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

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 bromodichloro-methane 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

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.

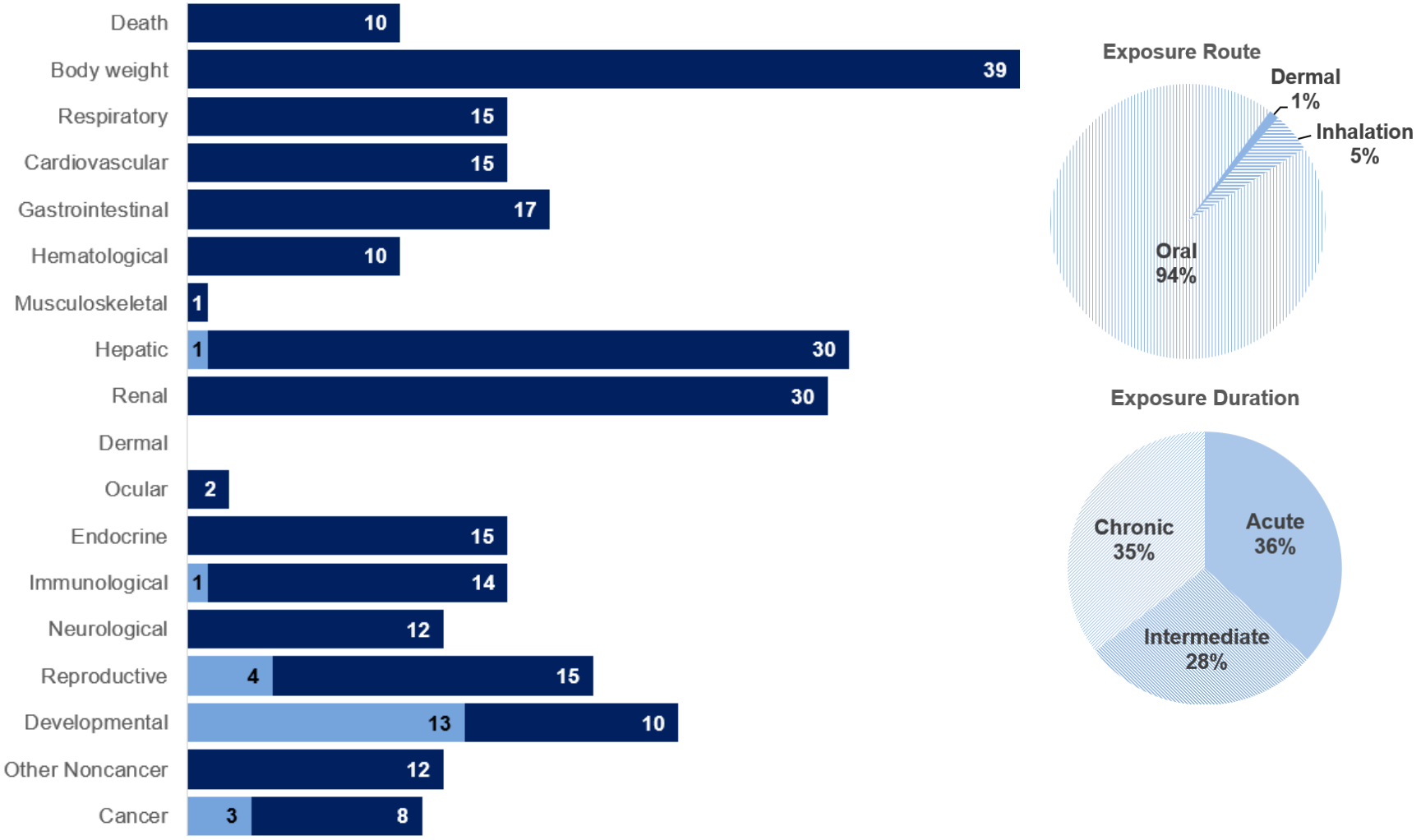
- **Immune Endpoints.** Immunological effects are a suspected health effect for humans based on moderate evidence in rats following acute and intermediate oral exposure. Decreased immune responses to stimulants were observed in rats.

- **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.

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.

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).

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 (µg/day) estimated from daily water ingestion, showering, and bathing recollection data; daily uptake range of 0.0001–0.34 µg/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 µg/L - Q2: 5–9 µg/L - Q3: 10–19 µg/L - Q4: ≥20 µg/L **Logistic regression adjustments:** maternal age, parity, maternal smoking, neighborhood family income	**Developmental effects:** BDCM concentrations ≥20 µg/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 µg/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 µg/L.
Grazuleviciene et al. 2013 Prospective cohort study of 3,074 women in Lithuania	**Exposure:** Internal dose of trihalomethanes (µg/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 µg/day - T2: 0.013–0.051 µg/day - T3: 0.051–0.436 µg/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).

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

Reference and study population	Exposure	Outcomes
		No association with congenital musculoskeletal or urogenital anomalies were found. The ORs for the T3 groups: Musculoskeletal anomalies 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 Urogenital anomalies 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 00.92–8.99
Hoffman et al. 2008 Cross-sectional study of 2,766 pregnant women from three U.S. communities	**Exposure:** Average residential BDCM concentration in community with moderate levels of chlorinated disinfection byproducts: - T1: 8.2–11.8 µg/L - T2: 11.9–14.1 µg/L - T3: 14.2–28.5 µg/L Average residential BDCM concentration in community with moderate levels of brominated disinfection byproducts: - T1: 15.8–20.1 µg/L - T2: 20.2–22.9 µg/L - T3: 23–29.2 µg/L **Bayesian adjustments:** other disinfection byproducts, maternal age, race/ethnicity, income, education, employment status, pre-pregnancy BMI, parity, caffeine intake	**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).

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

Reference and study population	Exposure	Outcomes
Iszatt et al. 2011 Case-control study of 468 cases with hypospadias and 485 controls in England	**Exposure:** Trihalomethanes intake based on estimates of individual water consumption and use. BDCM intake categorized by quartiles: - Q1: 0 µg/day - Q2: >0–1.0 µg/day - Q3: 2–5 µg/day - Q4: 6–50 µg/day **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	**Developmental effects:** After adjustment, intake of ≥6 µg/day BDCM was associated with an increased the risk of hypospadias (OR 1.65, 95% CI 1.02–2.69). However, there was no dose-response relationship (p=0.13 for trend). 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.
Jones et al. 2019 Prospective cohort study of 15,53 women reporting public water source for >10 years and participating in the Iowa Woman's Health Study	**Exposure:** BDCM in municipal water; concentration range categorized by quartile: - Q1: <0.25 µg/L - Q2: 0.25–1.16 µg/L - Q3: 1.17–3.78 µg/L - Q4: >3.78 µg/L **Statistical analysis adjustments:** age, physical activity, smoking status, NO_3-N level	**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 Q3 (HR 1.87, 95%CI 1.17–3.00). No association between BDCM concentration in municipal water and the risk of colon cancer (Q4 HR 1.16, 95%CI 0.94–1.45).
King et al. 2000 Retrospective cohort study of 49,756 women in Canada	**Exposure:** BDCM in municipal water; concentration range categorized by quartile: - Q1: <5 µg/L - Q2: 5–9 µg/L - Q3: 10–19 µg/L - Q4: ≥20 µg/L **Logistic regression adjustments:** maternal age, parity, maternal smoking, infant's sex, neighborhood family income	**Developmental effects:** Exposure to ≥20 µg/L BDCM almost doubled the risk of stillbirth (RR 1.98, 95% CI, 1.23–3.49). Analysis of continuous data showed a 29% increase in risk for stillbirth with each 10 µg/L BDCM (95% CI 1.10–1.53). 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).

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

Reference and study population	Exposure	Outcomes
MacLehose et al. 2008 Prospective cohort study of 1,315 women in three metropolitan areas	**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. **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)	**Reproductive effects:** For the ingested metric, an association between time to pregnancy and BDCM levels were found; the OR at highest concentration (≥12.8 µg/day) was 1.5 (95% CI 1.2–1.9); this would be indicative of a shorter time to pregnancy. 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.
Min and Min 2016 Cross-sectional study of 933 1999–2004 NHANES adult participants; not diagnosed with cancer and 19 died from cancer	**Exposure:** Blood bromodichloromethane levels: - T1: <1.00 µg/L - T2: 1.00–2.70 µg/L - T3: >2.71 µg/L **Statistical analysis adjustments:** age, sex, race/ethnicity, education family income, smoking status, alcohol consumption status, moderate physical activity, BMI, total cholesterol, hypertension, diabetes	**Cancer effects:** No association between total cancer mortality and BDCM levels (p=0.0869).

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

Reference and study population	Exposure	Outcomes
Rivera-Núñez and Wright 2013 Retrospective cohort study of 672,120 live births in the United States	**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. **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	**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. 3rd trimester BDCM was not associated with increased SGA (OR 0.91, 95% CI 0.83–1.00). 2nd trimester BDCM was not associated with increased preterm delivery (OR 1.09, 95% CI 0.97–1.23).
Rivera-Núñez et al. 2018 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	**Exposure:** BDCM in public water systems during the second trimester. Mean BDCM concentration was 6.4 µg/L. BDCM concentration categorized into tertiles: - T1: ≤4.1 µg/L - T2: >4.1–7.2 µg/L - T3: >7.2–49.5 µg/L **Statistical analysis adjustments:** maternal race, education, marital status, source of water, sum of four trihalomethanes, sum of five haloacetic acids	**Developmental effects:** No associations between BDCM and all causes of stillbirths. 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).
Summerhayes et al. 2012 Retrospective cohort study of 314,982 births in Australia	**Exposure:** BDCM in water distributed by public utility company. BDCM concentration range for third trimester categorized by deciles: - D1: 2.95–9.78 µg/L - D10: 21.96–52.55 µg/L **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	**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). 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). In general, larger associations were seen in nonsmokers than in smokers.

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.

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

Reference and study population	Exposure	Outcomes
	weighing ≥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 µg/L and OR 0.92 (95% CI 0.85–0.99) for 14–46 µg/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 µg/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

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			30	2/6, 1/6, 3/6 deaths in wild type strain at 30, 100, and 150 ppm, respectively
					Bd wt	10	30		Decreased body weight gain
					Hepatic	10	30		Centrilobular hepatocellular degeneration at ≥30 ppm and hepatocellular necrosis at ≥100 ppm
					Renal	1	10		Tubular degeneration and nephrosis
					Ocular	10	30		Mild eye irritation
					Other noncancer (urinary bladder)	150			
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			30	2/6, 4/6, 6/6 deaths at 30, 100, and 150 ppm, respectively
					Bd wt	100			
					Hepatic	1	10		Centrilobular hepatocellular degeneration at ≥10 ppm and hepatocellular necrosis at ≥100 ppm
					Renal	1	10		Tubular degeneration and nephrosis
					Other noncancer (urinary bladder)	150			
Torti et al. 2001									

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	30			
					Hepatic	30			Centrilobular hepatocellular degeneration was observed at ≥10 ppm in heterozygous strains
					Renal	3	10		Tubular degeneration; investigators provided severity scores but did not provide incidence data
					Other noncancer (urinary bladder)	30			
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			30	4/6 deaths in wild-type strain
					Bd wt	30			
					Hepatic	30			
					Renal	3	10		Tubular degeneration at ≥10 ppm; investigators provided severity scores for these lesions but did not provide incidence data
					Other noncancer (urinary bladder)	30			
Torti et al. 2001									

[a]The 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

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

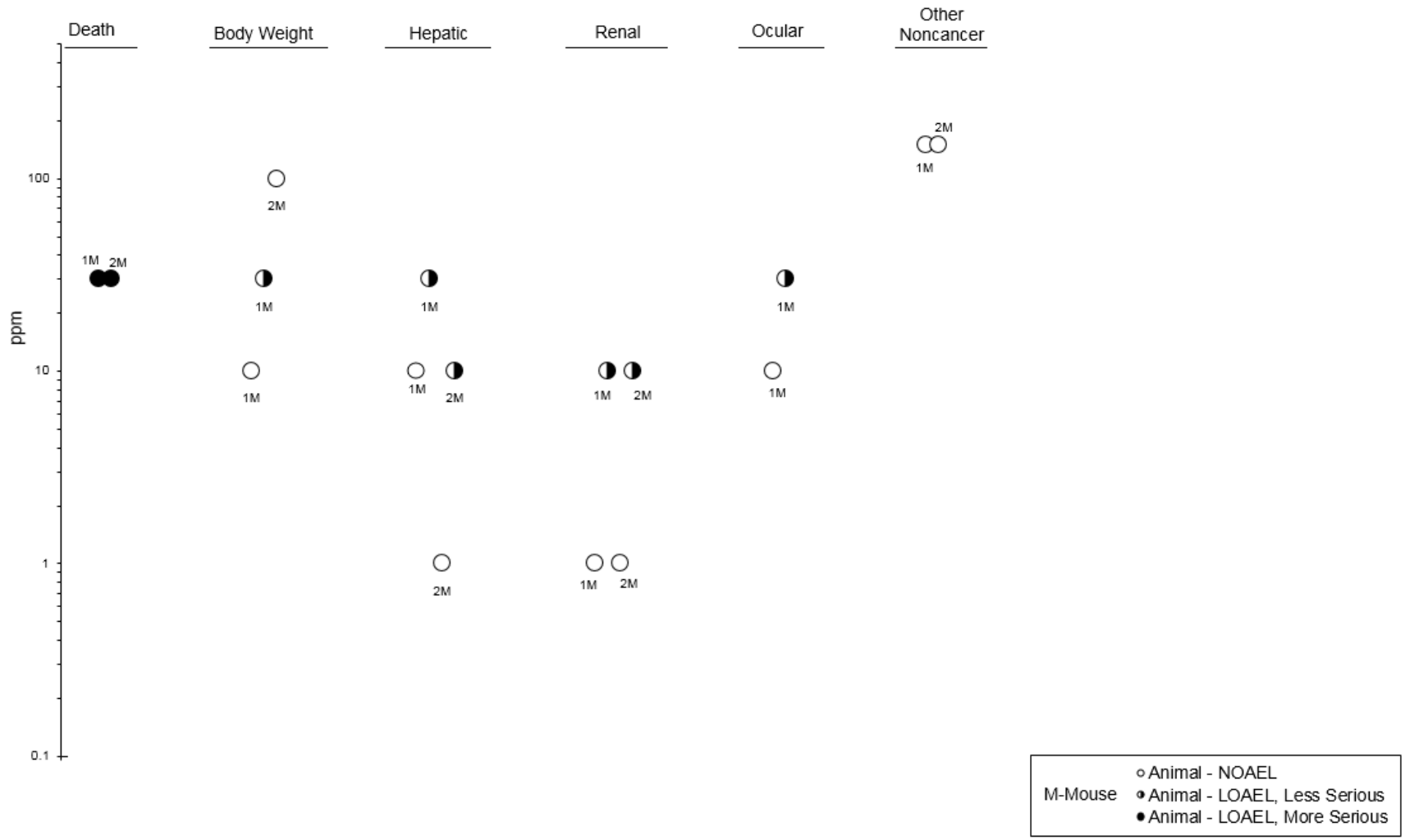


Figure 2-2. Levels of Significant Exposure to Bromodichloromethane – Inhalation
Intermediate (15-364 days)

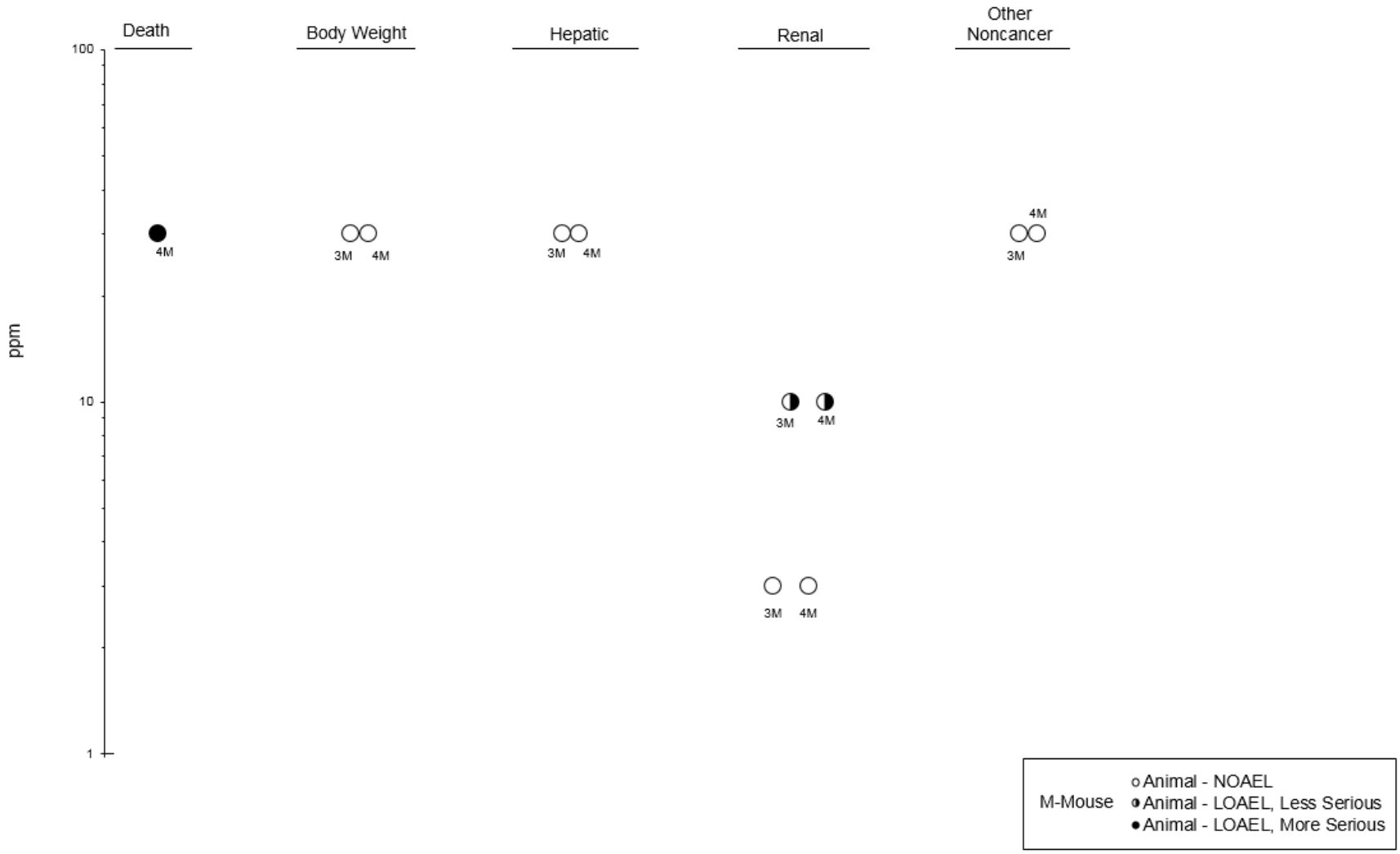


Table 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

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		75		Body weight on GD 20 reduced 35%
					Develop			75	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		75		Reduced serum progesterone
					Develop			75	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		75		Decreased serum progesterone and luteinizing hormone on GD 10
					Develop			75	Full-litter resorptions (80%) on GDs 6–10
Bielmeier et al. 2004									

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									

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		Decreased response to the T-cell stimulant, phytohemagglutinin (PHA), in mesenteric lymph node lymphocytes at 75 mg/kg/day Decreased response to concanavalin A (Con A) in mesenteric lymph node lymphocytes at 150 mg/kg/day Decreased response to Con A and PHA in the splenic lymphocytes and to *S. typhimurium* in the mesenteric lymph node lymphocytes at 300 mg/kg/day Impaired humoral immunity (response to sheep red blood cells) at 300 mg/kg/day

French et al. 1999

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	245.7			
					Hepatic	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	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 decreased at 200 mg/kg
					Other noncancer (blood glucose)	400			
Lilly et al. 1994									

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.

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		25	50	Decreased weight gain on GDs 6–8 at 25 mg/kg/day; weight loss at 50 mg/kg/day
					Develop	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									

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
					Bd wt	150	300		16.8% decrease in body weight
					Hepatic	75	150		Hepatocellular vacuolar degeneration

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									

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)

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
					Other noncancer (blood glucose)	125	250		30% decrease in blood glucose levels in males
Munson et al. 1982									
26	Mouse (B6C3F1) 5 M, 5 F	Once (GO)	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) 5 M, 5 F	14 days (GO)	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 (C57BLl/6 J) 6 F	5 days (GW)	0, 75, 150	BW, BC, OW, HP	Bd wt	150			
					Hepatic	150			
					Renal	150			
Thornton-Manning et al. 1994									
INTERMEDIATE EXPOSURE									
29	Rat (Wistar) 7 M	1 month (F)	0, 20, 60, 180	BW, OW, HE, BC, HP	Bd wt	60	180		19% decrease in body weight gain
					Resp	180			
					Cardio	180			
					Gastro	180			
					Hemato	180			
					Hepatic	60	180		Decrease in absolute liver weight, vacuolization, swelling, and necrosis

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			

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 ≥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 ≥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									

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									

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	100			
					Renal	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		6.5		Increase in aberrant crypt foci in colon
					Other noncancer (urinary bladder)	48.0			
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									

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

NTP 1987

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									

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	50			
					Renal	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	100 M 400 F			
					Resp	100 M 400 F			
					Cardio	100 M 400 F			
					Gastro	100 M 400 F			
					Hepatic	100 M 100 F	200 F		Enlarged centrilobular hepatocytes and microgranulomas
					Renal	50 M 400 F	100 M		Focal necrosis of the proximal renal tubular epithelium
					Endocr	100 M 400 F			

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
					Immuno	100 M 400 F			
					Neuro	100 M 400 F			
					Repro	100 M 400 F			
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	51			
					Resp	51			
					Cardio	51			
					Gastro	51			
					Hemato	51			
					Hepatic	51			
					Renal	51			
					Endocr	51			
					Immuno	51			
					Neuro	51			
					Repro	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									

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	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Resp	138.0			
					Cardio	138.0			
					Gastro	138.0			
					Hemato	138.0			
					Hepatic		6.1[c]		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

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	36.3			
					Resp	36.3			
					Cardio	36.3			
					Gastro	36.3			
					Hepatic	36.3			
					Renal	20.6	36.3		Renal tubular cell hyperplasia
					Endocr	36.3			
					Cancer				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									

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

NTP 1987

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	25			
					Resp	25			
					Cardio	25			
					Gastro	25			
					Hepatic	25			
					Renal	25			
					Endocr	25			
					Immuno	25			
					Repro	25			
					Cancer				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		90 M 190 F		Decreased body weight (approximately 30%) in males and females
					Hepatic	90M	190 F		Increased incidence of hepatic adenofibrosis
					Cancer			190 F	Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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	43.3			
					Gastro	43.3			
					Hepatic	43.3			
					Renal	43.3			
					Endocr	43.3			
					Cancer				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			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
					Bd wt	50 M 75 F	150 F		25% lower body weights than controls in females
					Resp	50 M 150 F			
					Cardio	50 M 150 F			
					Gastro	50 M 150 F			
					Hepatic	25 M 150 F	50M		Hepatic fatty metamorphosis

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	36			
					Resp	36			
					Cardio	36			
					Gastro	36			
					Hepatic	36			
					Renal	36			
					Endocr	36			
					Immuno	36			

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
					Repro	36			
					Cancer				No significant increases in neoplastic lesions
NTP 2006									

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.07 mg/kg/day based on the $BMDL_{05}$ of 7.15 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ 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 Bd wt = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; ED_{50} = 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; LD_{50} = 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

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

Acute (≤14 days)

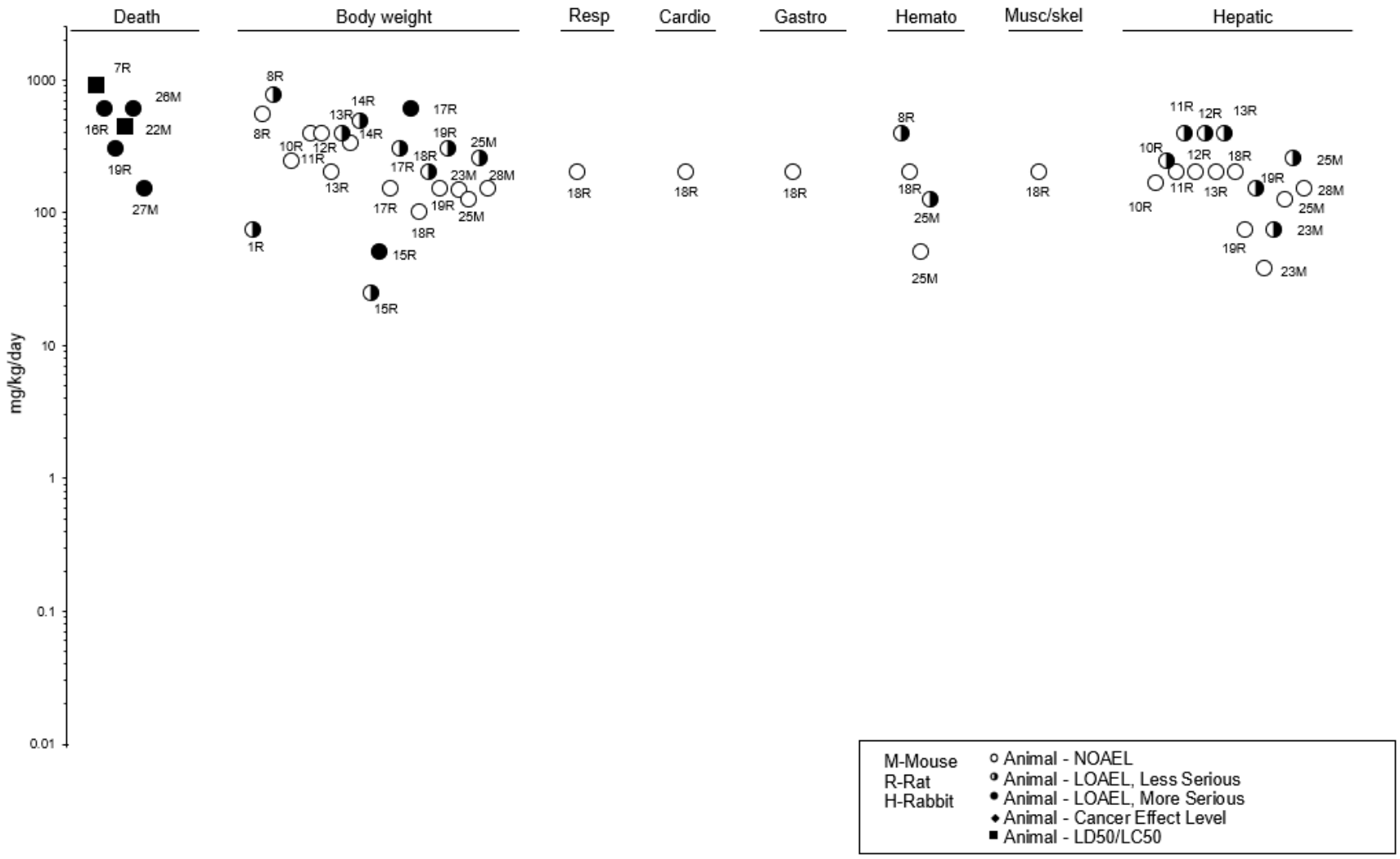


Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral
Acute (≤14 days)

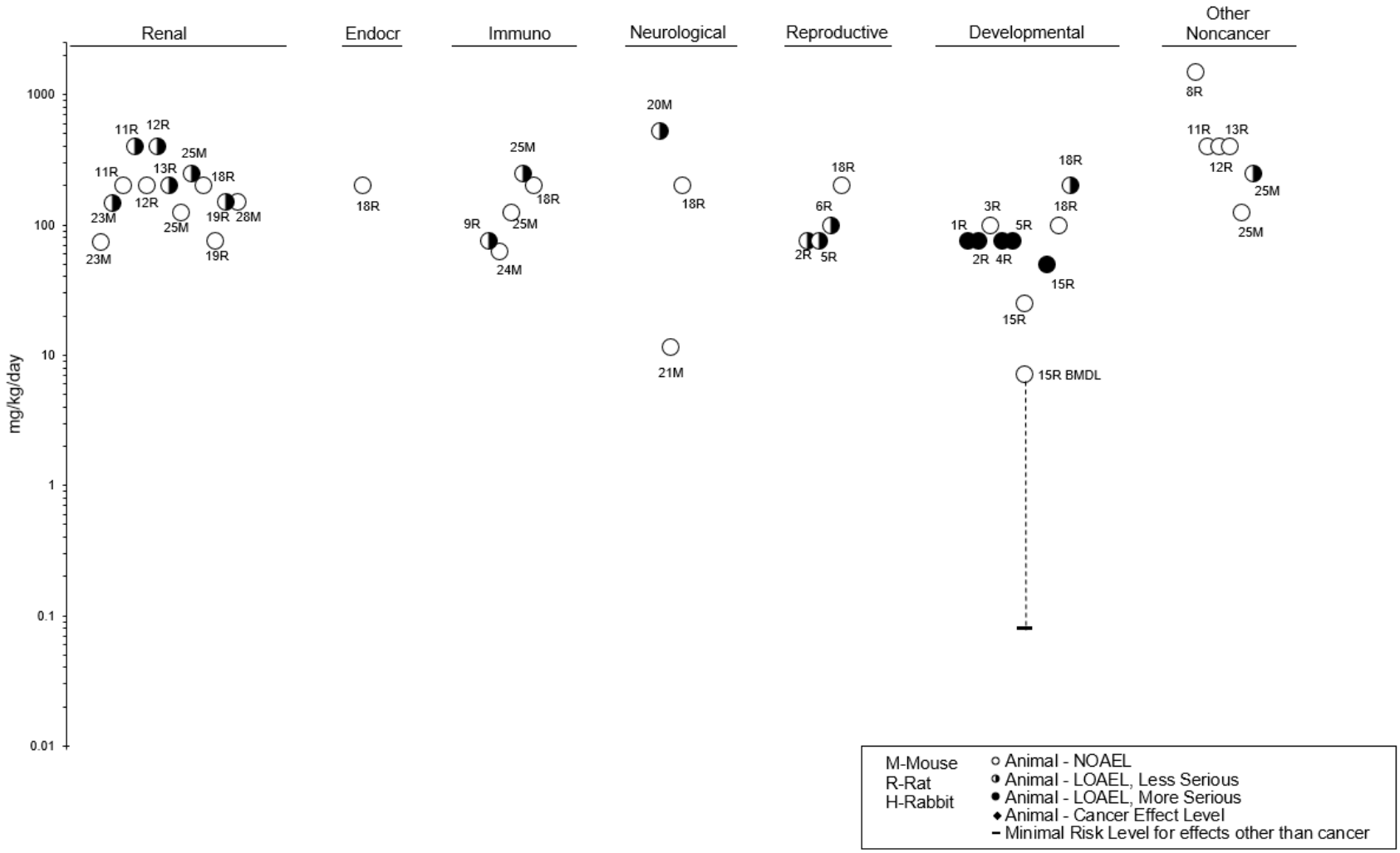


Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Intermediate (15-364 days)

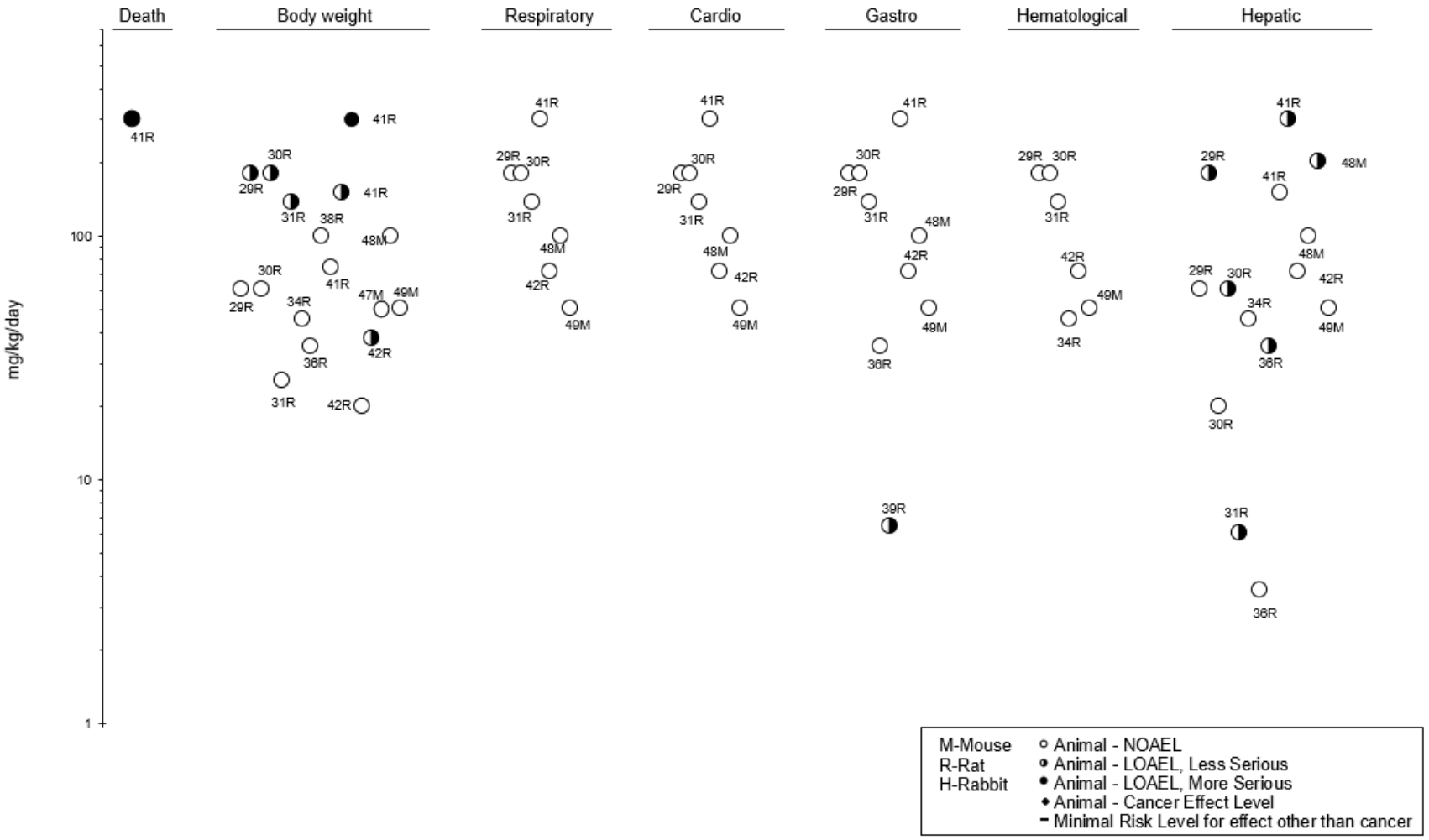


Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Intermediate (15-364 days)

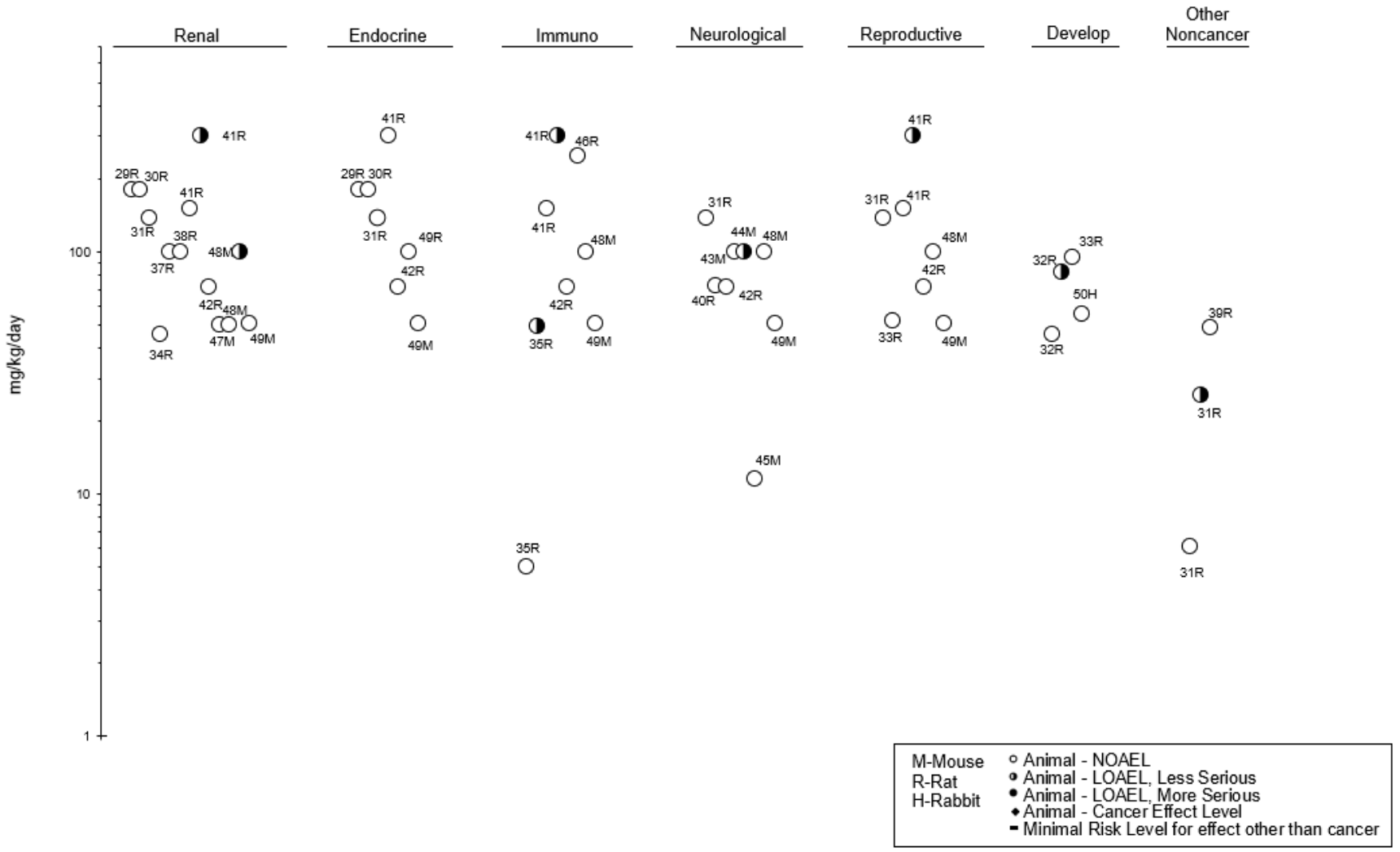


Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Chronic (≥365 days)

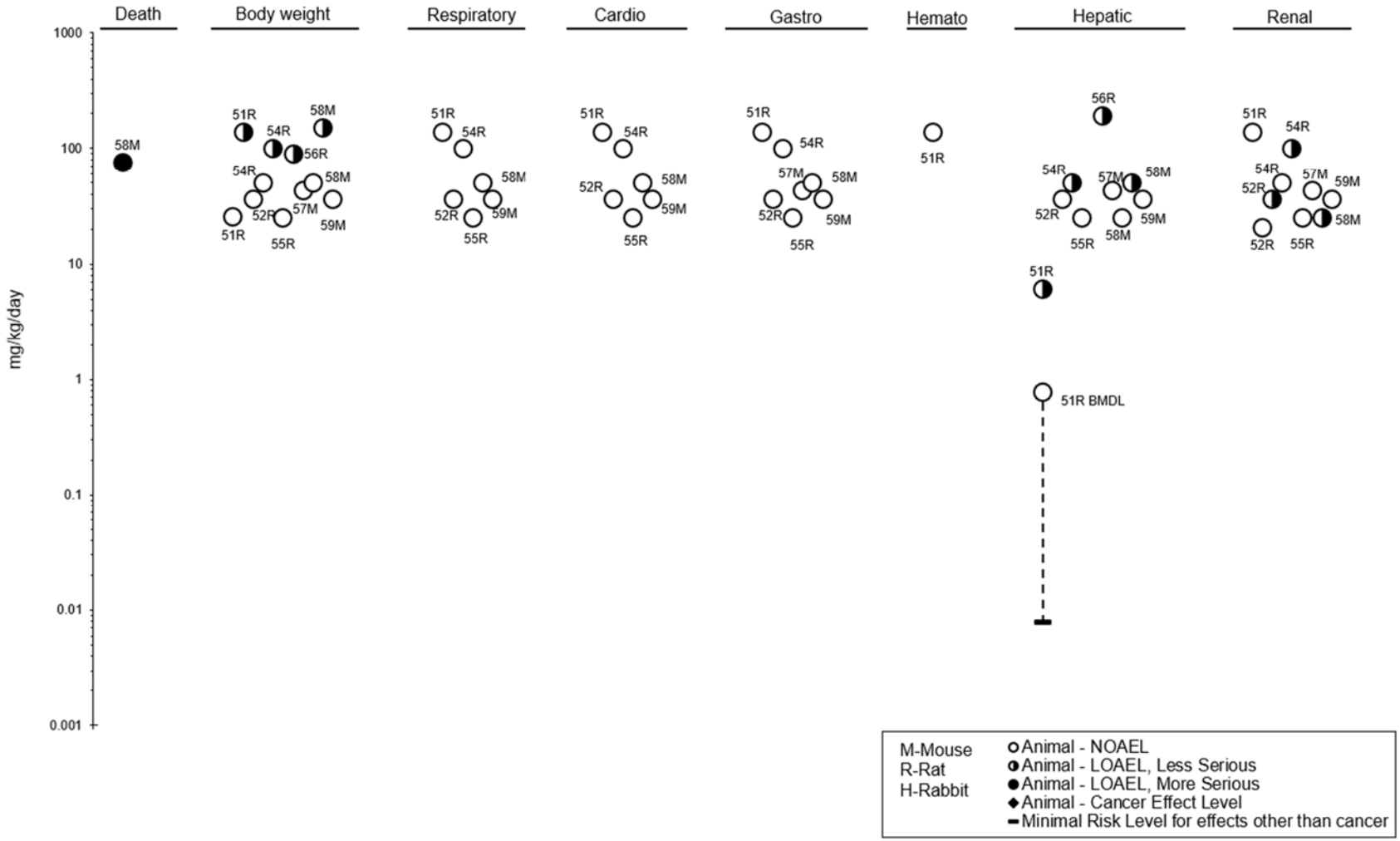
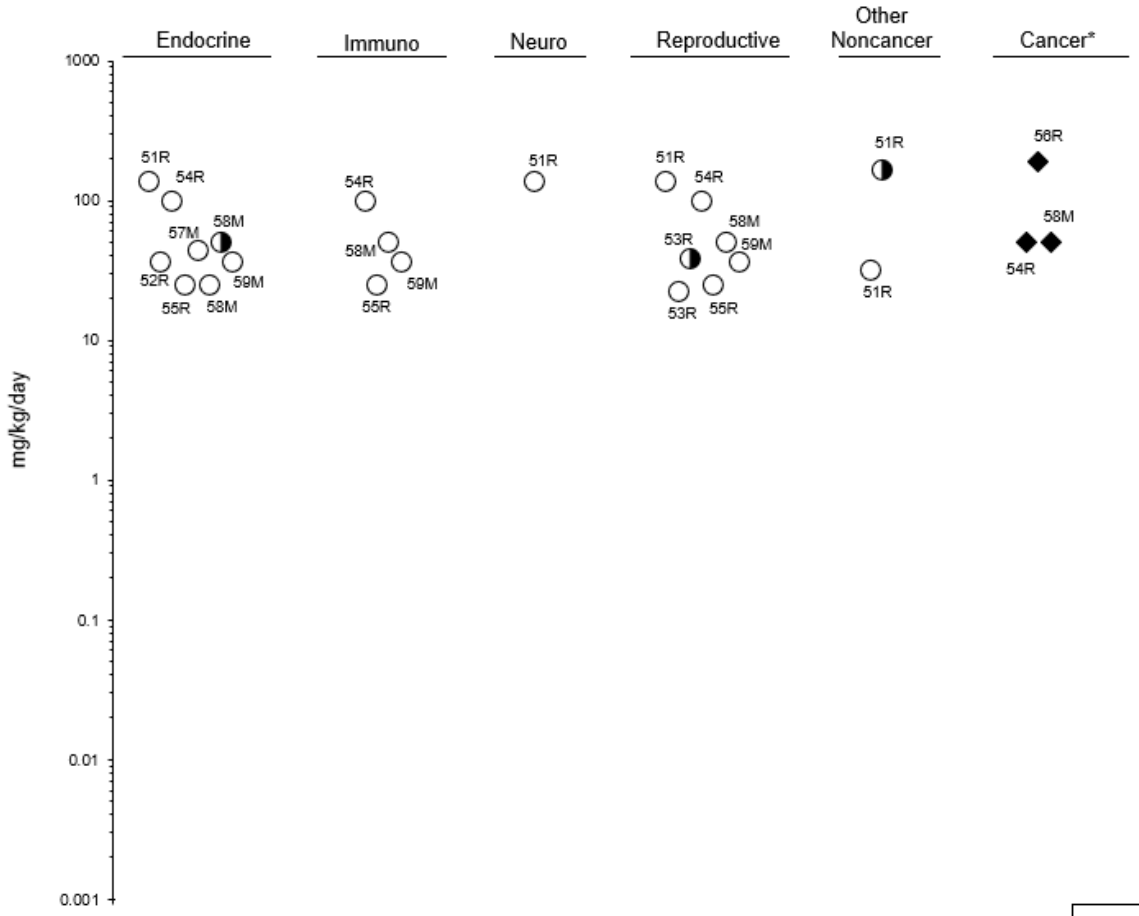


Figure 2-3. Levels of Significant Exposure to Bromodichloromethane – Oral

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

M-Mouse
R-Rat
H-Rabbit

- Animal - NOAEL
- Animal - LOAEL, Less Serious
- Animal - LOAEL, More Serious
- Animal - Cancer Effect Level
- Minimal Risk Level for effects other than cancer

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 LD_{50} 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. LD_{50} 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 ≤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 ≥30 ppm for 1 week resulted in decreases in body weight gain (Torti et al. 2001); increases in mortality were also observed at these

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.

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.

2.9 HEPATIC

Information on the hepatoxicity 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

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

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),

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.

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-1rA 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 tymphimurium* (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

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

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 µg/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

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 µg/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);

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 µg/day) versus the first tertile (0.000–0.013 µg/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 µg/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 µg/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.

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).

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 sternebrae 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.

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

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.

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
		Activation		
		With	Without	
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	NTP 1987
S. typhimurium (strains not reported)	Gene mutation	(+)[a]	–	Sofuni et al. 1996
S. typhimurium (TA1535, TA1537)	Gene mutation	+	+	Varma et al. 1988
S. typhimurium (TA98, TA100)	Gene mutation	+	–	Varma et al. 1988
S. typhimurium (strains not reported)	Gene mutation	–	–	Zeiger 1990
S. typhimurium (TA100)	Gene mutation	No data	+[b]	Simmon et al. 1977
S. typhimurium (TA97, TA98, TA100, TA1535, TA1537)	Gene mutation	No data	-	Mortelmans et al. 1986

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

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Saccharomyces cerevisiae (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

[a]Results were only positive in assays conducted by one of three laboratories.
[b]Results 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

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/m^3 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 *Salmonella* 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

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

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.