APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromodichloromethane
CAS Numbers: 75-27-4
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute
MRL 0.07 mg/kg/day
Critical Effect: Full-litter resorption
Reference: Narotsky et al. 1997
Point of Departure: $BMDL_{05}$ of 7.15 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 15
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.07 mg/kg/day was derived for bromodichloromethane based on an increased incidence of full-litter resorptions in rats administered bromodichloromethane via gavage on GDs 6–15 (Narotsky et al. 1997). The MRL is based on a $BMDL_{05}$ of 7.15 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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

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

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

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

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

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

[a]Considered a serious LOAEL.

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

Selection of the Point of Departure: The $BMDL_{05}$ of 7.15 mg/kg/day for full-litter resorption was selected as the basis of the MRL.

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

A $BMDL_{05}$ value of 7.15 mg/kg/day was calculated using the incidence data for rats administered bromodichloromethane via gavage in aqueous solution. Although the $BMDL_{05}$ of 7.15 mg/kg/day was lower than the empirical NOAEL of 25 mg/kg/day identified in the study, it was selected as the point of departure because it provides a better indicator of the dose-response relationship than the NOAEL, which is a single data point.

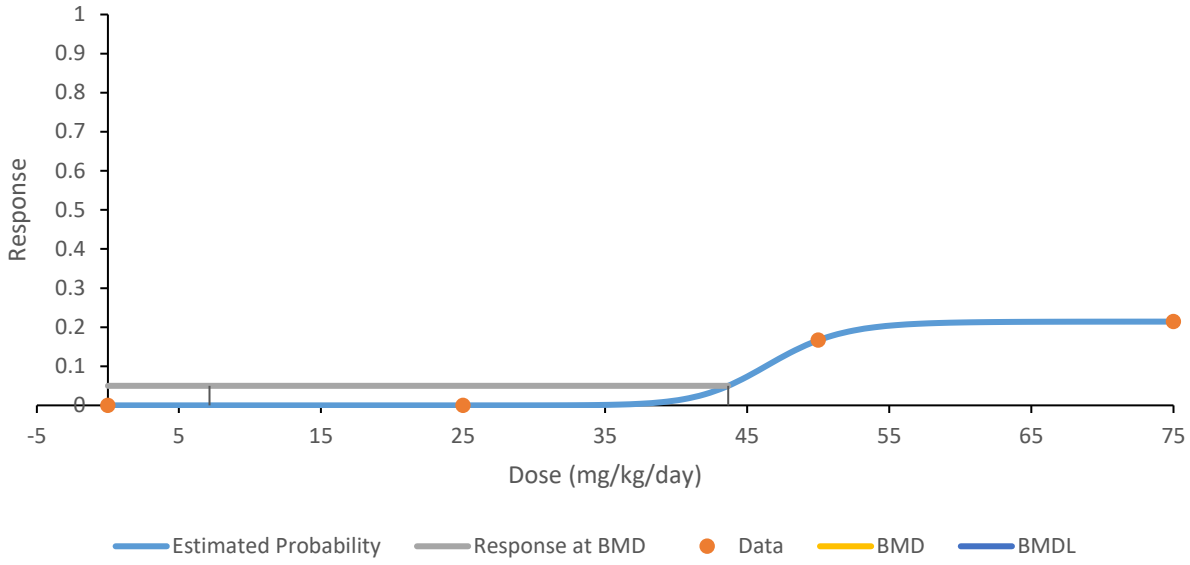
Table A-3. Model Predictions for Full-Litter Resorptions in Rats Orally Administered Bromodichloromethane in an Aqueous Vehicle (Narotsky et al. 1997)

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

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Dichotomous Hill).

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

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



Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{05}$ is divided by a total uncertainty factor of 100

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

MRL = $BMDL_{05}$ ÷ UFs
7.15 mg/kg/day ÷ (10 x 10) = 0.07 mg/kg/day

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

Agency Contacts (Chemical Managers): Susan Ingber

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

[a]Adjusted for intermittent exposure (5 days/7 days).

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

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

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

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

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

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

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

[a]Adjusted for intermittent exposure (5 days/7 days).

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

Agency Contacts (Chemical Managers): Susan Ingber

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

[a]Adjusted for intermittent exposure (5 days/7 days).

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

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

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

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

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

[a]Adjusted for intermittent exposure (5 days/7 days).

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

Summary of the Principal Study:

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

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

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

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

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

Selection of the Point of Departure: The $BMDL_{10}$ of 1.57 mg/kg/day for hepatocellular fatty degeneration in male rats was selected as the POD.

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

Intermittent Exposure: Not applicable.

The $BMDL_{10}$ is divided by a total uncertainty factor of 100

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

$$MRL = BMDL_{10} \div UFs$$
$$0.78 \text{ mg/kg/day} \div (10 \times 10) = 0.008 \text{ mg/kg/day}$$

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

Agency Contacts (Chemical Managers): Susan Ingber

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

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

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL (1st degree multistage) was selected.

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

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

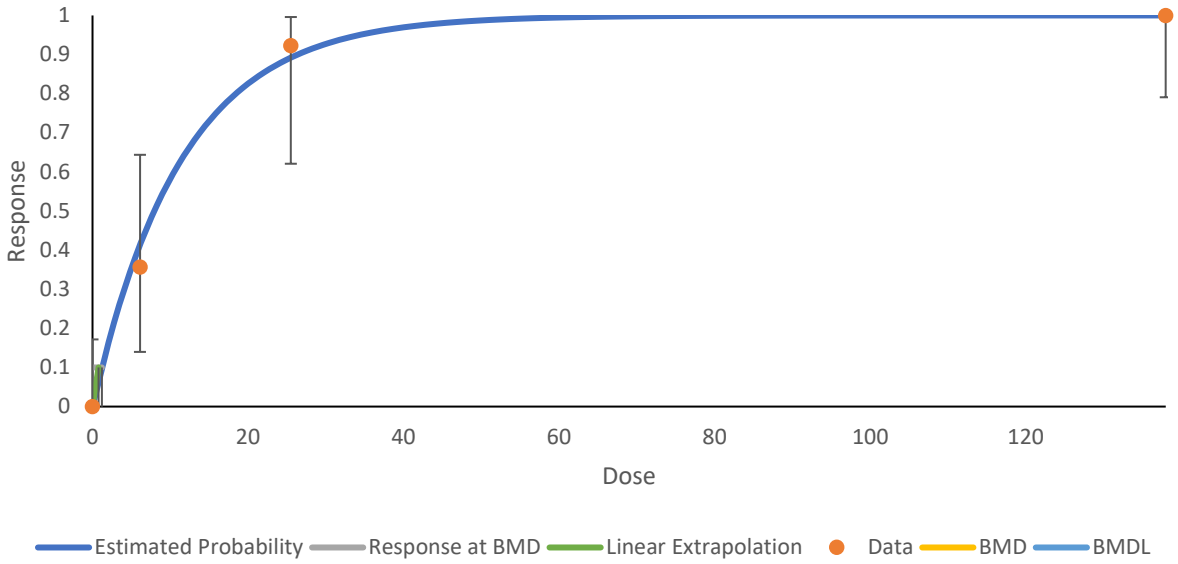
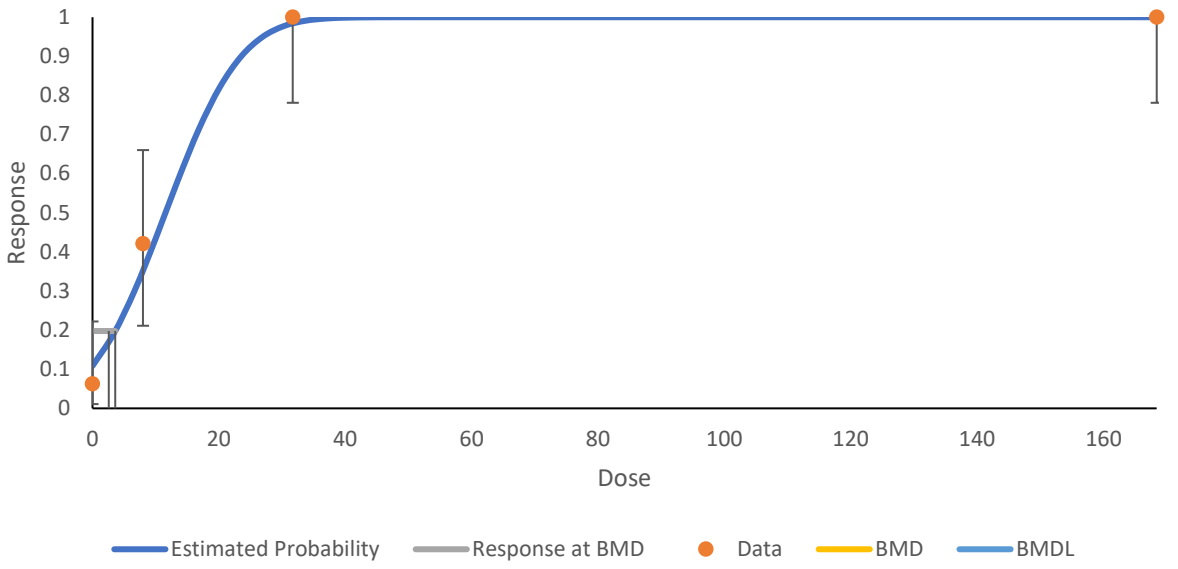


Figure A-3. Fit of Probit Model for Hepatocellular Fatty Degeneration in Female Rats Exposed to Bromodichloromethane (mg/kg/day)



APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BROMODICHLOROMETHANE

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

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

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

B.1.1 Literature Search

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

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

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

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

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

Database search date	Query string
	PRIMATES OR PRIMATE?)
	L75 QUE L73 OR L74

	L76 267 SEA FILE=TOXCENTER L44 AND L75
	L77 20 SEA FILE=TOXCENTER L76 AND MEDLINE/FS
	L78 240 DUP REM L76 (27 DUPLICATES REMOVED)
	ANSWERS '1-240' FROM FILE TOXCENTER
	D SCAN L78
	L2 0 SEA FILE=TOXCENTER 59665-18-8 OR 57049-13-5

Table B-3. Strategies to Augment the Literature Search

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

The 2019 results were:

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

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

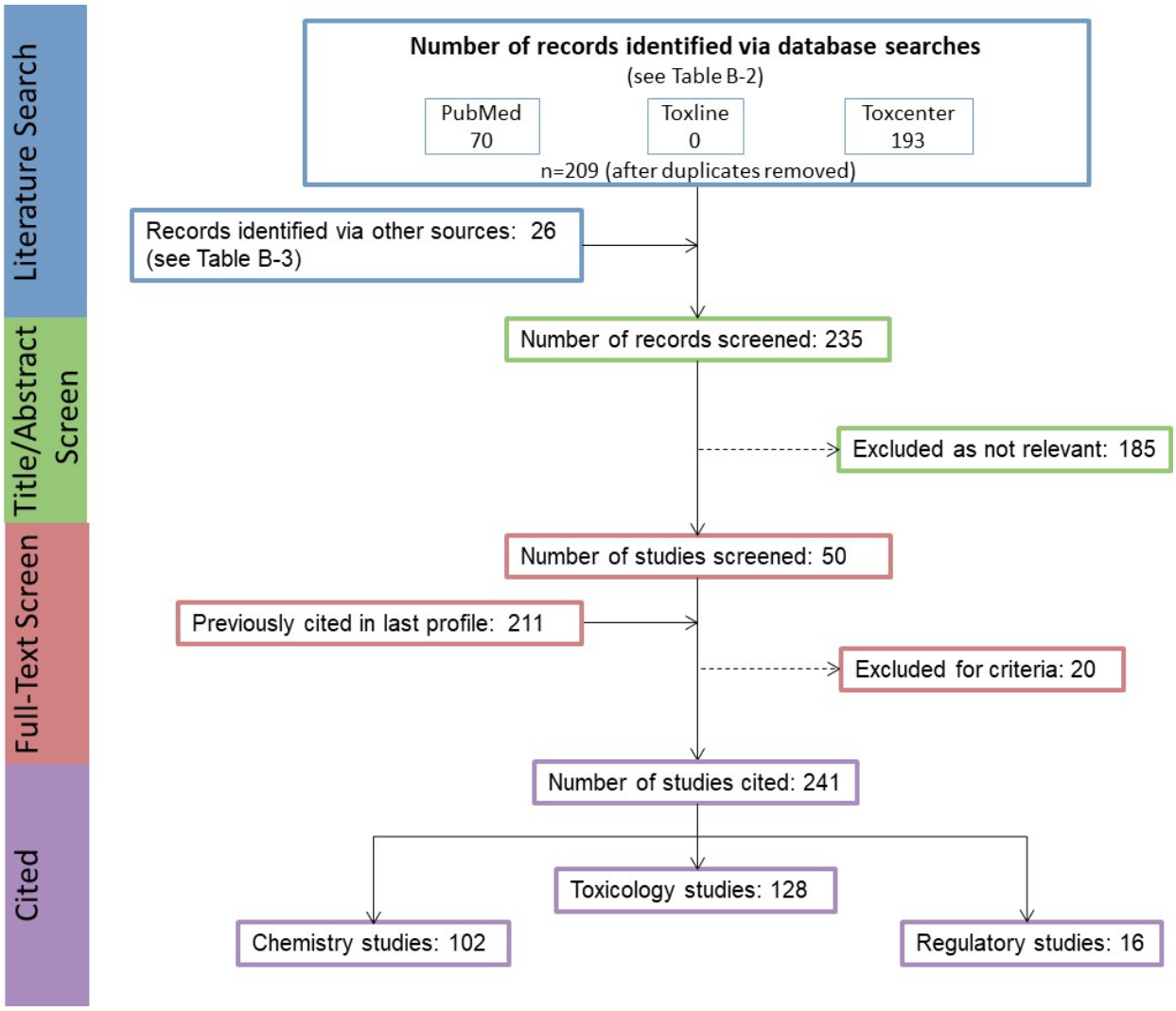
- Number of titles and abstracts screened: 235
- Number of studies considered relevant and moved to the next step: 50

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

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

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

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



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

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

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

C.1 PROBLEM FORMULATION

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

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

C.2.1 Literature Search

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

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

C.2.2 Literature Screening

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

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

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

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

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

APPENDIX C

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort														2 2	9 8		1 1
Case control															4 2		1 1
Population							1 0					1 1		1 0			1 0
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

APPENDIX C

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	2						2	2		2						2	
	2						2	2		2						0	
Intermediate-duration	3						2	2								3	
	0						0	2								0	
Chronic-duration																	
Oral studies																	
Acute-duration	16	1	1	1	3	1	9	8			1	3	3	4	7	5	
	12	0	0	0	2	0	7	6			0	2	2	3	7	1	
Intermediate-duration	11	7	7	9	6		9	11			7	2	8	6	3	2	
	5	0	0	1	0		6	2			0	1	1	2	1	1	
Chronic-duration	8	7	7	7	1		8	7			7		1	6		1	8
	4	0	0	0	0		4	3			1		0	1		1	3
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

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

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

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

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

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

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

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

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

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

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

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

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

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

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

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

*Key question used to assign risk of bias tier

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

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Hepatic Effects									
Inhalation acute exposure									
Torti et al. 2001 (C57BL/6 mouse)	++	+	++	+	+	+	**+**	+	First
Torti et al. 2001 (FVN mouse)	++	+	++	+	+	+	**+**	+	First
Inhalation intermediate exposure									
Torti et al. 2001 (C57BL/6 mouse)	++	+	++	+	+	+	**+**	+	First
Torti et al. 2001 (FVN mouse	++	+	++	+	+	+	**+**	+	First
Oral acute exposure									
Condie et al. 1983 (mouse)	-	+	+	+	+	-	**+**	+	First
Keegan et al. 1998 (rat)	-	+	+	+	+	+	**+**	+	First
Lilly et al. 1994 (rat, GW)	+	+	+	+	+	+	**+**	+	First
Lilly et al. 1994 (rat, GO)	+	+	+	+	+	+	**+**	+	First
Lilly et al. 1996 (rat)	+	+	+	+	+	+	**+**	+	First
Munson et al. 1982 (mouse)	-	+	+	+	+	+	**+**	+	First
Ruddick et al. 1983 (rat)	+	+	+	+	+	+	**+**	+	First
Thornton-Manning et al. 1994 (rat)	+	+	+	+	+	+	**+**	+	First
Thornton-Manning et al. 1994 (mouse)	+	+	+	+	+	+	**+**	+	First
Oral intermediate exposure									
Aida et al. 1989 (rat, F)	-	+	+	+	+	+	**+**	+	First
Aida et al. 1989 (rat, W)	-	+	+	+	+	+	**+**	+	First
Aida et al. 1992 (rat)	+	+	+	+	+	+	**+**	+	First
Chu et al. 1982 (rat)	-	+	+	+	+	-	**+**	+	First
Hooth et al. 2002 (rat)	+	+	+	+	+	+	**+**	+	First

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

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	**Confidence in outcome assessment?***	All measured outcomes reported?	
NTP 1987 (rat)	++	+	+	+	+	++	+	+	First
NTP 1987 (mouse)	++	+	+	+	+	++	+	+	First
NTP 2006 (rat)	++	+	+	+	+	++	+	++	First
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	First
Oral chronic exposure									
Aida et al. 1992 (rat)	+	+	+	+	+	+	+	+	First
George et al. 2002 (rat)	+	+	+	+	+	+	+	+	First
George et al. 2002 (mouse)	+	+	+	+	+	+	+	+	First
NTP 1987 (rat)	++	+	+	+	+	++	+	++	First
NTP 1987 (mouse)	++	+	+	+	+	++	+	++	First
NTP 2006 (rat)	++	+	+	+	+	++	+	++	First
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	First
Tumasonis et al. 1985 (rat)	-	+	+	+	+	+	+	+	First
Outcome: Renal Effects									
Inhalation acute exposure									
Torti et al. 2001 (C57BL/6 mouse)	++	+	++	+	+	+	+	+	First
Torti et al. 2001 (FVN mouse)	++	+	++	+	+	+	+	+	First
Inhalation intermediate exposure									
Torti et al. 2001 (C57BL/6 mouse)	++	+	++	+	+	+	+	+	First
Torti et al. 2001 (FVN mouse)	++	+	++	+	+	+	+	+	First
Oral acute exposure									
Condie et al. 1983 (mouse)	-	+	+	+	+	-	+	+	First
Lilly et al. 1994 (rat, GW)	+	+	+	+	+	+	+	+	First

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

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

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

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

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

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in exposure characterization?	Detection bias: **Confidence in outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Risk of bias tier
NTP 2006 (rat)	++	+	+	+	+	++	+	++	First
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	First
Oral chronic exposure									
Aida et al. 1992 (rat)	+	+	+	+	+	+	+	+	First
Klinefelter et al. 1995 (rat)	-	+	+	+	+	+	+	+	First
NTP 1987 (rat)	++	+	+	+	+	++	+	++	First
NTP 1987 (mouse)	++	+	+	+	+	++	+	++	First
NTP 2006 (rat)	++	+	+	+	+	++	+	++	First
NTP 2006 (mouse)	++	+	+	+	+	++	+	++	First
Outcome: Developmental Effects									
Oral Acute Exposure									
Bielmeier et al. 2001 (rat, GDs 6–10)	-	+	+	+	+	+	+	++	First
Bielmeier et al. 2001 (Sprague-Dawley rat, GDs 6–10)	-	+	+	+	+	+	+	++	First
Bielmeier et al. 2001 (rat, GDs 8–9)	-	+	+	+	+	+	+	++	First
Bielmeier et al. 2001 (rat, GDs 6–10 or 6–15)	-	+	+	+	+	+	+	++	First
Bielmeier et al. 2004 (rat)	-	+	+	+	+	+	+	++	First
Narotsky et al. 1997 (rat)	++	+	+	+	+	+	+	++	First
Ruddick et al. 1983 (rat)	+	+	+	+	+	+	+	+	First

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

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

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable
*Key question used to assign risk of bias tier

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

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

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

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

C.6.1 Initial Confidence Rating

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

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C.6.2 Adjustment of the Confidence Rating

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

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

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

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

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

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

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

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

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

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

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

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

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

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

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

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

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

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

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

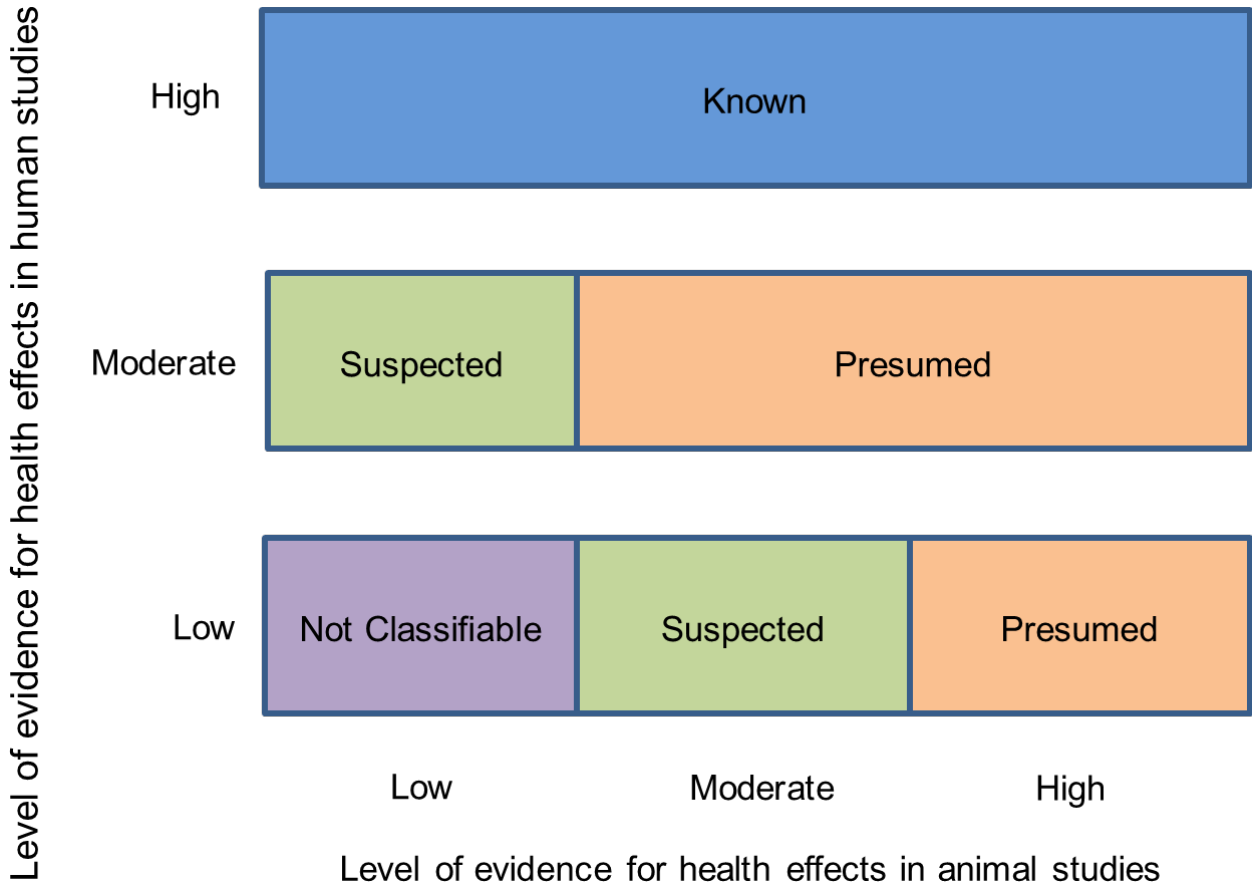
Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

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

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

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

Figure C-1. Hazard Identification Scheme



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

Presumed Health Effects

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

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

Suspected Health Effects

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

Not Classifiable Effects

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

Table C-19. Hazard Identification Conclusions for Bromodichloromethane

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

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

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

Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	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%)
					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; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

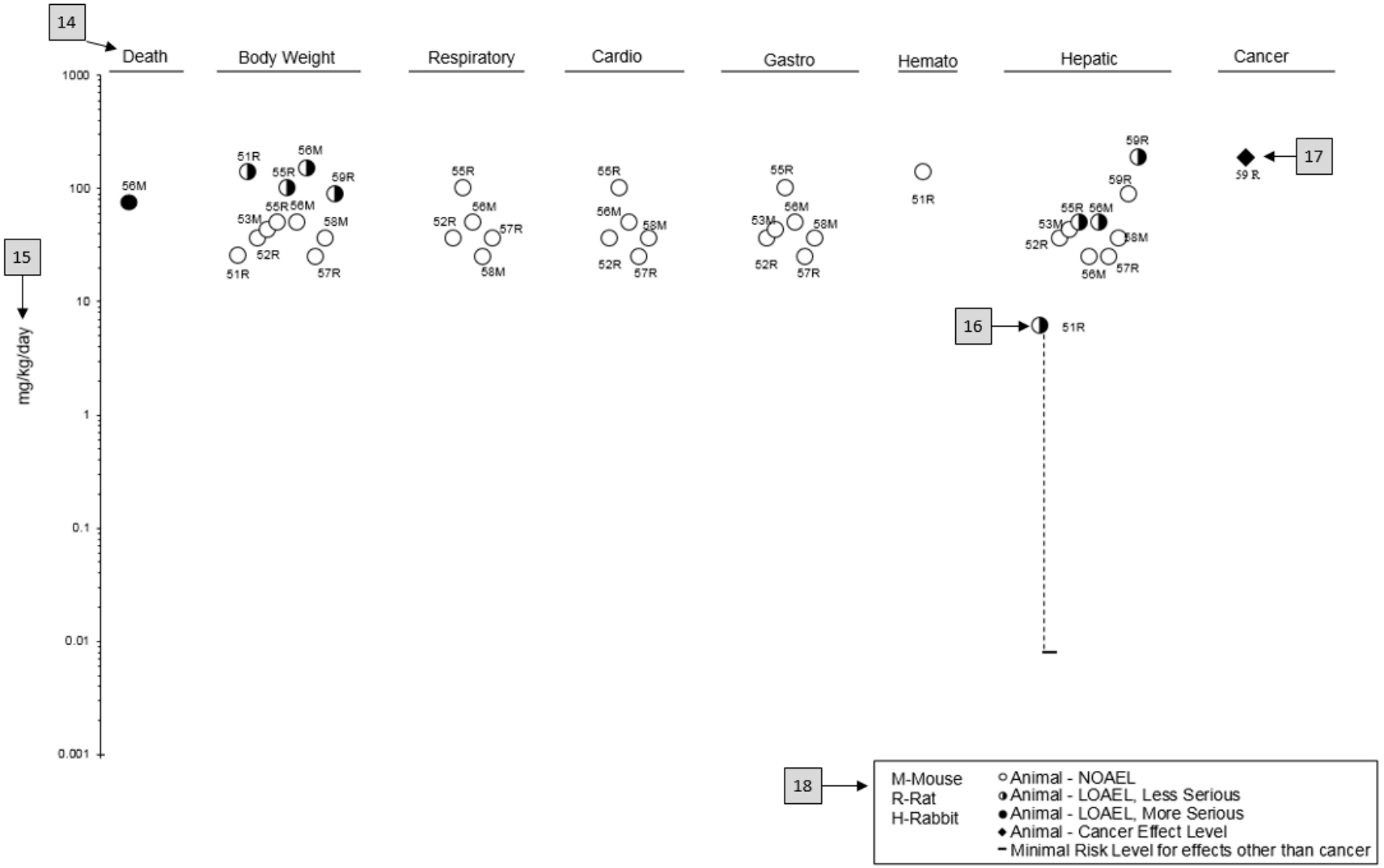
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[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).

APPENDIX D

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

13 → Chronic (≥365 days)



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

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

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

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

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

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

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

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

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

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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

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

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

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

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

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

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

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

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

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

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

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

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

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

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

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

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

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

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

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

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

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

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

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

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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

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

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

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

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

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

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result