	Munson et al. 1982
Fischer 344 rat	Once (GW) or (GO)	200	400	Renal tubule degeneration and necrosis	Lilly et al. 1994

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Table A-1. Summary of Relevant LOAEL Values Following Acute Oral Exposure to Bromodichloromethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
CD-1 mouse	14 days (GO)	37	74	Centrilobular pallor	Condie et al. 1983
Fischer 344 rat	5 days (GW)	75	150	Hepatocellular vacuolar degeneration	Thornton-Manning et al. 1994
Fischer 344 rat	Once (G)	163.8	245.7	Increases in alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase	Keegan et al. 1998
CD-1 mouse	14 days (GW)	125	250	Aspartate aminotransferase and alanine aminotransferase levels	Munson et al. 1982
Fischer 344 rat	Once (GW) or (GO)	200	400	Vacuolar degeneration and necrosis	Lilly et al. 1994
Fischer 344 rat	Once (GW)	200	400	Centrilobular necrosis and vacuolar degeneration	Lilly et al. 1996
Immunological effects					
F344 rat	5 days (GW)	–	75	Impaired response to T-lymphocyte stimulants	French et al. 1999
CD-1 mouse	14 days (GW)	125	250	Altered response to sheep red blood cells	Munson et al. 1982

^aConsidered a serious LOAEL.

G = gavage; GD = gestation day; GO = gavage in oil vehicle; GW = gavage in water vehicle; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

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The lowest LOAEL for an acute-duration study was 50 mg/kg/day for full-litter resorptions in rats (Narotsky et al. 1997) and this was selected as the critical effect for the MRL. Although the Narotsky et al. (1997) and Bielmeier et al. (2001) studies have consistently shown an increase in pregnancy loss in F344 rats administered bromodichloromethane via gavage on GDs 6–10, other studies have not found this effect in Sprague-Dawley rats or in rabbits. No pregnancy losses were observed in Sprague-Dawley rats administered gavage doses as high as 100 mg/kg/day on GDs 6–10 (Bielmeier et al. 2001) or 200 mg/kg/day on GDs 6–15 (Ruddick et al. 1983), exposed via drinking water to 82.0 mg/kg/day on GDs 6–21 (Christian et al. 2001a), or exposed in drinking water to 29.5–109 mg/kg/day in a 2-generation study (Christian et al. 2001b). Additionally, no pregnancy losses were observed in New Zealand white rabbits exposed to doses as high as 55.3 mg/kg/day on GDs 6–29 (Christian et al. 2001a). Support for the applicability of the pregnancy loss effect for derivation of an MRL comes from human studies that found significant associations between bromodichloromethane in tap water and an increased risk of spontaneous abortion (Waller et al. 1998) or stillbirths (King et al. 2000); it is noted that these studies involved exposure to multiple disinfection byproducts, including other trihalomethanes.

Selection of the Principal Study: As summarized in Table A-1, Bielmeier et al. (2001) and Narotsky et al. (1997) conducted several studies evaluating full-litter resorptions in rats. Together, the studies demonstrate a dose-response relationship between bromodichloromethane exposure and full-litter resorption. The incidence of full-litter resorptions in selected studies conducted by these investigators are presented in Table A-2. Since the Narotsky et al. (1997) studies tested lower concentrations and identified a NOAEL, it was selected as the principal study for the MRL.

Table A-2. Incidence of Full-Litter Resorptions in F344 Rats Administered Bromodichloromethane via Gavage

	Dose (mg/kg/day)				
	0	25	50	75	100
Narotsky et al. 1997 (GW)	0/14 (0%)	0/12 (0%)	2/12 (17%)	3/14 (21%)	
Narotsky et al. 1997 (GO)	0/12 (0%)	0/14 (0%)	1/13 (8%)	10/12 (83%)	
Bielmeier et al. 2001 (GDs 6–15)	0%			50%	
Bielmeier et al. 2001 (GDs 9)	0%			64%	100%

G = gavage; GD = gestation day; GO = gavage in oil vehicle; GW = gavage in water vehicle

Summary of the Principal Study:

Narotsky MG, Pegram RA, Kavlock RJ. 1997. Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. *Fundam Appl Toxicol* 40:30-36.

Groups of pregnant F344 rats (12–14/group) were administered 0, 25, 50, or 75 mg/kg/day bromodichloromethane by gavage in corn oil or an aqueous vehicle on GDs 6–15. Endpoints monitored included maternal weight and clinical signs. Pups were examined and weighed individually on PNDs 1 and 6. Dams were killed on PND 6, and the number of uterine implantations were recorded. The uteri of rats that did not deliver were stained to detect cases of full-litter resorptions.

Clinical signs seen only in the corn oil vehicle rats included hunched back (75 mg/kg/day) and chromodacryorrhea/lacrimation (≥ 50 mg/kg/day). Piloerection occurred at 75 mg/kg/day with both vehicles and at 50 mg/kg/day with the aqueous vehicle. Body weight gain on GDs 6–8 was reduced about 83% in rats dosed with 25 mg/kg/day in aqueous vehicle and about 61% with the oil vehicle (statistically

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significant only in aqueous vehicle group). Rats in the higher dose groups lost weight (both vehicles). Body weight gains were not reported at other time periods. Full-litter resorptions occurred in 50 and 75 mg/kg/day groups for both vehicles, but were not observed in controls or 25 mg/kg/day groups. The incidences of full-litter resorption are presented in Table A-2. In surviving litters, there was no significant effect on gestation length, postnatal viability, or pup weight on PND 1 or 6. In a toxicokinetic study also conducted, bromodichloromethane levels in the blood declined faster in aqueous vehicle groups than in corn oil vehicle groups; the blood half-times were 2.7 and 3.6 hours, respectively.

Selection of the Point of Departure: The BMDL₀₅ of 7.15 mg/kg/day for full-litter resorption was selected as the basis of the MRL.

Benchmark dose (BMD) modeling was conducted to identify a point of departure using the incidence data for full-litter resorptions in rats administered bromodichloromethane in an aqueous vehicle. The oil vehicle data were not modeled since administration in an aqueous vehicle is most likely to mimic human exposure to bromodichloromethane in water. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.1.1) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. Since the endpoint was developmental toxicity, a BMR of 5% was used. The model predictions for the gavage in aqueous solution are presented in Table A-3 and the fit of the selected model is presented in Figure A-1.

A BMDL₀₅ value of 7.15 mg/kg/day was calculated using the incidence data for rats administered bromodichloromethane via gavage in aqueous solution. Although the BMDL₀₅ of 7.15 mg/kg/day was lower than the empirical NOAEL of 25 mg/kg/day identified in the study, it was selected as the point of departure because it provides a better indicator of the dose-response relationship than the NOAEL, which is a single data point.

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Table A-3. Model Predictions for Full-Litter Resorptions in Rats Orally Administered Bromodichloromethane in an Aqueous Vehicle (Narotsky et al. 1997)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₀₅ (mg/kg/day)	BMDL ₀₅ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	2	0.77	0.68	-0.48	0.67	0.67	32.30	36.34	10.61
Logistic	2	1.49	0.47	-0.57	0.98	0.98	31.10	41.00	25.03
LogLogistic ^d	2	0.77	0.68	-0.52	0.66	0.66	30.34	35.59	9.60
LogProbit ^d	1	5.70	0.02	-1.22	-1.13	1.50	38.92	ND	ND
Multistage (1-degree) ^e	2	1.06	0.59	0.00	-0.93	-0.93	31.22	18.28	9.48
<i>Multistage (2-degree)^e</i>	3	<i>0.75</i>	<i>0.86</i>	<i>-0.60</i>	<i>0.60</i>	<i>0.60</i>	<i>28.43</i>	<i>32.80</i>	<i>10.43</i>
Multistage (3-degree) ^e	2	0.77	0.68	-0.59	0.61	0.61	32.43	33.22	10.43
Probit	2	1.27	0.53	-0.53	0.90	0.90	30.81	39.58	23.38
Dichotomous Hill^f	1	0.00	0.99	-0.00	0.00	0.00	31.36	43.66	7.15
Weibull ^c	2	0.82	0.67	-0.54	0.68	0.68	30.40	35.31	10.47

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

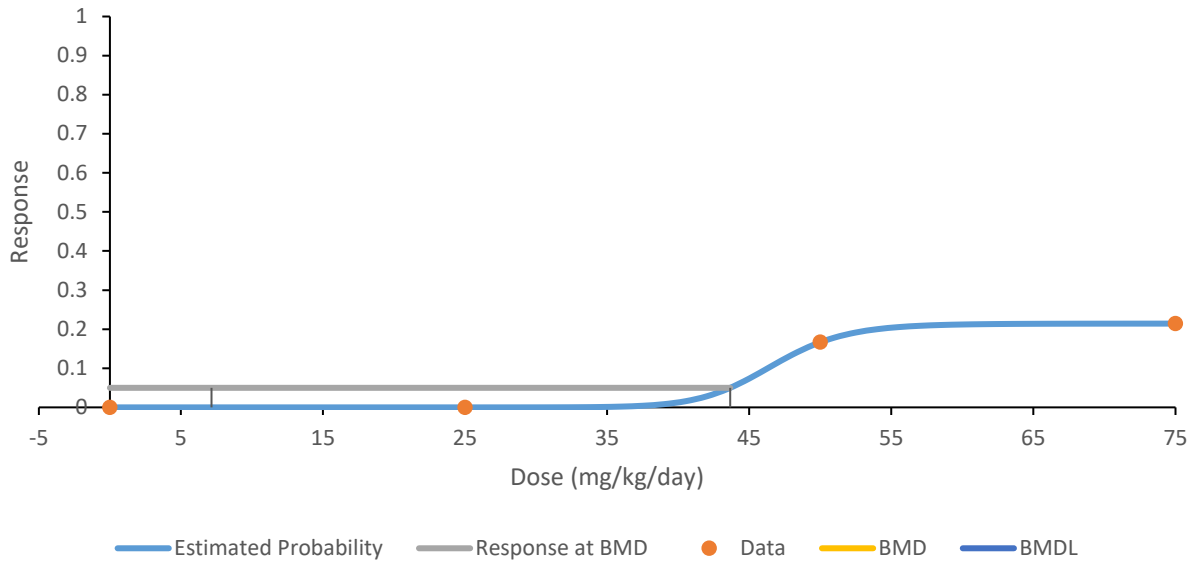
^eBetas restricted to ≥ 0 .

^fSelected model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Dichotomous Hill).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₀₅₀ = exposure concentration associated with 5% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit p-value <0.1

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Figure A-1. Fit of Dichotomous Hill Model to Data on Incidence of Full-Litter Resorption in Rats Administered Bromodichloromethane in Aqueous Vehicle



Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The BMDL₀₅ is divided by a total uncertainty factor of 100

- 10 for extrapolation from animals to humans
- 10 for human variability

$$\text{MRL} = \text{BMDL}_{05} \div \text{UFs}$$

$$7.15 \text{ mg/kg/day} \div (10 \times 10) = 0.07 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information: EPA (2005b) estimated that the average exposure of the general population to bromodichloromethane is 20 µg/person/day (0.0003 mg/kg/day assuming a reference body weight of 70 kg) from surface water systems and 8.1 µg/person/day (0.0001 mg/kg/day) from groundwater systems. These average intakes are approximately 1,000-fold lower than the MRL.

Agency Contacts (Chemical Managers): Susan Ingber

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The available intermediate oral data were not considered adequate for derivation of an intermediate-duration oral MRL. However, the chronic MRL of 0.008 mg/kg/day was considered protective for intermediate-duration exposure.

Rationale for Not Deriving an MRL: Intermediate-duration studies have evaluated a wide range of possible targets of bromodichloromethane toxicity. Studies conducted by Aida et al. (1989, 1992) and NTP (1987, 2006) have included histopathological examination of most major tissues; the Aida et al. (1989, 1992) studies also included examination of hematological and serum clinical chemistry parameters. In addition, other studies have evaluated potential targets in the immune system (French et al. 1999), neurological system (Balster and Borzelleca 1982; Moser et al. 2007), reproductive system (Christian et al. 2001b), and developmental toxicity (Christian et al. 2001a, 2001b). These studies have identified LOAEL values for liver, kidney, immune, neurobehavioral, and developmental effects; the LOAELs for these effects are summarized in Table A-4. Based on these LOAELs, the liver appears to be the most sensitive target of toxicity. The observed effects include alterations in serum enzymes (alanine aminotransferase and aspartate aminotransferase), hepatocellular vacuolization, swelling, fatty degeneration, and necrosis in rats (Aida et al. 1989, 1992; Hooth et al. 2002; NTP 1987) and mice (NTP 1987) administered bromodichloromethane via gavage, drinking water, or feed for 1–6 months. The lowest LOAEL was 6.1 mg/kg/day in rats exposed for 6 months (Aida et al. 1992).

The lowest LOAEL for other effects range from 49 mg/kg/day for immunological effects to 100 mg/kg/day for neurobehavioral effects. The data supporting these other endpoints are not as strong as for liver effects, and there are some inconsistencies in the results depending on the endpoint examined. The immunological effect observed at 49 mg/kg/day is a decreased response by splenic lymphocytes to concanavalin A in rats exposed to bromodichloromethane in drinking water for 26 weeks (French et al. 1999). The study did not find an altered response to another T-cell mitogen (phytohemagglutinin-p) or a significant response to *Salmonella* stimulation to B-lymphocytes. Acute exposure studies at higher doses (≥ 75 mg/kg/day) have found more consistent responses to T-lymphocyte mitogens (French et al. 1999) and sheep red blood cells (Munson et al. 1982). The renal effects observed in 13-week gavage studies (NTP 1987) included proximal tubule epithelial cell degeneration in rats at 214 mg/kg/day and proximal tubular necrosis in mice at ≥ 71 mg/kg/day. Other intermediate-duration studies in rats have not reported renal effects; however, the doses tested were lower than the NTP (1987) study (Aida et al. 1989, 1992; Chu et al. 1982; Lipsky et al. 1993; Lock et al. 2004; NTP 2006). The results of acute (Lilly et al. 1994, 1996; Thornton-Mannin et al. 1994) and chronic (George et al. 2002; NTP 1987) studies support the identification of the kidney as a sensitive target of toxicity. Christian et al. (2001a) reported minor delays in skeletal ossification in the offspring of rats exposed to 82 mg/kg/day in drinking water on GDs 6–21. This was not found in a 2-generation study utilizing similar dose levels (Christian et al. 2001b). The last effect that has been observed following intermediate exposure is impaired learning in an operant behavior test in mice receiving gavage administration of 100 mg/kg/day for 60 days (Balster and Borzelleca 1982). Balster and Borzelleca (1982) conducted several neurobehavioral studies and found negative results in the passive avoidance learning test at 100 mg/kg/day (30-day exposure) and in tests of motor performance and exploratory behavior at 11.6 mg/kg/day (90-day exposure). Moser et al. (2007) also found no alterations in performance on functional battery tests in rats exposed to 71.7 mg/kg/day for 6 months.

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Table A-4. Summary of Relevant LOAEL Values Following Intermediate-Duration Oral to Bromodichloromethane

Species	Duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Wistar rats	6 months (F)	–	6.1	Hepatocellular fatty degeneration (males only)	Aida et al. 1992
Eker rats	4 or 10 months (W)	3.5	35	Centrilobular swelling	Hooth et al. 2002
Wistar rats	1 month (GO)	20	60	Hepatocellular vacuolization	Aida et al. 1989
Wistar rats	1 month (F)	60	180	Hepatocellular vacuolization, swelling, and necrosis	Aida et al. 1989
B6C3F1 mice	13 weeks (GO)	71 ^a	142 ^a	Enlarged centrilobular hepatocytes and vacuolization (females only)	NTP 1987
F344 rats	13 weeks (GO)	107 ^a	214 ^a	Centrilobular degeneration, mild bile duct hyperplasia	NTP 1987
Immunological effects					
F344 rats	26 weeks (GW)	5	49	Decreased response to mitogen in splenic lymphocytes	French et al. 1999
Kidney effects					
B6C3F1 mice	13 weeks (GO)	36 ^a	71 ^a	Proximal tubular epithelial cell focal necrosis (males only)	NTP 1987
F344 rats	13 weeks (GO)	107 ^a	214 ^a	Proximal tubular epithelial cell degeneration	NTP 1987
Developmental effects					
Sprague-Dawley rats	GDs 6–21 (W)	45	82	Minor delays in ossification	Christian et al. 2001a

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Table A-4. Summary of Relevant LOAEL Values Following Intermediate-Duration Oral to Bromodichloromethane

Species	Duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurobehavioral effects					
ICR mice	60 days (GW)		100	Alterations in operant behavior	Balster and Borzelleca 1982

^aAdjusted for intermittent exposure (5 days/7 days).

F = feed; GD = gestation day; GO = gavage in oil; GW = gavage in water; LOAEL = lowest observed adverse effect level; NOAEL = no observed-adverse-effect level; W = water

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Based on the available data, the liver appears to be the most sensitive target of bromodichloromethane intermediate-duration toxicity.

Nine studies have investigated the potential of bromodichloromethane to induce liver effects in laboratory animals (Aida et al. 1989, 1992; Chu et al. 1982; Hooth et al. 2002; NTP 1987, 2006); the results of these studies are summarized in Table A-5. Comparisons of NOAEL/LOAEL values across studies show a considerable amount of overlap, which likely results from differences in exposure routes and vehicles that could influence absorption, metabolism, and delivery of the compound to target organs; strain differences and exposure duration may have also influenced the results. A 1-month study by Aida et al. (1989) allows for a comparison of the effect levels between gavage with oil vehicle and feed exposure. The NOAEL and LOAEL values were 20 and 60 mg/kg/day, respectively, for hepatocellular vacuolization in rats administered bromodichloromethane via gavage in olive oil. In contrast, the NOAEL and LOAEL values for feed administration were 60 and 180 mg/kg/day for hepatocellular vacuolization, swelling, and necrosis. These results suggest that gavage administration is a more toxic exposure route than feed. In a PBPK modeling study conducted by NTP (2006), the plasma AUCs were lower for drinking water exposure than gavage in oil exposure. The study also found that a higher percentage of bromodichloromethane was metabolized by cytochrome P450 than by glutathione transferase.

A comparison between the results of the Aida et al. (1989) gavage study and the NTP (1987) 3-month gavage studies suggest that Wistar rats may be more sensitive than F344 rats based on the NOAEL of 197 mg/kg/day for F344 rats, which is higher than the LOAEL of 60 mg/kg/day in Wistar rats; a toxicokinetic basis for this difference has not been established. Studies conducted by Aida and associates also demonstrate an increasing toxicity with exposure duration. After 6 months of exposure to bromodichloromethane in the feed, hepatocellular degeneration was observed at 6.1 mg/kg/day; in contrast, the NOAEL for the 1-month feed study was 60 mg/kg/day.

Although gavage administration may be a more toxic route of exposure, continuous exposure laboratory animal studies (administration in feed or drinking water) are likely more representative of general population exposure to bromodichloromethane in tap water. Of the drinking water and feed studies, Aida et al. (1992) identified the lowest LOAEL of 6.1 mg/kg/day. Derivation of an intermediate-duration oral MRL based on the Aida et al. (1992) study was considered using the NOAEL/LOAEL approach; the fatty degeneration incidence data were not suitable for BMD modeling because the maximal response (100%) was observed at all non-control dose levels in the males. Using the LOAEL as the point of departure for the MRL and an uncertainty factor of 1,000 (10 for extrapolation from a LOAEL, 10 for extrapolation from animal studies, and 10 for human variability) would result in an MRL of 0.006 mg/kg/day. This MRL is lower than the chronic-duration MRL also based on hepatic fatty degeneration in rats exposed to bromodichloromethane for 2 years (Aida et al. 1992). The intermediate and chronic studies identified the same LOAEL values; however, there was greater confidence in the chronic MRL because a larger number of animals were examined at 24 months (13–19/exposure group compared to 5/exposure group in the 6-month study) and the chronic data allowed for use of BMD modeling.

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Table A-5. Summary of Hepatic Effects Following Intermediate-Duration Oral to Bromodichloromethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Feed administration					
Wistar rats	6 months	–	6.1	Hepatocellular fatty degeneration (males only)	Aida et al. 1992
Wistar rats	1 month	60	180	Hepatocellular vacuolization, swelling, and necrosis	Aida et al. 1989
Gavage (oil vehicle) administration					
Wistar rats	1 month	20	60	Hepatocellular vacuolization	Aida et al. 1989
B6C3F1 mice	13 weeks	71 ^a	142 ^a	Enlarged centrilobular hepatocytes and vacuolization (females only)	NTP 1987
F344 rats	13 weeks	107 ^a	214 ^a	Centrilobular degeneration, mild bile duct hyperplasia	NTP 1987
Drinking water administration					
Eker rats	4 or 10 months	3.5	35	Centrilobular swelling	Hooth et al. 2002
F344/N rats	22 days	71	–		NTP 2006
B6C3F1 mice	22 days	51	–		NTP 2006
Sprague-Dawley rats	28 days	45	–		Chu et al. 1982

^aAdjusted for intermittent exposure (5 days/7 days).

LOAEL = lowest observed adverse effect level; NOAEL = no observed-adverse-effect level

Agency Contacts (Chemical Managers): Susan Ingber

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Bromodichloromethane
CAS Numbers:	75-27-4
Date:	March 2020
Profile Status:	Final
Route:	Oral
Duration:	Chronic
MRL	0.008 mg/kg/day
Critical Effect:	Hepatocellular fatty degeneration
Reference:	Aida et al. 1992
Point of Departure:	BMDL ₁₀ of 0.78 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	51
Species:	Rat

MRL Summary: A chronic-duration oral MRL of 0.008 mg/kg/day was derived for bromodichloromethane based on an increased incidence of hepatocellular fatty degeneration in male rats exposed to bromodichloromethane in the diet for 24 months (Aida et al. 1992). The MRL is based on a BMDL₁₀ of 0.78 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the possible association between exposure to bromodichloromethane and adverse health effects in humans; in particular, these studies evaluate potential hepatic, developmental, and reproductive endpoints. No significant associations between blood bromodichloromethane levels and aspartate aminotransferase levels were found in a study utilizing the NHANES database (Burch et al. 2015). Nine studies have examined whether bromodichloromethane in drinking water was associated with alterations in birth weight, congenital anomalies, or stillbirths. One study found a significant association for stillbirths (King et al. 2000). Mixed results were found for birth weight, birth length, or small for gestational age (SGA) (Cao et al. 2016; Danileviciute et al. 2012; Rivera-Núñez and Wright 2013; Summerhayes et al. 2012; Wright et al. 2004) and for the malformations, in particular neural tube defects, heart anomalies, and hypospadias (Dodds and King 2001; Grazuleviciene et al. 2013; Iszatt et al. 2011) with some studies finding significant associations. Of the three studies examining possible associations between bromodichloromethane and reproductive parameters, significant associations between bromodichloromethane in water and a shorter time to pregnancy (MacLehose et al. 2008) and a decreased menstrual cycle length (Windham et al. 2003) were found; no association was found between blood bromodichloromethane levels and sperm parameters (Zeng et al. 2013). Although some studies have found significant associations, the studies do not establish causality and bromodichloromethane levels in drinking water only accounted for a small portion of the risk of these effects.

Nine studies have evaluated the chronic toxicity of bromodichloromethane in rats and mice (Aida et al. 1992; George et al. 2002; Klinefelter et al. 1995; NTP 1987, 2006; Tumasonis et al. 1985). These studies have identified three sensitive targets of non-neoplastic toxicity: liver, kidney, and sperm; the LOAELs for these effects are presented in Table A-6. In the liver, the accumulation of fat resulted in hepatocellular degeneration in rats exposed to ≥ 6.1 mg/kg/day in the diet for 1–2 years (Aida et al. 1992) and fatty metamorphosis in rats and mice administered via gavage ≥ 36 mg/kg/day for 2 years (NTP 1987). A fourth study reported hepatic adenofibrosis in rats following a lifetime exposure to 190 mg/kg/day in drinking water (Tumasonis et al. 1985). Renal and sperm effects have also been observed at dose levels of 36–39 mg/kg/day (George et al. 2002; Klinefelter et al. 1995; NTP 1987). Although the results of the

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Table A-6. Summary of Relevant LOAEL Values Following Chronic-Duration Oral to Bromodichloromethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Wistar rats	1–2 years	–	6.1	Hepatocellular fatty degeneration and granulomas (males only)	Aida et al. 1992
F344 rats	2 years	–	36 ^a	Fatty metamorphosis	NTP 1987
B6C3F1 mice	2 years	18 ^a	36 ^a	Fatty metamorphosis (males only)	NTP 1987
Wistar rats	Lifetime	–	190	Hepatic adenofibrosis (females only)	Tumasonis et al. 1985
Kidney effects					
F344 rats	2 years	20	36.3	Renal tubular cell hyperplasia	George et al. 2002
F344 rats	2 years		36 ^a	Tubular epithelial cell cytomegaly (males only)	NTP 1987
B6C3F1 mice		18 ^a	36 ^a	Tubular epithelial cell cytomegaly (males only)	NTP 1987
Reproductive effects					
F344 rats	1 year	22	39	Decreased sperm velocity	Klinefelter et al. 1995

^aAdjusted for intermittent exposure (5 days/7 days).

LOAEL = lowest observed adverse effect level; NOAEL = no observed-adverse-effect level

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NTP (1987) rat and mice studies suggest that the liver and kidneys are equally sensitive to bromodichloromethane toxicity, the Aida et al. (1992) studies did not find kidney effects at doses as high as 138.0 mg/kg/day in males and 168.4 mg/kg/day in females. Bolus administration versus continuous exposure may have accounted for the differences between the studies. PBPK modeling conducted by NTP (2006) found an approximately 10-fold difference in maximal bromodichloromethane blood levels following administration of 50 mg/kg via gavage and 33 mg/kg via drinking water; likewise, the 24-hour AUC was 1.5 times higher following gavage. Given these possible differences, gavage administration may not be a relevant route of exposure for estimating an MRL for humans since the general population is primarily exposed to bromodichloromethane in tap water. Among the drinking water and feed studies, the lowest LOAEL was 6.1 mg/kg/day for liver effects; thus, fatty degeneration of the liver was selected as the critical effect for the chronic-duration oral MRL.

Selection of the Principal Study: The hepatotoxicity of bromodichloromethane has been investigated in eight studies of rats or mice administered the compound via gavage (NTP 1987), feed (Aida et al. 1992), or drinking water (George et al. 2002; NTP 2006; Tumasonis et al. 1985); the results of these studies are presented in Table A-7. Four studies have identified LOAEL values in rats or mice for damage associated with fat accumulation (Aida et al. 1992; NTP 1987) or for adenofibrosis (Tumasonis et al. 1985). The lowest LOAEL was 6.1 mg/kg/day identified by Aida et al. (1992); this study was selected as the principal study for the MRL.

Table A-7. Summary of Hepatic Effects Following Chronic-Duration Oral to Bromodichloromethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Feed administration					
Wistar rats	1–2 years	–	6.1	Fatty degeneration	Aida et al. 1992
Gavage (oil vehicle) administration					
F344 rats		–	36 ^a	Fatty metamorphosis	NTP 1987
B6C3F1 mice	2 years	18 ^a	36 ^a	Fatty metamorphosis	NTP 1987
Drinking water administration					
Wistar rats	Lifetime	–	190	Hepatic adenofibrosis	Tumasonis et al. 1985
B6C3F1 mice	2 years	43.3			George et al. 2002
F344 rats	2 years	36.3			George et al. 2002
B6C3F1 mice	2 years	36	–		NTP 2006
F344/N rats	2 years	25	–		NTP 2006

^aAdjusted for intermittent exposure (5 days/7 days).

LOAEL = lowest observed adverse effect level; NOAEL = no observed-adverse-effect level

Summary of the Principal Study:

Aida Y, Yasuhara K, Takada K, et al. 1992. Chronic toxicity of microencapsulated bromodichloromethane administered in the diet to Wistar rats. *J Toxicol Sci* 17:51-68.

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Groups of 40 male and 40 female Wistar rats were exposed to 0.014, 0.055, or 0.22% bromodichloromethane microencapsulated in the diet for up to 2 years; a control group of 70 male and 70 female rats was exposed to placebo granules added to the diet at the same concentration as the high-dose group. The investigators estimated the doses to be 6.1, 25.5, and 138.0 mg/kg/day for males and 8.0, 31.7, and 168.4 mg/kg/day for females. The following parameters were used to assess toxicity: daily observations, body weights (measured weekly for 6 months, biweekly during months 6–12, and monthly for the last year of the study), food intake (measured at the same frequency as body weight), hematology indices (erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet and leukocyte counts), clinical chemistry indices (urea nitrogen, creatinine, glucose, triglycerides, cholinesterase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase), liver and kidney weights, histopathological examination of major tissues and organs, and staining of liver sections for the detection of mucous substances in the bile ducts. Histopathological examination was also conducted in animals sacrificed after 12 (9/sex for controls and 5/sex/bromodichloromethane group) and 18 (9/sex for controls and 5/sex/bromodichloromethane group) months of exposure.

No dose-related alterations in mortality were observed. Mild piloerection and emaciation were observed in the 138.0/168.4 mg/kg/day group; the symptoms were first observed after 1 month of exposure and persisted throughout the study. No significant alterations in food intake were observed. Significant decreases in body weights were observed in the 138.0/168.4 mg/kg/day group after 12 and 18 months of exposure; males weighed 25 and 23% less than controls and females weighed 31 and 39% of controls. Increases in absolute and relative liver weights were observed in all exposed groups at 12 months and in the two highest groups after 18 months of exposure. Increases in relative kidney weights were observed in the 138.0/168.4 mg/kg/day group. No hematological alterations were observed. The following significant alterations in clinical chemistry parameters were observed after 12 months of exposure: increases in blood glucose levels in males only at 6.1 and 25.5 mg/kg/day; increased creatinine in females only at 168.4 mg/kg/day; increased gamma glutamyl transpeptidase at 138.0/168.4 mg/kg/day; decreased triglycerides in males at 6.1, 25.5, and 138.0 mg/kg/day and females at 168.4 mg/kg/day; decreased aspartate aminotransferase in males at 25.5 and 138.0 mg/kg/day and females at 168.4 mg/kg/day; decreased alanine aminotransferase at 8.0 (females only) and 138.0/168.4 mg/kg/day; and decreased cholinesterase in females at 31.7 and 168.4 mg/kg/day. After 18 months of exposure, the following alterations were observed: decreased blood glucose in females only at 168.4 mg/kg/day; decreased triglycerides at 25.5/31.7 and 138.0/168.4 mg/kg/day; decreased cholinesterase in males at 138.0 mg/kg/day and in females at 8.0, 31.7, and 168.4 mg/kg/day; slightly increased alanine aminotransferase in females 168.4 mg/kg/day; increased gamma-glutamyl transpeptidase at 31.7 mg/kg/days (females only) and 138.0/168.4 mg/kg/day; and increased blood urea nitrogen in females at 168.4 mg/kg/day. After 12 months of exposure, the following effects were observed in the liver: fatty degeneration in males at ≥ 6.1 mg/kg/day and in females at ≥ 31.7 mg/kg/day; bile duct proliferation in males at 138.0 mg/kg/day and in females at ≥ 31.7 mg/kg/day; cholangiofibrosis at 138.0/168.4 mg/kg/day; and granulomas in females at ≥ 31.7 mg/kg/day. After 18 months of exposure, the liver effects included: fatty degeneration in males at ≥ 6.1 mg/kg/day and in females at ≥ 31.7 mg/kg/day; cholangiofibrosis at 138.0/168.4 mg/kg/day; and granulomas at 31.7 (females only) and 138.9/168.4 mg/kg/day. After 24 months of exposure, liver effects included: fatty degeneration at ≥ 6.1 mg/kg/day; granulomas in males at ≥ 6.1 mg/kg/day and in females ≥ 31.7 mg/kg/day; and cholangiofibrosis at 138.0/168.4 mg/kg/day. The incidences of these lesions are presented in Table A-8. No other exposure-related increases in non-neoplastic lesions were observed. No increases in neoplastic lesions were observed; however, cholangiocarcinomas were observed in 3/40 females in the 168.4 mg/kg/day group, compared to 0/70 controls.

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Table A-8. Incidences of Liver Lesions in Male and Female Rats Exposed to Bromodichloromethane in the Diet for 12, 18, or 24 Months (Aida et al. 1992)

	12 months				18 months				24 months			
	Doses (mg/kg/day)				Doses (mg/kg/day)				Doses (mg/kg/day)			
Males	0	6.1	25.5	138.0	0	6.1	25.5	138.0	0	6.1	25.5	138.0
Fatty degeneration	0/9	5/5	5/5	5/5	1/9	3/5	5/5	5/5	0/24	5/14	12/13	19/19
Granuloma	0/9	0/5	0/5	1/5	0/9	0/5	2/5	4/5	0/24	4/14	9/13	19/19
Bile duct proliferation	1/9	1/5	0/5	5/5	9/9	5/5	5/5	5/5	24/24	13/14	13/13	19/19
Cholangiofibrosis	0/9	0/5	0/5	5/5	0/9	0/5	0/5	3/5	0/24	0/14	0/13	4/19
Females	0	8.0	31.7	168.4	0	8.0	31.7	168.4	0	8.0	31.7	168.4
Fatty degeneration	0/9	0/5	5/5	4/5	0/9	1/5	5/5	5/5	2/32	8/19	18/18	18/18
Granuloma	0/9	0/5	5/5	5/5	0/9	0/5	5/5	5/5	0/32	0/19	17/18	18/18
Bile duct proliferation	0/9	0/5	3/5	5/5	6/9	2/5	4/5	5/5	28/32	16/19	17/18	18/18
Cholangiofibrosis	0/9	0/5	0/5	5/5	0/9	0/5	0/5	4/5	0/32	0/19	0/18	12/18

Selection of the Point of Departure: The BMDL₁₀ of 1.57 mg/kg/day for hepatocellular fatty degeneration in male rats was selected as the POD.

The Aida et al. (1992) study identifies a LOAEL of 6.1 mg/kg/day for fatty degeneration in male rats exposed to bromodichloromethane for 12, 18, or 24 months; a significant increase in the incidence of granulomas was also observed in males exposed to ≤ 6.1 mg/kg/day for 24 months. The lowest LOAELs in female rats were 31.7 mg/kg/day for fatty degeneration following exposure for 12 or 18 months and 8.0 mg/kg/day for fatty degeneration following exposure for 24 months. BMD modeling was conducted to identify a point of departure using the incidence data for fatty degeneration at 24 months; the 24-month data were selected over the 12- and 18-month data due to the large number of animals examined (13–19/sex at 25 months versus 5/sex at 12 and 18 months). The data were fit to some of the available dichotomous models in EPA's BMDS (version 3.1.1) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p -value > 0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL was selected as the point of departure when the difference between the BMDLs estimated from these models was > 3 -fold; otherwise, the BMDL from the model with the lowest AIC was chosen. A BMR of 10% over the control incidence was used. The model predictions for males and females are presented in Table A-9 and the fit of the selected models are presented in Figures A-2 and A-3. The lowest BMDL₁₀ values in the male and female rats were 0.78 for the first-degree Multistage model and 2.57 mg/kg/day for the Probit model; the BMDL₁₀ for the males was selected as the point of departure for the MRL since it was lower than the female BMDL₁₀.

Intermittent Exposure: Not applicable.

The BMDL₁₀ is divided by a total uncertainty factor of 100

- 10 for extrapolation from animals to humans
- 10 for human variability

$$\begin{aligned} \text{MRL} &= \text{BMDL}_{10} \div \text{UFs} \\ 0.78 \text{ mg/kg/day} &\div (10 \times 10) = 0.008 \text{ mg/kg/day} \end{aligned}$$

Other Additional Studies or Pertinent Information: EPA (2005b) estimated that the average exposure of the general population to bromodichloromethane is 20 $\mu\text{g}/\text{person}/\text{day}$ (0.0003 mg/kg/day assuming a reference body weight of 70 kg) from surface water systems and 8.1 $\mu\text{g}/\text{person}/\text{day}$ (0.0001 mg/kg/day) from groundwater systems. These average intakes are approximately 25-fold lower than the MRL.

Agency Contacts (Chemical Managers): Susan Ingber

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Table A-9. Model Predictions for Hepatocellular Fatty Degeneration in Rats Exposed to Bromodichloromethane in the Diet for 24 Months (Aida et al. 1992)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			Overall largest AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD				
Male Rats									
Gamma ^c	2	0.00	1.00	-0.00	0.00	0.00	29.30	2.08	0.80
Logistic	3	5.63	0.13	-1.88	0.96	-1.88	36.20	4.77	3.25
LogLogistic ^d	2	0.04	0.98	-0.00	0.02	0.19	29.38	2.97	0.94
LogProbit ^d	1	0.00	0.95	-0.00	0.01	0.06	31.31	2.95	0.86
Multistage (1-degree)^{e,f}	2	0.31	0.86	-0.00	-0.42	-0.42	29.63	1.21	0.78
Multistage (2-degree) ^e	2	0.00	1.00	-0.00	-0.00	0.00	29.30	1.60	0.80
Multistage (3-degree) ^e	1	0.00	1.00	-0.00	-0.00	0.00	31.30	1.60	0.80
Dichotomous Hill	0	0.04	NA	-0.00	0.02	0.19	33.38	ND-1	ND-1
Probit	2	3.59	0.17	-1.17	1.39	1.39	33.90	4.37	2.87
Female Rats									
Gamma ^c	2	1.09	0.58	0.05	-0.44	0.94	46.76	ND-2	ND-2
Logistic	3	6.31	0.09	-1.76	0.71	1.76	52.31	ND-3	ND-3
LogLogistic ^d	2	0.01	1.00	0.00	-0.00	0.08	44.84	6.03	2.84
LogProbit ^d	1	0.00	1.00	0.00	0.00	0.00	46.83	6.56	2.67
<i>Multistage (1-degree)^e</i>	<i>2</i>	<i>2.14</i>	<i>0.34</i>	<i>0.14</i>	<i>-1.03</i>	<i>1.03</i>	<i>47.95</i>	ND-1	ND-1
Multistage (2-degree) ^e	2	0.09	1.00	0.01	-0.03	0.09	44.84	3.72	1.10
Multistage (3-degree) ^e	1	0.00	1.00	0.00	-0.00	-0.00	46.83	4.32	1.01
Dichotomous Hill	1	0.00	0.94	0.00	-0.00	0.08	46.84	6.02	2.84
Probit^f	3	1.38	0.71	-0.84	0.63	-0.84	44.59	3.60	2.57
Weibull ^c	2	1.44	0.49	0.07	-0.61	1.03	47.27	ND-2	ND-2

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

^fSelected model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL (1st degree multistage) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL₁₀ = 95% lower confidence limit on the BMD for a benchmark response of 10% extra risk; DF = degrees of freedom; ND-1 = not determined, BMDL was 10 times lower than the lowest non-zero dose; ND-2 = not determined, lower limit includes zero; ND-3 = not determined, goodness-of-fit p-value <0.1

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Figure A-2. Fit of 1st Degree Multistage Model for Hepatocellular Fatty Degeneration in Male Rats Exposed to Bromodichloromethane (mg/kg/day)

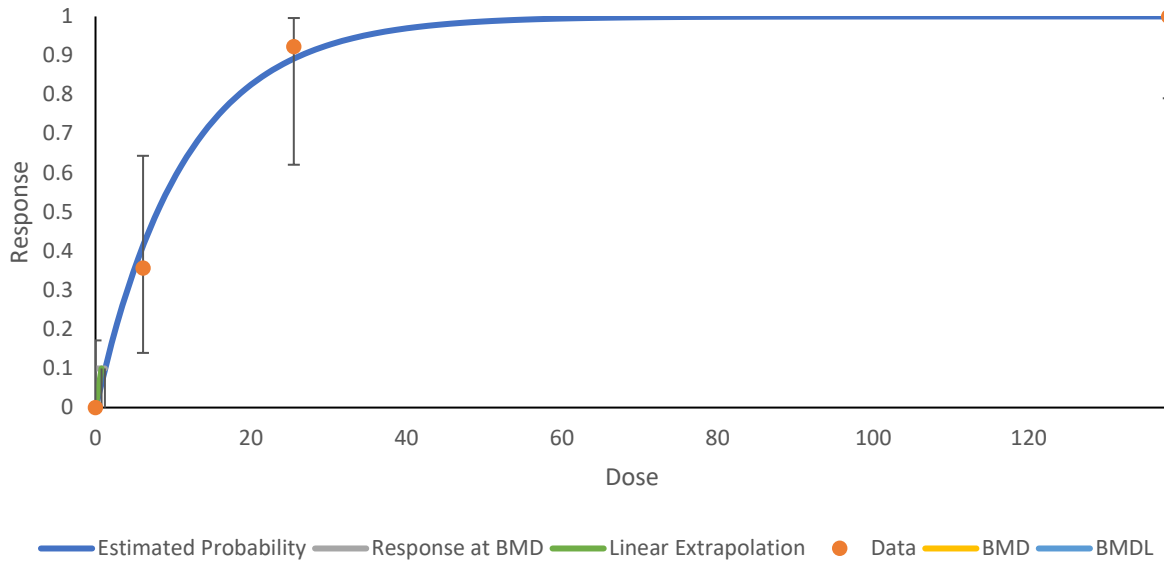
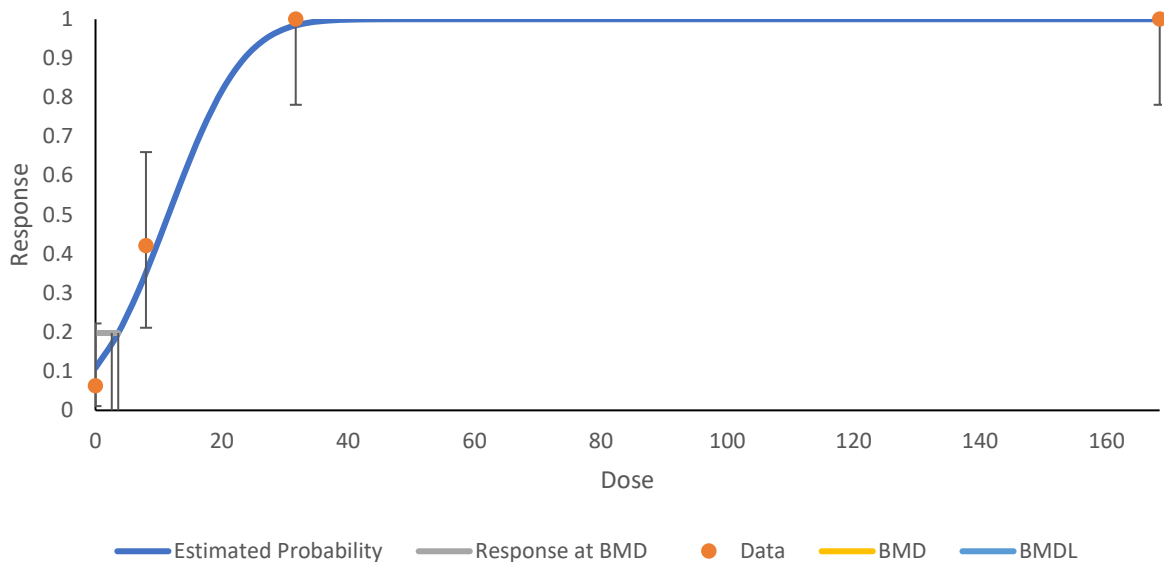


Figure A-3. Fit of Probit Model for Hepatocellular Fatty Degeneration in Female Rats Exposed to Bromodichloromethane (mg/kg/day)



APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BROMODICHLOROMETHANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to bromodichloromethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for bromodichloromethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of bromodichloromethane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of bromodichloromethane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects

Species

- Human

- Laboratory mammals

Route of exposure

- Inhalation

- Oral

- Dermal (or ocular)

- Parenteral (these studies will be considered supporting data)

Health outcome

- Death

- Systemic effects

- Body weight effects

- Respiratory effects

- Cardiovascular effects

- Gastrointestinal effects

- Hematological effects

- Musculoskeletal effects

- Hepatic effects

- Renal effects

- Dermal effects

- Ocular effects

- Endocrine effects

- Immunological effects

- Neurological effects

- Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for bromodichloromethane released for public comment in 2018. The following main databases were searched in May 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for bromodichloromethane. The query strings used for the literature search are presented in Table B-2.

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The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to bromodichloromethane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database	search date	Query string
PubMed		
	05/2019	(75-27-4[rn] OR "bromodichloromethane"[nm] OR "BDCM"[tw] OR "Bromo-dichloromethane"[tw] OR "Bromodichlormethane"[tw] OR "Bromodichloromethane"[tw] OR "Dichlorobromomethane"[tw] OR "Dichloromonobromomethane"[tw] OR "Methane, bromodichloro-"[tw] OR "Monobromodichloromethane"[tw]) AND (2014/12/01 : 3000[dp] OR 2015/12/01 : 3000[edat] OR 2015/12/01 : 3000[crdt] OR 2015/12/01 : 3000[mhda])
Toxline		
	05/2019	(75-27-4[rn] OR "BDCM" OR "Bromo-dichloromethane" OR "Bromodichlormethane" OR "Bromodichloromethane" OR "Dichlorobromomethane" OR "Dichloromonobromomethane" OR "Methane, bromodichloro-" OR "Monobromodichloromethane") AND (ANEUP [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 2015 through 2019
Toxcenter		
	05/2019	FILE 'TOXCENTER' ENTERED AT 10:31:35 ON 03 MAY 2019
	L41	3645 SEA FILE=TOXCENTER 75-27-4
	L42	3548 SEA FILE=TOXCENTER L41 NOT PATENT/DT
	L43	3483 SEA FILE=TOXCENTER L42 NOT TSCATS/FS
	L44	446 SEA FILE=TOXCENTER L43 AND ED>=20150101 ACT TOXQUERY/Q
	L45	----- QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L46	QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPB OR EPIDEMIOLOGY/ST,CT, IT)
	L47	QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L48	QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L49	QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L50	QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)

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Table B-2. Database Query Strings

Database search date	Query string
L51 OR	QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS DIETARY OR DRINKING(W)WATER?)
L52	QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
L53 L54 OR	QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OVUM?)
L55 L56	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
L57 SPERMAS? OR	QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
L58 SPERMATOX? OR	QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
L59 DEVELOPMENTAL?)	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
L60 L61 INFANT?)	QUE (ENDOCRIN? AND DISRUPT?) QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
L62 L63 L64 OR	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER? NEOPLAS?)
L65 CARCINOM?)	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
L66 GENETIC(W)TOXIC?)	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
L67 L68 L69 L70	QUE (NEPHROTOX? OR HEPATOTOX?) QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) QUE L45 OR L46 OR L47 OR L48 OR L49 OR L50 OR L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR L67 OR L68 OR L69
L71 MURIDAE SWINE	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
L72 LAGOMORPHA	QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L73 L74 OR	QUE L70 OR L71 OR L72 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL?)

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Table B-2. Database Query Strings

Database search date	Query string
L75	PRIMATES OR PRIMATE?) QUE L73 OR L74 -----
L76	267 SEA FILE=TOXCENTER L44 AND L75
L77	20 SEA FILE=TOXCENTER L76 AND MEDLINE/FS
L78	240 DUP REM L76 (27 DUPLICATES REMOVED) ANSWERS '1-240' FROM FILE TOXCENTER D SCAN L78
L2	0 SEA FILE=TOXCENTER 59665-18-8 OR 57049-13-5

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
05/2019	Data submitted to EPA; Compounds searched: 75-27-4
NTP	
05/2019	"75-27-4" "Bromodichloromethane" "Dichlorobromomethane" "Monobromodichloromethane" "BDCM" "Bromo-dichloromethane" "Methane, bromodichloro-" "Dichloromonobromomethane" "Bromodichloromethane"
Regulations.gov	
05/2019	"75-27-4" "Bromodichloromethane" "Dichlorobromomethane" "Monobromodichloromethane"
NIH RePORTER	
05/2019	Text Search: "BDCM" OR "Bromo-dichloromethane" OR "Bromodichloromethane" OR "Bromodichloromethane" OR "Dichlorobromomethane" OR "Dichloromonobromomethane" OR "Methane, bromodichloro-" OR "Monobromodichloromethane" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 209
- Number of records identified from other strategies: 28
- Total number of records to undergo literature screening: 237

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on bromodichloromethane:

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- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

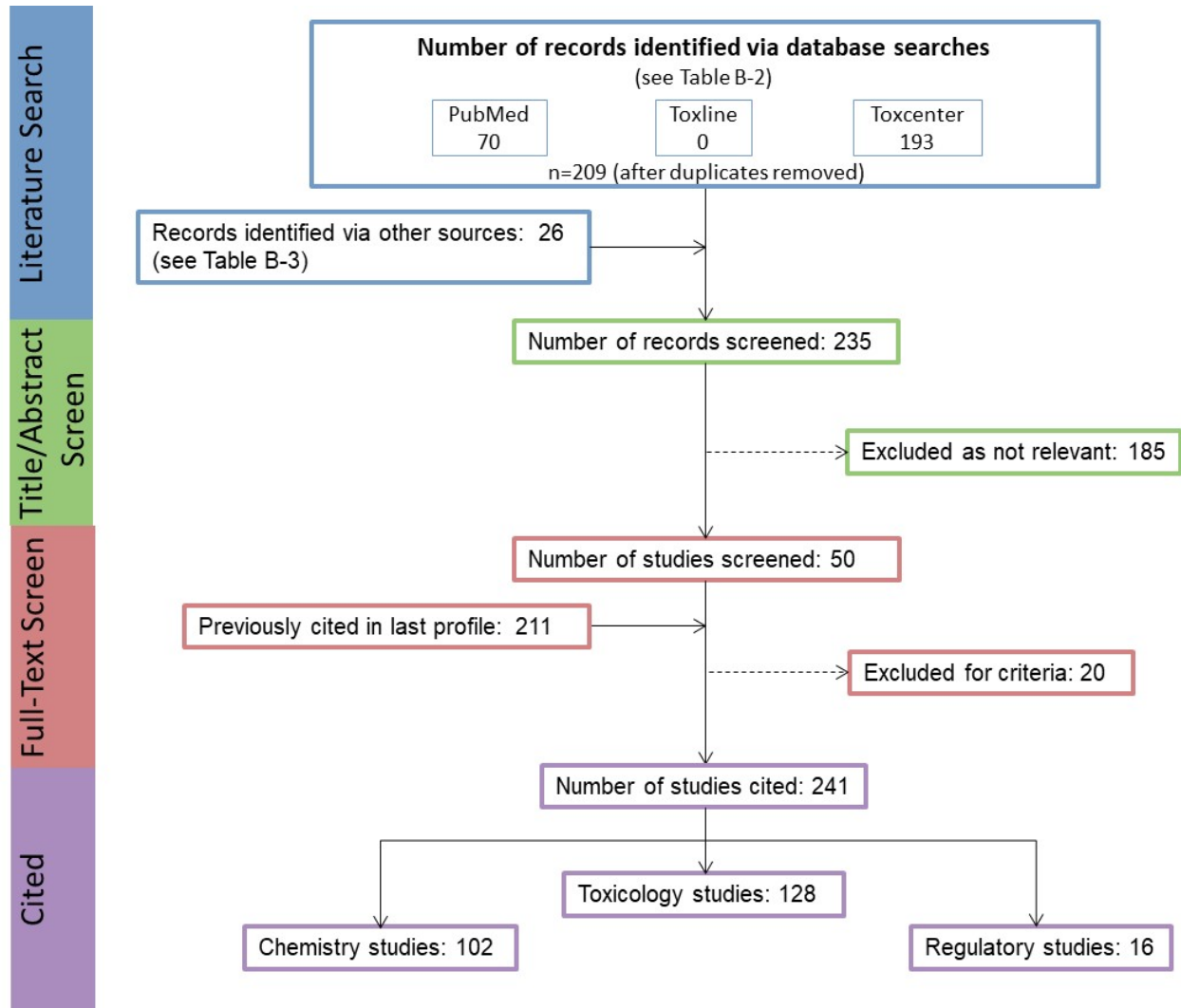
- Number of titles and abstracts screened: 235
- Number of studies considered relevant and moved to the next step: 50

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 50
- Number of studies cited in the pre-public draft of the toxicological profile: 211
- Total number of studies cited in the profile: 241

A summary of the results of the literature search and screening is presented in Figure B-1.

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Figure B-1. May 2019 Literature Search Results and Screen for Bromodichloromethane

APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR BROMODICHLOROMETHANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to bromodichloromethane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to bromodichloromethane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to bromodichloromethane. The inclusion criteria used to identify relevant studies examining the health effects of bromodichloromethane are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of bromodichloromethane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for bromodichloromethane released for public comment in 2018. See Appendix B for the databases searched and the search strategy.

A total of 209 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of bromodichloromethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 236 records were reviewed; 12 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 12 health effects documents identified in the update literature was performed. From those 12 documents, 8 studies were included in the qualitative review. Additionally, 77 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 85.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Bromodichloromethane and overviews of the results of the inhalation and oral exposure studies (no dermal exposure studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2 and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for bromodichloromethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited number of endpoints (hepatic, immunological, reproductive, and developmental effects) and reported immunological, reproductive, and developmental effects. Animal studies examined a number of endpoints following inhalation or oral exposure. These studies examined most endpoints and reported body weight, gastrointestinal, hematological, hepatic, renal, ocular, endocrine, immunological, reproductive, developmental, and other noncancer (alterations in blood glucose) effects. Hepatic, renal, immunological, reproductive, and developmental effects were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. Eighty-five studies (published in 54 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

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Table C-3. Overview of the Health Outcomes for Bromodichloromethane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort														2	9		1
Case control														2	8		1
Population							1					1		1	2		1
Case series							0					1		0			0
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Number of studies examining endpoint	0	1	2	3	4	5-9	≥10										
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10										

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Table C-4. Overview of the Health Outcomes for Bromodichloromethane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological ^a	Neurological ^a	Reproductive ^a	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	2						2	2		2						2	
Intermediate-duration	2						2	2		2						0	
Chronic-duration	3						2	2								3	
	0						0	2								0	
Oral studies																	
Acute-duration	16	1	1	1	3	1	9	8			1	3	3	4	7	5	
Intermediate-duration	12	0	0	0	2	0	7	6			0	2	2	3	7	1	
Chronic-duration	11	7	7	9	6		9	11			7	2	8	6	3	2	
	5	0	0	1	0		6	2			0	1	1	2	1	1	
Acute-duration	8	7	7	7	1		8	7			7		1	6		1	8
Intermediate-duration	4	0	0	0	0		4	3			1		0	1		1	3
Chronic-duration																	
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Number of studies examining endpoint			0	1	2	3	4	5-9	≥10								
Number of studies reporting outcome			0	1	2	3	4	5-9	≥10								

^aNumber of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT’s Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias** (++)
- **Probably low risk of bias** (+)
- **Probably high risk of bias** (-)
- **Definitely high risk of bias** (--)

In general, “definitely low risk of bias” or “definitely high risk of bias” was used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then “probably low risk of bias” or “probably high risk of bias” response was typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias

Were the comparison groups appropriate?

Confounding bias

Did the study design or analysis account for important confounding and modifying variables?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were the research personnel and human subjects blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies**Selection bias**

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were experimental conditions identical across study groups?

Were the research personnel blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of “definitely low” or “probably low” risk of bias on the key questions **AND** received a rating of “definitely low” or “probably low” risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of “definitely high” or “probably high” risk of bias for the key questions **AND** received a rating of “definitely high” or “probably high” risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of bromodichloromethane health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

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Table C-8. Summary of Risk of Bias Assessment for Bromodichloromethane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	Study design or analysis account for important confounding and modifying variables?*	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?*	Confidence in outcome assessment?*	All measured outcomes reported?	
Outcome: Hepatic Effects							
<i>Cross-sectional studies</i>							
Burch et al. 2015	++	-	+	+	+	+	Third
Outcome: Immunological Effects							
<i>Cohort studies</i>							
Vlaanderen et al. 2017	++	-	+	+	+	+	Third
Outcome: Reproductive Effects							
<i>Cohort studies</i>							
MacLehose et al. 2008	++	-	+	-	+	+	Third
Windham et al. 2003	++	-	+	-	+	+	Third
<i>Cross-sectional studies</i>							
Zeng et al. 2013	++	-	+	+	+	+	Third
Outcome: Developmental Effects							
<i>Cohort studies</i>							
Cao et al. 2016	++	-	+	+	+	+	Third
Chen et al. 2019	++	-	+	+	+	+	Third
Dodds and King 2001	++	-	+	-	+	+	Third
Grazuleviciene et al. 2013	++	-	+	-	+	+	Third
King et al. 2000	++	-	+	-	+	+	Third
Rivera-Núñez and Wright 2013	++	-	+	-	+	+	Third
Summerhayes et al. 2012	++	-	+	-	+	+	Third
Waller et al. 1998	++	-	+	-	+	+	Third

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Table C-8. Summary of Risk of Bias Assessment for Bromodichloromethane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	Study design or analysis account for important confounding and modifying variables?*	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?*	Confidence in outcome assessment?*	All measured outcomes reported?	
Wright et al. 2004	++	-	+	-	+	+	Third
<i>Case-control Studies</i>							
Danileviciute et al. 2012	++	-	+	-	+	+	Third
Iszatt et al. 2011	++	-	+	-	+	+	Third
Rivera-Núñez et al. 2018	++	-	+	-	+	+	Third
Wright et al. 2017	++	-	+	-	+	+	Third

++ = definitely low risk of bias; + = probably low risk of bias; - = probably high risk of bias; -- = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

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Table C-9. Summary of Risk of Bias Assessment for Bromodichloromethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	Confidence in outcome assessment?*	All measured outcomes reported?		
Lilly et al. 1994 (rat, GO)	+	+	+	+	+	+	+	+	+	First
Lilly et al. 1996 (rat)	+	+	+	+	+	+	+	+	+	First
Munson et al. 1982 (mouse)	-	+	+	+	+	+	+	+	+	First
Ruddick et al. 1983 (rat)	+	+	+	+	+	+	+	+	+	First
Thornton-Manning et al. 1994 (rat)	+	+	+	+	+	+	+	+	+	First
Thornton-Manning et al. 1994 (mouse)	+	+	+	+	+	+	+	+	+	First
<i>Oral intermediate exposure</i>										
Aida et al. 1989 (rat, F)	-	+	+	+	+	+	+	+	+	First
Aida et al. 1989 (rat, W)	-	+	+	+	+	+	+	+	+	First
Aida et al. 1992 (rat)	+	+	+	+	+	+	+	+	+	First
Chu et al. 1982 (rat)	-	+	+	+	+	-	+	+	+	First
Lipsky et al. 1993 (rat)	-	+	+	+	+	-	+	+	+	First
Lock et al. 2004 (rat)	-	+	+	+	+	+	+	+	+	First
Lock et al. 2004 (mouse)	-	+	+	+	+	+	+	+	+	First
NTP 1987 (rat)	++	+	+	+	+	++	+	++	+	First
NTP 1987 (mouse)	++	+	+	+	+	++	+	++	+	First
NTP 2006 (rat)	++	+	+	+	+	++	+	++	+	First
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	+	First
<i>Oral chronic exposure</i>										
Aida et al. 1992 (rat)	+	+	+	+	+	+	+	+	+	First
George et al. 2002 (rat)	+	+	+	+	+	+	+	+	+	First
George et al. 2002 (mouse)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (rat)	++	+	+	+	+	++	+	++	+	First

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Table C-9. Summary of Risk of Bias Assessment for Bromodichloromethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	Confidence in outcome assessment?*	All measured outcomes reported?		
NTP 1987 (mouse)	++	+	+	+	+	++	+	++	First	
NTP 2006 (rat)	++	+	+	+	+	++	+	++	First	
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	First	
Outcome: Immunological Effects										
<i>Oral acute exposure</i>										
French et al. 1999 (rat, 5 days)	-	+	+	+	+	+	+	+	First	
French et al. 1999 (rat, 14 days)	-	+	+	+	+	+	+	+	First	
Munson et al. 1982	-	+	+	+	+	+	+	+	First	
<i>Oral intermediate exposure</i>										
French et al. 1999 (mouse, 16 days; GW)	-	+	+	+	+	+	+	+	First	
French et al. 1999 (rat, 26 weeks; W)	-	+	+	+	+	+	+	+	First	
Outcome: Reproductive Effects										
<i>Oral acute exposure</i>										
Bielmeier et al. 2001 (rat, GDs 8–9)	-	+	+	+	+	+	+	++	First	
Bielmeier et al. 2004 (rat)	-	+	+	+	+	+	+	++	First	
Bielmeier et al. 2007 (rat)	-	+	+	+	+	+	+	++	First	
Ruddick et al. 1983 (rat)	+	+	+	+	+	+	+	+	First	
<i>Oral intermediate exposure</i>										
Aida et al. 1992 (rat)	+	+	+	+	+	+	+	+	First	
Christian et al. 2001b	++	+	+	+	+	+	+	+	First	
NTP 1987 (rat)	++	+	+	+	+	++	+	++	First	
NTP 1987 (mouse)	++	+	+	+	+	++	+	++	First	

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Table C-9. Summary of Risk of Bias Assessment for Bromodichloromethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	Confidence in outcome assessment?*	All measured outcomes reported?		
<i>Oral intermediate exposure</i>										
Christian et al. 2001a (rat)	++	+	+	+	+	+	+	+	+	First
Christian et al. 2001a (rabbit)	++	+	+	+	+	+	+	+	+	First
Christian et al. 2001b (rat)	++	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; - = probably high risk of bias; -- = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

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C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to bromodichloromethane and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to bromodichloromethane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

APPENDIX C

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
 Exposure occurred prior to the outcome
 Outcome was assessed on individual level rather than at the population level
 A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
 A sufficient number of subjects were tested
 Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
 Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
 A sufficient number of animals per group were tested
 Appropriate parameters were used to assess a potential adverse effect
 Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining hepatic, renal, immunological, reproductive, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Bromodichloromethane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Hepatic effects					
<i>Cross-sectional studies</i>					
Burch et al. 2015	No	No	Yes	Yes	Low
Outcome: Immunological effects					
<i>Cohort studies</i>					
Vlaanderen et al. 2017	No	Yes	Yes	Yes	Moderate

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Table C-13. Presence of Key Features of Study Design for Bromodichloromethane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Reproductive effects					
<i>Cohort studies</i>					
MacLehose et al. 2008	No	No	Yes	Yes	Low
Windham et al. 2003	No	No	Yes	Yes	Low
<i>Cross-sectional studies</i>					
Zeng et al. 2013	No	No	Yes	Yes	Low
Outcome: Developmental effects					
<i>Cohort studies</i>					
Cao et al. 2016	No	No	Yes	Yes	Low
Chen et al. 2019	No	No	Yes	Yes	Low
Dodds and King 2001	No	No	Yes	Yes	Low
Grazuleviciene et al. 2013	No	No	Yes	Yes	Low
King et al. 2000	No	No	Yes	Yes	Low
Rivera-Núñez and Wright 2013	No	No	Yes	Yes	Low
Summerhayes et al. 2012	No	No	Yes	Yes	Low
Waller et al. 1998	No	No	Yes	Yes	Low
Wright et al. 2004	No	No	Yes	Yes	Low
<i>Case-control studies</i>					
Danileviciute et al. 2012	No	No	Yes	Yes	Low
Iszatt et al. 2011	No	No	Yes	Yes	Low
Rivera-Núñez et al. 2018	No	No	Yes	Yes	Low
Wright et al. 2017	No	No	Yes	Yes	Low

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Table C-14. Presence of Key Features of Study Design for Bromodichloromethane—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Hepatic Effects					
<i>Inhalation acute exposure</i>					
Torti et al. 2001 (C57BL/6 mouse)	Yes	No	Yes	Yes	Moderate
Torti et al. 2001 (FVN mouse)	Yes	No	Yes	Yes	Moderate
<i>Inhalation intermediate exposure</i>					
Torti et al. 2001 (C57BL/6 mouse)	Yes	No	Yes	Yes	Moderate
Torti et al. 2001 (FVN mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral acute exposure</i>					
Condie et al. 1983 (mouse)	Yes	No	Yes	Yes	Moderate
Keegan et al. 1998 (rat)	Yes	No	No	Yes	Low
Lilly et al. 1994 (rat, GW)	Yes	No	Yes	Yes	Moderate
Lilly et al. 1994 (rat, GO)	Yes	No	Yes	Yes	Moderate
Lilly et al. 1996 (rat)	Yes	No	Yes	Yes	Moderate
Munson et al. 1982 (mouse)	Yes	No	No	Yes	Low
Ruddick et al. 1983 (rat)	Yes	No	Yes	Yes	Moderate
Thornton-Manning et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Thornton-Manning et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral intermediate exposure</i>					
Aida et al. 1989 (rat, F)	Yes	No	Yes	Yes	Moderate
Aida et al. 1989 (rat, W)	Yes	No	Yes	Yes	Moderate
Aida et al. 1992 (rat)	Yes	Yes	Yes	Yes	High
Chu et al. 1982 (rat)	Yes	No	Yes	Yes	Moderate
Hooth et al. 2002 (rat)	Yes	No	Yes	Yes	Moderate
NTP 1987 (rat)	Yes	Yes	Yes	Yes	High
NTP 1987 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2006 (rat)	Yes	No	Yes	Yes	Moderate
NTP 2006 (mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral chronic exposure</i>					
Aida et al. 1992 (rat)	Yes	Yes	Yes	Yes	High
George et al. 2002 (rat)	Yes	No	Yes	Yes	Moderate
George et al. 2002 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1987 (rat)	Yes	Yes	Yes	Yes	High
NTP 1987 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2006 (rat)	Yes	No	Yes	Yes	Moderate
NTP 2006 (mouse)	Yes	No	Yes	Yes	Moderate

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Table C-14. Presence of Key Features of Study Design for Bromodichloromethane—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Tumasonis et al. 1985 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal Effects					
<i>Inhalation acute exposure</i>					
Torti et al. 2001 (C57BL/6 mouse)	Yes	No	Yes	Yes	Moderate
Torti et al. 2001 (FVN mouse)	Yes	No	Yes	Yes	Moderate
<i>Inhalation intermediate exposure</i>					
Torti et al. 2001 (C57BL/6 mouse)	Yes	No	Yes	Yes	Moderate
Torti et al. 2001 (FVN mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral acute exposure</i>					
Condie et al. 1983 (mouse)	Yes	No	Yes	Yes	Moderate
Lilly et al. 1994 (rat, GW)	Yes	No	Yes	Yes	Moderate
Lilly et al. 1994 (rat, GO)	Yes	No	Yes	Yes	Moderate
Lilly et al. 1996 (rat)	Yes	No	Yes	Yes	Moderate
Munson et al. 1982 (mouse)	Yes	No	No	Yes	Low
Ruddick et al. 1983 (rat)	Yes	No	Yes	Yes	Moderate
Thornton-Manning et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Thornton-Manning et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral intermediate exposure</i>					
Aida et al. 1989 (rat, F)	Yes	No	Yes	Yes	Moderate
Aida et al. 1989 (rat, W)	Yes	No	Yes	Yes	Moderate
Aida et al. 1992 (rat)	Yes	Yes	Yes	Yes	High
Chu et al. 1982 (rat)	Yes	No	Yes	Yes	Moderate
Lipsky et al. 1993 (rat)	Yes	No	Yes	Yes	Moderate
Lock et al. 2004 (rat)	Yes	No	Yes	Yes	Moderate
Lock et al. 2004 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1987 (rat)	Yes	Yes	Yes	Yes	High
NTP 1987 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2006 (rat)	Yes	No	Yes	Yes	Moderate
NTP 2006 (mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral chronic exposure</i>					
Aida et al. 1992 (rat)	Yes	Yes	Yes	Yes	High
George et al. 2002 (rat)	Yes	No	Yes	Yes	Moderate
George et al. 2002 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1987 (rat)	Yes	Yes	Yes	Yes	High
NTP 1987 (mouse)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Bromodichloromethane—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
NTP 2006 (rat)	Yes	No	Yes	Yes	Moderate
NTP 2006 (mouse)	Yes	No	Yes	Yes	Moderate
Outcome: Immunological Effects					
<i>Oral acute exposure</i>					
French et al. 1999 (rat, 5 days)	Yes	No	Yes	Yes	Moderate
French et al. 1999 (rat, 14 days)	Yes	No	Yes	Yes	Moderate
Munson et al. 1982 (mouse)	Yes	No	No	Yes	Low
<i>Oral intermediate exposure</i>					
French et al. 1999 (mouse, 16 days; GW)	Yes	No	Yes	Yes	Moderate
French et al. 1999 (rat, 26 weeks, W)	Yes	No	Yes	Yes	Moderate
Outcome: Reproductive Effects					
<i>Oral acute exposure</i>					
Bielmeier et al. 2001 (rat, GDs 8–9)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2004 (rat)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2007 (rat)	Yes	No	No	Yes	Low
Ruddick et al. 1983 (rat)	Yes	Yes	No	Yes	Moderate
<i>Oral intermediate exposure</i>					
Aida et al. 1992 (rat)	Yes	Yes	No	Yes	Moderate
Christian et al. 2001b	Yes	Yes	Yes	Yes	High
NTP 1987 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1987 (mouse)	Yes	Yes	No	Yes	Moderate
NTP 2006 (rat)	Yes	Yes	No	Yes	Moderate
NTP 2006 (mouse)	Yes	Yes	No	Yes	Moderate
<i>Oral chronic exposure</i>					
Aida et al. 1992 (rat)	Yes	Yes	No	Yes	Moderate
Klinefelter et al. 1995 (rat)	Yes	Yes	Yes	Yes	High
NTP 1987 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1987 (mouse)	Yes	Yes	No	Yes	Moderate
NTP 2006 (rat)	Yes	Yes	No	Yes	Moderate
NTP 2006 (mouse)	Yes	Yes	No	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Bromodichloromethane—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Developmental Effects					
<i>Oral Acute Exposure</i>					
Bielmeier et al. 2001 (rat, GDs 6–10)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2001 (Sprague-Dawley rat, GDs 6–10)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2001 (rat, GDs 8–9)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2001 (rat, GDs 6–10 or 6–15)	Yes	Yes	No	Yes	Moderate
Bielmeier et al. 2004 (rat)	Yes	Yes	No	Yes	Moderate
Narotsky et al. 1997 (rat)	Yes	Yes	No	Yes	Moderate
Ruddick et al. 1983 (rat)	Yes	Yes	Yes	No	Moderate
<i>Oral intermediate exposure</i>					
Christian et al. 2001a (rat)	Yes	Yes	Yes	Yes	High
Christian et al. 2001a (rabbit)	Yes	Yes	Yes	Yes	High
Christian et al. 2001b (rat)	Yes	Yes	No	Yes	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Bromodichloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hepatic Effects		
<i>Inhalation acute exposure</i>		
Animal studies		
Torti et al. 2001 (C57BL/6 mouse)	Moderate	Moderate
Torti et al. 2001 (FVN mouse)	Moderate	
<i>Inhalation intermediate exposure</i>		
Animal studies		
Torti et al. 2001 (C57BL/6 mouse)	Moderate	Moderate
Torti et al. 2001 (FVN mouse)	Moderate	

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Table C-15. Initial Confidence Rating for Bromodichloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
<i>Oral acute exposure</i>		
Animal studies		
Condie et al. 1983 (mouse)	Moderate	Moderate
Keegan et al. 1998 (rat)	Low	
Lilly et al. 1994 (rat, GW)	Moderate	
Lilly et al. 1994 (rat, GO)	Moderate	
Lilly et al. 1996 (rat)	Moderate	
Munson et al. 1982 (mouse)	Low	
Ruddick et al. 1983 (rat)	Moderate	
Thornton-Manning et al. 1994 (rat)	Moderate	
Thornton-Manning et al. 1994 (mouse)	Moderate	
<i>Oral intermediate exposure</i>		
Animal studies		
Aida et al. 1989 (rat, F)	Moderate	High
Aida et al. 1989 (rat, W)	Moderate	
Aida et al. 1992 (rat)	High	
Chu et al. 1982 (rat)	Moderate	
Hooth et al. 2002 (rat)	Moderate	
NTP 1987 (rat)	High	
NTP 1987 (mouse)	High	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	
<i>Oral chronic exposure</i>		
Human studies		
Burch et al. 2015	Low	Low
Animal studies		
Aida et al. 1992 (rat)	High	High
George et al. 2002 (rat)	Moderate	
George et al. 2002 (mouse)	Moderate	
NTP 1987 (rat)	High	
NTP 1987 (mouse)	High	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	
Tumasonis et al. 1985 (rat)	High	
Outcome: Renal Effects		
<i>Inhalation acute exposure</i>		
Animal studies		
Torti et al. 2001 (C57BL/6 mouse)	Moderate	Moderate
Torti et al. 2001 (FVN mouse)	Moderate	

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Table C-15. Initial Confidence Rating for Bromodichloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
<i>Inhalation intermediate exposure</i>		
Animal studies		
Torti et al. 2001 (C57BL/6 mouse)	Moderate	Moderate
Torti et al. 2001 (FVN mouse)	Moderate	
<i>Oral acute exposure</i>		
Animal studies		
Condie et al. 1983 (mouse)	Moderate	Moderate
Lilly et al. 1994 (rat, GW)	Moderate	
Lilly et al. 1994 (rat, GO)	Moderate	
Lilly et al. 1996 (rat)	Moderate	
Munson et al. 1982 (mouse)	Low	
Ruddick et al. 1983 (rat)	Moderate	
Thornton-Manning et al. 1994 (rat)	Moderate	
Thornton-Manning et al. 1994 (mouse)	Moderate	
<i>Oral intermediate exposure</i>		
Animal studies		
Aida et al. 1989 (rat, F)	Moderate	High
Aida et al. 1989 (rat, W)	Moderate	
Aida et al. 1992 (rat)	High	
Chu et al. 1982 (rat)	Moderate	
Lipsky et al. 1993 (rat)	Moderate	
Lock et al. 2004 (rat)	Moderate	
Lock et al. 2004 (mouse)	Moderate	
NTP 1987 (rat)	High	
NTP 1987 (mouse)	High	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	
<i>Oral chronic exposure</i>		
Animal studies		
Aida et al. 1992 (rat)	High	High
George et al. 2002 (rat)	Moderate	
George et al. 2002 (mouse)	Moderate	
NTP 1987 (rat)	High	
NTP 1987 (mouse)	High	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	

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Table C-15. Initial Confidence Rating for Bromodichloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Immunological Effects		
<i>Oral acute exposure</i>		
Animal studies		
French et al. 1999 (rat, 5 days)	Moderate	Moderate
French et al. 1999 (rat, 14 days)	Moderate	
Munson et al. 1982 (mouse)	Low	
<i>Oral intermediate exposure</i>		
Animal studies		
French et al. 1999 (mouse, 16 days; GW)	Moderate	Moderate
French et al. 1999 (rat, 26 weeks; W)	Moderate	
<i>Acute dermal exposure</i>		
Human studies		
Vlaanderen et al. 2017	Moderate	Moderate
Outcome: Reproductive Effects		
<i>Oral acute exposure</i>		
Animal studies		
Bielmeier et al. 2001 (rat, GDs 8–9)	Moderate	Moderate
Bielmeier et al. 2004 (rat)	Moderate	
Bielmeier et al. 2007 (rat)	Low	
Ruddick et al. 1983 (rat)	Moderate	
<i>Oral intermediate exposure</i>		
Animal studies		
Aida et al. 1992 (rat)	Moderate	High
Christian et al. 2001b	High	
NTP 1987 (rat)	Moderate	
NTP 1987 (mouse)	Moderate	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	
<i>Oral chronic exposure</i>		
Human studies		
MacLehose et al. 2008	Low	Low
Windham et al. 2003	Low	
Zeng et al. 2013	Low	

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Table C-15. Initial Confidence Rating for Bromodichloromethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Animal studies		
Aida et al. 1992 (rat)	Moderate	High
Klinefelter et al. 1995 (rat)	High	
NTP 1987 (rat)	Moderate	
NTP 1987 (mouse)	Moderate	
NTP 2006 (rat)	Moderate	
NTP 2006 (mouse)	Moderate	
Outcome: Developmental Effects		
<i>Oral acute exposure</i>		
Animal studies		
Bielmeier et al. 2001 (F344 rat, GDs 6–10)	Moderate	Moderate
Bielmeier et al. 2001 (Sprague-Dawley rat, GDs 6–10)	Moderate	
Bielmeier et al. 2001 (rat, GDs 8–9)	Moderate	
Bielmeier et al. 2001 (rat, GDs 6–10 or 6–15)	Moderate	
Bielmeier et al. 2004 (rat)	Moderate	
Narotsky et al. 1997 (rat)	Moderate	
Ruddick et al. 1983 (rat)	Moderate	
<i>Oral intermediate exposure</i>		
Animal studies		
Christian et al. 2001a (rat)	High	High
Christian et al. 2001b (rat)	Moderate	
Christian et al. 2001a (rabbit)	High	
<i>Oral chronic exposure</i>		
Human studies		
Cao et al. 2016	Low	Low
Chen et al. 2019	Low	
Danileviciute et al. 2012	Low	
Dodds and King 2001	Low	
Grazuleviciene et al. 2013	Low	
Iszatt et al. 2011	Low	
King et al. 2000	Low	
Rivera-Núñez et al. 2018	Low	
Rivera-Núñez and Wright 2013	Low	
Summerhayes et al. 2012	Low	
Waller et al. 1998	Low	
Wright et al. 2004	Low	
Wright et al. 2017	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic, renal, immunological, reproductive, and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with bromodichloromethane exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
 - No downgrade if most studies are in the risk of bias first tier
 - Downgrade one confidence level if most studies are in the risk of bias second tier
 - Downgrade two confidence levels if most studies are in the risk of bias third tier
- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
 - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
 - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
 - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direction of the effect
- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
 - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
 - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
 - Nature of the exposure in human studies and route of administration in animal studies— inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
 - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

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Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
 - Downgrade one confidence level if one of the factors is considered indirect
 - Downgrade two confidence levels if two or more of the factors are considered indirect
- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥ 10 for tests of ratio measures (e.g., odds ratios) and ≥ 100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
 - No downgrade if there are no serious imprecisions
 - Downgrade one confidence level for serious imprecisions
 - Downgrade two confidence levels for very serious imprecisions
- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
 - Downgrade one level of confidence for cases where there is serious concern with publication bias

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Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 large magnitude of effect	High
Outcome: Renal Effects			
Animal studies	High	-1 inconsistency	Moderate
Outcome: Immunological Effects			
Human studies	Moderate	-2 risk of bias, -1 imprecision	Very Low
Animal studies	Moderate	None	Moderate
Outcome: Reproductive Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	-1 inconsistency, -1 imprecision	Low
Outcome: Developmental Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 large magnitude of effect	High

Table C-17. Confidence in the Body of Evidence for Bromodichloromethane

Outcome	Confidence in body of evidence	
	Human studies	Animal studies
Hepatic effects	Very Low	High
Renal effects	No data	Moderate
Immunological effects	Very Low	Moderate
Reproductive effects	Very Low	Low
Developmental effects	Very Low	High

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
 - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias
- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
 - Upgrade one confidence level for evidence of a monotonic dose-response gradient
 - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies
- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
 - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect
- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
 - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for bromodichloromethane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for bromodichloromethane is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Bromodichloromethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Very Low	Health effect	Inadequate
Renal effects	No data		No data
Immunological effects	Very Low	Health effect	Inadequate
Reproductive effects	Very Low	Health effect	Inadequate
Developmental effect	Very Low	Health effect	Inadequate
Animal studies			
Hepatic effects	High	Health effect	High
Renal effects	Moderate	Health effect	Moderate
Immunological effects	Moderate	Health effect	Moderate
Reproductive effects	Low	Health effect	Low
Developmental effect	High	Health effect	High

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C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
 - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
 - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
 - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
 - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
 - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
 - Low level of evidence in human studies **AND** low level of evidence in animal studies

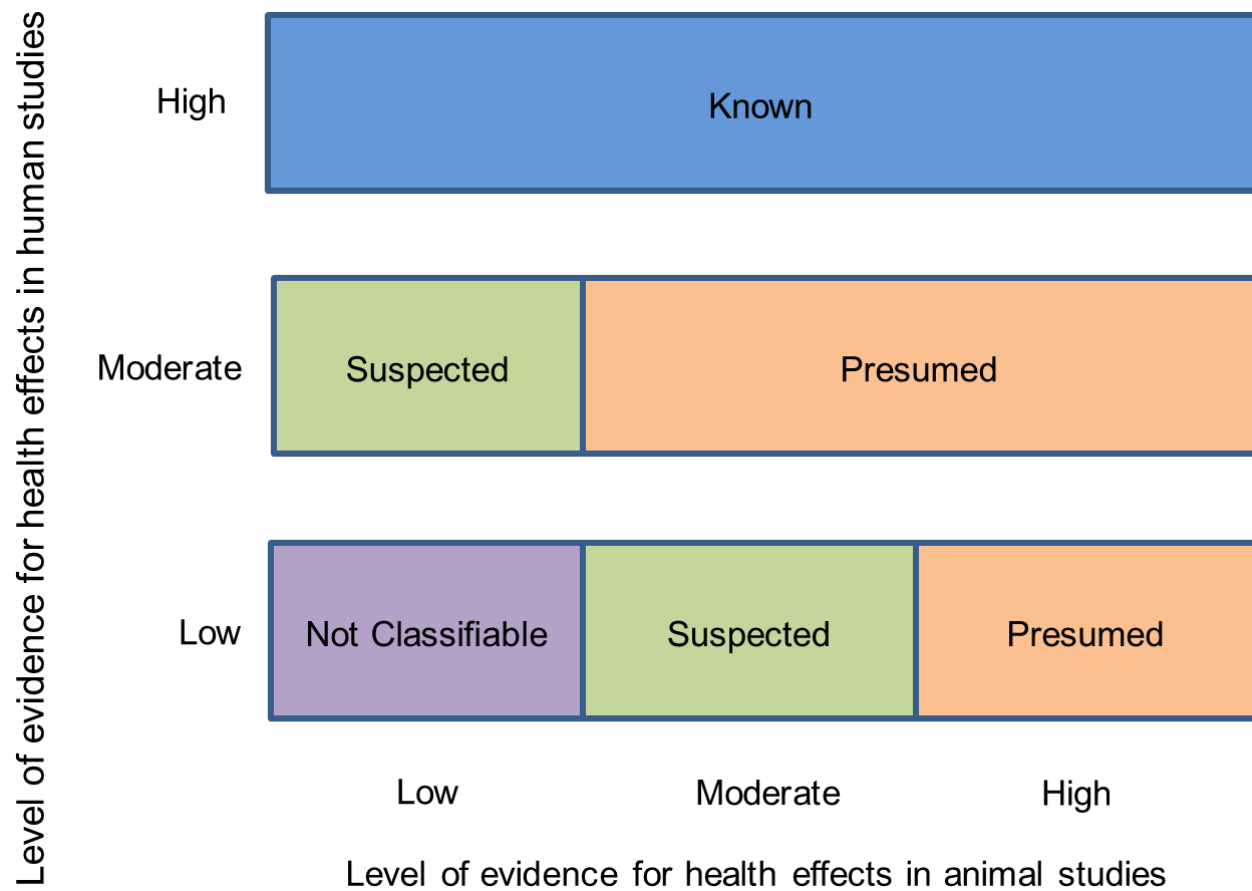
Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of “not identified” was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of “inadequate” was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

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Figure C-1. Hazard Identification Scheme

The hazard identification conclusions for bromodichloromethane are listed below and summarized in Table C-19.

Presumed Health Effects

- Hepatic effects
 - Inadequate evidence from a cross-sectional study (Burch et al. 2015) examining the association between serum bromodichloromethane levels and alanine aminotransferase levels.
 - High level of evidence in mice following acute inhalation exposure (Torti et al. 2001) and in rats and mice following acute (Condie et al. 1983; Keegan et al. 1998; Lilly et al. 1994, 1996; Munson et al. 1982; Thornton-Manning et al. 1994), intermediate (Aida et al. 1992; Hooth et al. 2002; NTP 1987), and chronic (Aida et al. 1992; NTP 1987) oral exposure.
- Developmental effects
 - Although a number of epidemiology studies found associations between exposure to bromodichloromethane and developmental effects, the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
 - High level of evidence from acute (Bielmeier et al. 2001, 2004; Narotsky et al. 1997) and intermediate (Christian et al. 2001a) oral exposure in rats. The most sensitive

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developmental endpoint was full-litter resorption in F344 rats, but not in Sprague-Dawley rats (Bielmeier et al. 2001, 2004; Narotsky et al. 1997).

Suspected Health Effects

- Renal effects
 - No human data are available on the potential renal toxicity of bromodichloromethane.
 - Moderate evidence of renal toxicity in mice following acute or intermediate inhalation exposure and in rats and mice following acute (Condie et al. 1983; Lilly et al. 1994, 1996; Munson et al. 1982; Thornton-Manning et al. (1994), intermediate (NTP 1987), and chronic (George et al. 2002; NTP 1987) oral exposure.
- Immunological effects
 - Very low evidence in an epidemiological study that evaluated immune markers in subjects swimming in chlorinated water for 40 minutes (Vlaanderen et al. 2017). No data are available on whether inhalation, oral, or dermal exposure to bromodichloromethane impairs immune function.
 - Moderate evidence in animal studies based on two studies that found altered responses to immune stimulants after acute gavage administration (French et al. 1999; Munson et al. 1982) or intermediate oral exposure in rats (French et al. 1999).

Not Classifiable Effects

- Reproductive effects
 - Inadequate evidence in cohort and cross-sectional studies that examined sperm parameters (Zeng et al. 2013), menstrual cycle (Windham et al. 2003), and time to pregnancy (MacLehose et al. 2008).
 - Low evidence in animal studies (Aida et al. 1992; Bielmeier et al. 2001, 2004, 2007; Christian et al. 2001b; Klinefelter et al. 1995; NTP 1987, 2006; Ruddick et al. 1983). Studies evaluating the histopathology of the reproductive system have not found alterations at nonlethal doses (Aida et al. 1992; NTP 1987, 2006). Bielmeier et al. (2001, 2004, 2007) reported significant alterations in reproductive hormone levels in pregnant rats, and Klinefelter et al. (1995) reported decreases in sperm velocity, but no changes in sperm motility. No alterations in reproductive function were observed in a 2-generation study in rats (Christian et al. 2001b). The lack of consistency across studies and the indirectness of the observed effects decreased the initial confidence in these studies.

Table C-19. Hazard Identification Conclusions for Bromodichloromethane

Outcome	Hazard identification
Hepatic effects	Presumed health effect
Renal effects	Suspected health effect
Immunological effects	Suspected health effect
Reproductive effects	Not classifiable
Developmental effects	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

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substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

- (1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.
- (2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥ 365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).
- (4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

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more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

- (6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).
- (7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.
- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.
- (10) Reference. The complete reference citation is provided in Chapter 8 of the profile.
- (11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

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- (14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.
- (15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).
- (17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.
- (18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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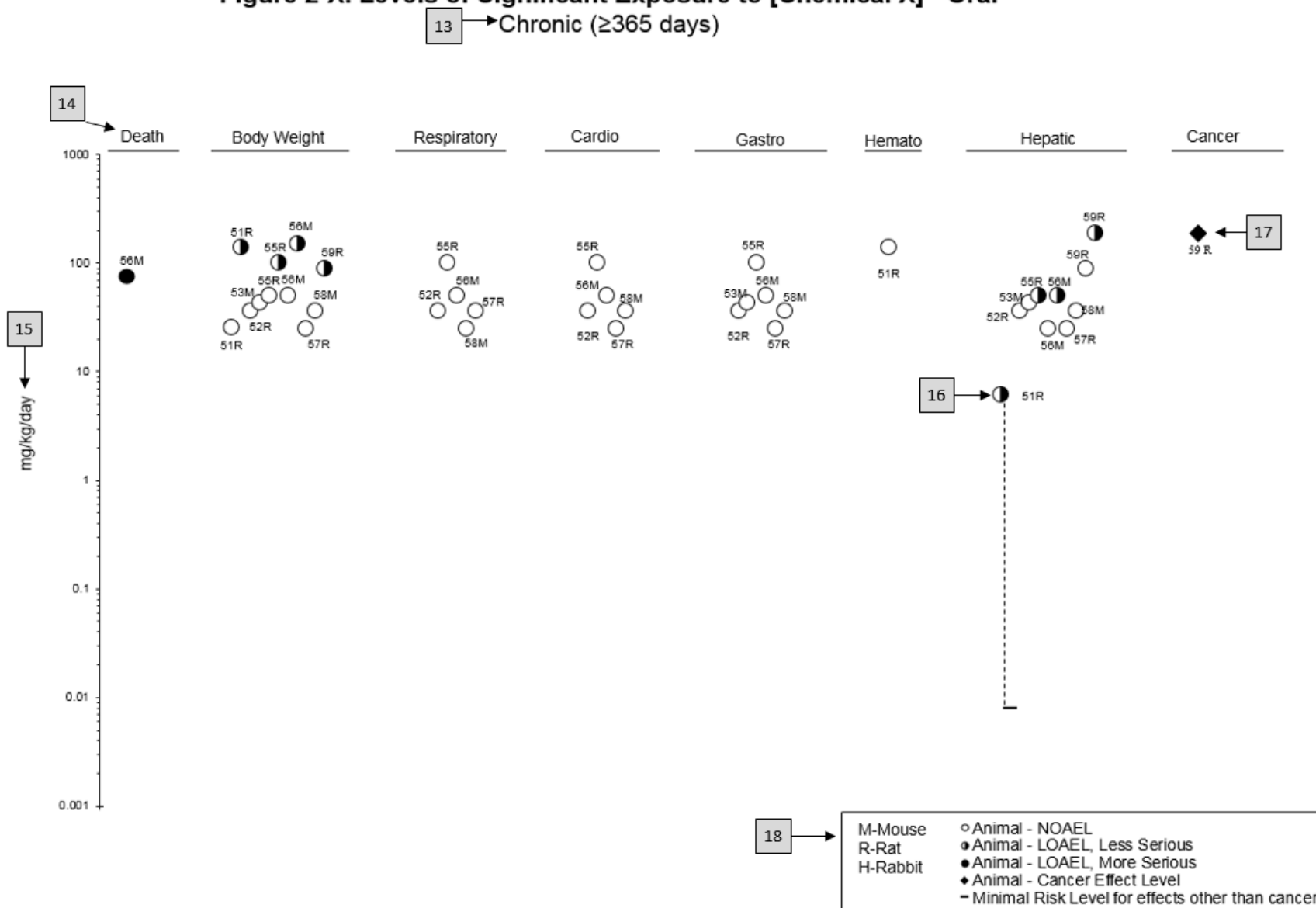
Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral ← 1

	4 Species	5 Exposure parameters	5 Doses (mg/kg/day)	6 Parameters monitored	7 Endpoint	8 NOAEL (mg/kg/day)	8 Less serious LOAEL (mg/kg/day)	9 Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
2	51 Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt Hemato Hepatic	25.5 138.0	138.0 6.1 ^c		Decreased body weight gain in males (23–25%) and females (31–39%) Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
	Aida et al. 1992								
	52 Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic Renal Endocr	36.3 20.6 36.3	36.3		Increased incidence of renal tubular cell hyperplasia
	George et al. 2002								
	59 Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
	Tumasonis et al. 1985								

11 → ^aThe number corresponds to entries in Figure 2-x.
^bUsed to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL₀₅ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
^cUsed to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL₁₀ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 **Children and Other Populations that are Unusually Susceptible**
Section 3.3 **Biomarkers of Exposure and Effect**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see <https://www.atsdr.cdc.gov/MHMI/index.asp>). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

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Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: <https://www.cdc.gov/nceh/>.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: <https://www.niehs.nih.gov/>.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: <http://www.acmt.net>.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: <http://www.aapcc.org/>.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤ 14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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 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.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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 period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

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Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥ 365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

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 that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—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 has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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.

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

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

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Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

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

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

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Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m³ or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

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Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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.

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

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) 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 human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD _x	dose that produces a X% change in response rate of an adverse effect
BMDL _x	95% lower confidence limit on the BMD _x
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

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FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ -glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

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NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

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VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q ₁ *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result