Toxicological Profile for Bromomethane

March 2020

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

CS274127-A

DISCLAIMER

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FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

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

VERSION HISTORY

Date	Description
March 2020	Final toxicological profile released
April 2018	Draft for public comment toxicological profile released
September 1992	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Bromomethane is a gas at room temperatures, but can be liquified under sufficient pressure, and is a liquid below 38°F (Piccirillo and Piccirillo 2010). Bromomethane is primarily used in the form of a gas, compressed liquid, or in solution as a fumigant for the control of insects, fungi, and rodents. Under the U.S. Environmental Protection Agency (EPA) Clean Air Act, production and most uses of bromomethane in the United States were phased out in 2005; however, bromomethane is still allowed to be used under two critical use exemptions—to eliminate quarantine pests and for agricultural use where there are no technically or financially feasible alternatives.

Bromomethane naturally occurs in oceans, from which it is released into the atmosphere. Bromomethane in the atmosphere breaks down slowly, with a half-life of 11 months. Bromomethane in water and soil is likely to volatilize at a faster rate than it would break down. Bromomethane levels in ambient air are relatively low. The maximum annual mean 24-hour bromomethane concentration at 104 sites across the United States was 0.15 ppbv in 2018 (EPA 2019a).

The most likely route of human exposure is by inhalation because bromomethane exists as a gas at room temperature. Bromomethane has very little odor at concentrations that may produce toxicity; therefore, exposure to hazardous levels may occur without awareness of exposure. However, tracer amounts of acrolein have been added to help facilitate odor recognition. Exposure to inhaled bromomethane is more likely to occur in workers than in the general population. The general population is not likely to be exposed to bromomethane via the oral route; however, exposure to a small amount of bromomethane could occur via contaminated water or food.

1.2 SUMMARY OF HEALTH EFFECTS

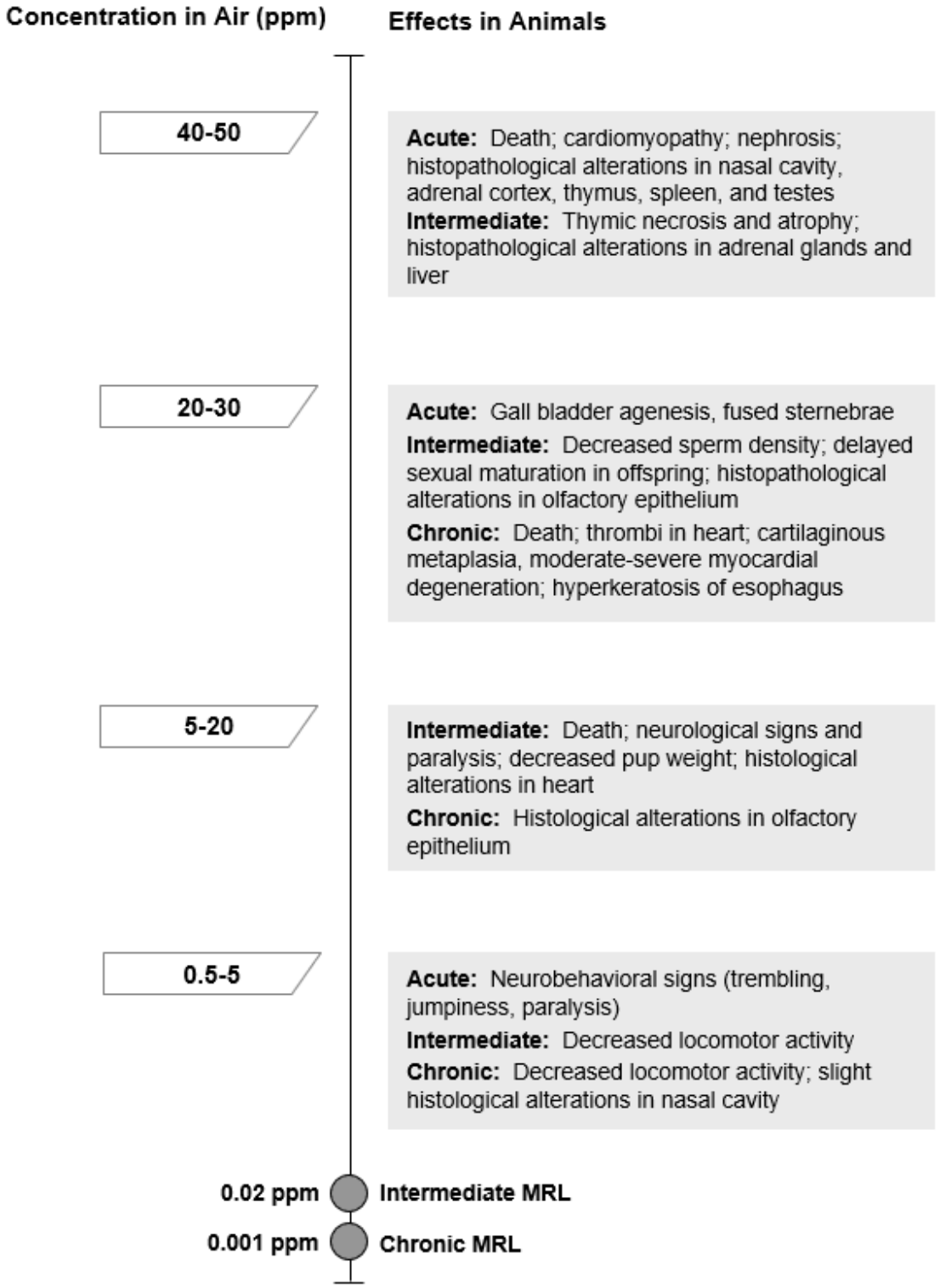
As noted in Section 1.1, because bromomethane exists as a gas at room temperature, inhalation is the most likely exposure route. However, it is possible that humans could be exposed to very small amounts in food or water. Given the predominance of the inhalation exposure route, most animal toxicity studies have examined effects of inhaled bromomethane, with few studies evaluating effects of oral exposure. In addition to animal studies, some information is available from studies of exposed workers to bromomethane vapor, although reliable quantitative estimates of exposure have not been reported in these

studies. The available data in humans and animals provide strong evidence that the respiratory tract and the nervous system are the most sensitive targets of bromomethane toxicity following inhalation exposure (Figure 1-1). There is some evidence of developmental effects following inhalation exposure of rats, although this has not been substantiated in other studies. Other effects observed in inhalation studies include cardiovascular, reproductive, hepatic, and renal effects; however, these effects occur at higher exposures. Based on the small number of oral studies in animals, the primary target of gavage exposure to bromomethane is damage to the stomach (Figure 1-2). However, chronic-duration oral studies did not identify target organ systems for bromomethane. Dermal and ocular exposure to bromomethane vapor or liquid produces damage at the site of contact.

Respiratory Effects. In humans, the lungs appear to be the primary target of toxicity in the respiratory tract; cough, edema, hemorrhagic lesions, and dyspnea have been reported following acute exposure (Akca et al. 2009; Greenberg 1971; O'Neal 1987; Prain and Smith 1952). In laboratory animals, most of the observed damage to the respiratory tract is confined to the nasal cavity, although some studies have reported thrombi or hemorrhagic lesions, congestion, or pneumonia in the lungs (Eustis et al. 1988; Irish et al. 1940; Kato et al. 1986). Within the nasal cavity, the bromomethane-induced damage is limited to the olfactory epithelium; the observed effects include degeneration, hyperplasia, metaplasia, and loss of sensory cells (Eustis et al. 1988; Gotoh et al. 1994; Hastings et al. 1991; Hurtt et al. 1987, 1988; NTP 1992; Reuzel et al. 1987, 1991; Youngentob and Schwob 2006). Comparison of LOAEL values from intermediate- and chronic-duration studies suggests that the nasal effects are exposure duration-related (NTP 1992).

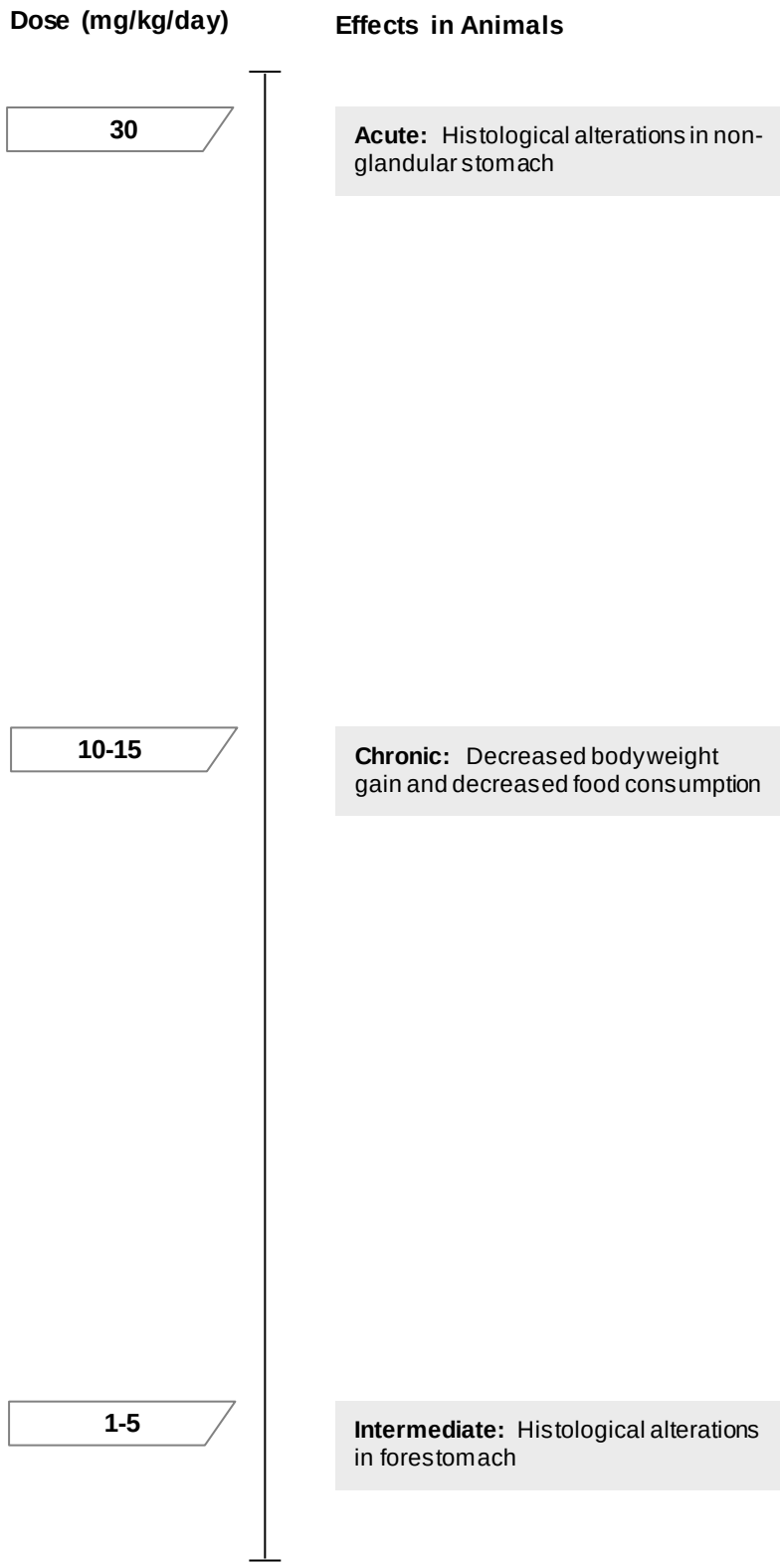
Neurological Effects. Neurological effects have been observed in fumigators, other workers exposed post-fumigation, and non-workers accidentally exposed to bromomethane. The initial neurological effects observed in humans exposed to high levels of bromomethane occur within a few hours of exposure and include headache, weakness, and nausea and vomiting (Akca et al. 2009; Deschamps and Turpin 1996; Marraccini et al. 1983; Wyers 1945). Depending on the exposure level, these symptoms may progress into ataxia, tremors, paralysis, and clonic seizures (Balagopal et al. 2011; Deschamps and Turpin 1996; Hine 1969; Hustinx et al. 1993; Prain and Smith 1952; Prockop and Smith 1986). The neurological effects typically begin to wane after several days, but recovery may not be complete even after many months (Bishop 1992; Deschamps and Turpin 1996; Longley and Jones 1965; O'Neal 1987; Rathus and Landy 1961). Only limited information is available on the effects of long-term inhalation exposure of humans to low levels of bromomethane. Headache, weakness, and increased prevalence of neurological signs such as muscle ache, fatigue, and dizziness have been noted in workers exposed repeatedly or for

Figure 1-1. Health Effects in Animals Following Inhalation Exposure to Bromomethane[a]



[a]Concentrations were duration adjusted

Figure 1-2. Health Effects in Animals Following Oral Exposure to Bromomethane



extended periods in the workplace (Anger et al. 1986; Hine 1969; Kantarjian and Shaheen 1963; Kishi et al. 1988). A variety of concentration-related neurological effects ranging from alterations in neurotransmitter levels to cerebral and cerebellar degeneration have been observed in laboratory animals. Mild and transient neurobehavioral signs (decreased locomotor activity in mice) are the most sensitive effects of inhaled bromomethane; it is noted that impaired performance on neurobehavioral tests have not been consistently found at all testing durations. As exposure levels increase, overt signs of neurotoxicity such as abnormal gait, tremors, ataxia, hind-limb paralysis, and convulsions have been reported in rats, mice, rabbits, and monkeys (Breslin et al. 1990; Eustis et al. 1988; Irish et al. 1940; NTP 1992). At higher concentrations, histological damage, particularly necrosis and degeneration, was observed in the cerebrum and cerebellum of rats and mice exposed to bromomethane for ≥2 weeks (Eustis et al. 1988; Kato et al. 1986; NTP 1992); increases in mortality were also observed at these concentrations.

Developmental Effects. There is some evidence that inhaled bromomethane is a developmental toxicant. Increased incidences of gallbladder agenesis and fused sternebrae (a minor variation) and decreases in fetal weight have been observed in the offspring of rabbits exposed to a maternally toxic concentration (80 ppm) (Breslin et al. 1990). However, other inhalation studies in rats and rabbits respectively using similar or lower exposure levels (Hardin et al. 1981; NIOSH 1980) and an oral exposure study in rats and rabbits (Kaneda et al. 1998) have not reported developmental effects.

Gastrointestinal Effects. For oral exposure, damage to the epithelium of the forestomach has been observed in rats administered bromomethane in oil via gavage. However, no adverse gastrointestinal effects were associated with oral exposure of dogs exposed to dietary bromomethane in microencapsulated form at higher doses for up to 2 years. There is some question as to whether the forestomach effects in rats are due to the bolus administration of a very reactive chemical and whether gavage administration is an appropriate model for human exposure to bromomethane. Thus, there is uncertainty regarding the relevance of this effect to humans.

Other Targets. Other targets of bromomethane toxicity that have been observed in laboratory animal inhalation studies include the heart (myocardial fibrosis and degeneration and cardiomyopathy) (Eustis et al. 1988; Kato et al. 1986; NTP 1992), liver (necrosis) (Hurrt et al. 1987), kidneys (nephrosis) (Eustis et al. 1988), and the male reproductive system (decreased sperm density and testicular degeneration) (EPA 1988a; Eustis et al. 1988; Kato et al. 1986); these effects are typically observed at higher concentrations that are near-lethal or lethal.

Dermal Effects. Erythema, edema, and blisters have been observed in humans dermally exposed to liquefied bromomethane or bromomethane vapor. A study in animals found histological damage to the epidermis and dermis following a very brief (≤5 minutes) direct dermal contact to liquefied bromomethane. In addition, the temperature of liquidized bromomethane can be below -93°C; therefore, exposed tissue can freeze and develop erythema, edema, and blisters (Vivas et al. 2015). This could be a possible contributor to dermal effects of bromomethane.

Ocular Effects. In humans exposed to bromomethane vapor, conjunctivitis, erythema, and edema of the eyelids have been reported (Langard et al. 1996; O'Neal 1987; Prain and Smith 1952; Wyers 1945).

Cancer Effects. There are limited data on the carcinogenic potential of bromomethane in humans. Several studies of agricultural workers (Alavanja et al. 2003; Barry et al. 2012) and a study of workers exposed to a variety of brominated chemicals (Wong et al. 1984) have found increases in specific types of cancer; however, the workers were exposed to numerous chemicals and none of the studies established that bromomethane was the causative agent. No evidence of carcinogenic effects was observed in rats or mice exposed via inhalation to bromomethane for at least 2 years (NTP 1992; Reuzel et al. 1987, 1991) or in rats administered bromomethane via gavage (Danse et al. 1984; IRIS 2002).

The U.S. Department of Health and Human Services (NTP 2016) has not categorized the carcinogenicity of bromomethane. The International Agency for Research on Cancer (IARC 2016) classified bromomethane as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). EPA (IRIS 2002) has determined that bromomethane is classified as a Group D carcinogen (not classifiable as to human carcinogenicity).

1.3 MINIMAL RISK LEVELS (MRLs)

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

MRLs for bromomethane are summarized Table 1-1. As noted in Section 1.1, the most likely route of human exposure is by inhalation because bromomethane exists as a gas at room temperature. Numerous studies have been conducted in laboratory animals for acute, intermediate, and chronic exposure

durations, with sufficient data to derive intermediate- and chronic-duration inhalation MRLs. Neurotoxicity and lesions of the upper respiratory tract are the most sensitive effects of inhalation exposure to bromomethane (Figure 1-3). The general population is not likely to be exposed to bromomethane via the oral route; thus, very few animal studies on the oral toxicity of bromomethane have been conducted. One acute- and one intermediate-duration gavage studies show that the most sensitive effect of oral exposure to bromomethane is stomach lesions; however, these studies administered bromomethane by gavage. As discussed in Section 1.2, there is uncertainty as to whether the observed forestomach lesions in animals are unique to gavage administration of bromomethane, and how these effects are related to humans who have no forestomach. Chronic-duration oral studies did not identify target organs for bromomethane; the only effect observed in chronic-duration oral studies is decreased body weight.

Table 1-1. Minimal Risk Levels (MRLs) for Bromomethane[a]

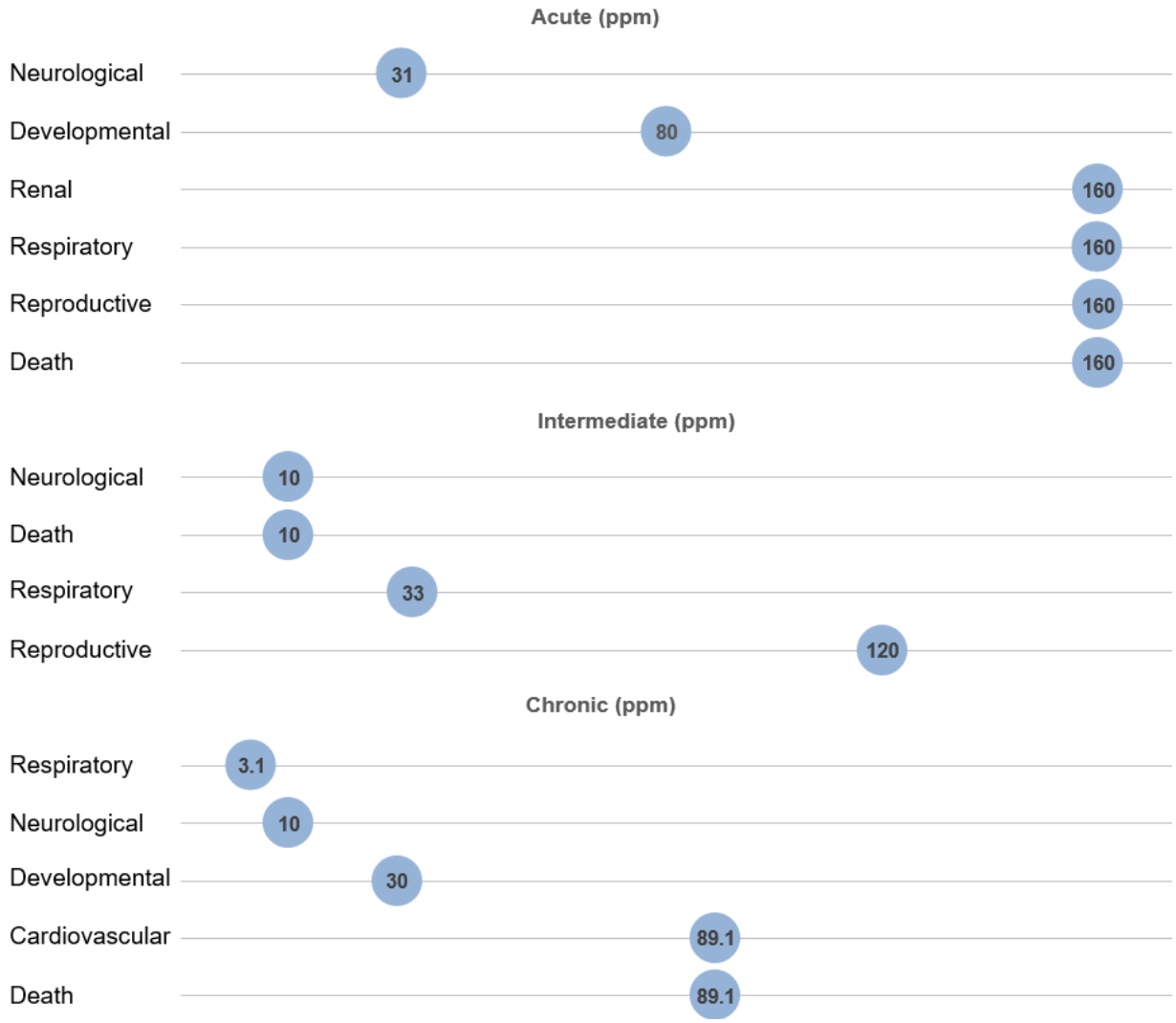
Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.02	Neurobehavioral effects	1.8 ppm ($LOAEL_{HEC}$)	90	NTP 1992
Chronic	0.001	Nasal lesions	0.11 ($LOAEL_{HEC}$)	90	Reuzel et al. 1991
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

$LOAEL_{HEC}$ = lowest-observed-adverse-effect level, human equivalent concentration

Figure 1-3. Summary of Sensitive Targets of Bromomethane – Inhalation

The respiratory tract and neurological system are the most sensitive target of bromomethane inhalation exposure.



CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of bromomethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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

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

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; available dermal data for bromomethane examined skin effects only.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be

insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Bromomethane exists as a gas at room temperature; therefore, inhalation is the predominant route of exposure. Oral exposure is unlikely, but it could occur due to small amounts of bromomethane in food or water. Given the importance of the inhalation route, most toxicity studies have examined effects of inhaled bromomethane, with animal studies conducted for acute, intermediate, and chronic exposure durations, as illustrated in Figure 2-1. In addition, some information is available from studies or case reports of exposed workers to bromomethane vapor, although reliable quantitative estimates of exposure have not been reported in these studies. Epidemiological studies conducted in bromomethane workers have been conducted, but worker populations were exposed to numerous chemicals. A few animal studies have examined the toxicity of oral exposure, and no information on humans exposed to oral bromomethane was identified.

Available studies in humans and animals provide evidence that adverse effects to the neurological system and respiratory tract are the most sensitive effects of inhalation exposure. Other adverse effects of inhalation exposure include developmental, reproductive, renal, hepatic, and cardiovascular effects; however, these effects occur at exposure levels that are near or above levels causing lethality. Available acute- and intermediate-duration oral studies show that the gastrointestinal system is the primary target of gavage exposure in rats; however, gastrointestinal effects were not observed in a study of dogs administered bromomethane in a microencapsulated form in the diet. There is some question as to whether the forestomach effects in rats are due to the bolus administration of a very reactive chemical and whether gavage administration is an appropriate model for human exposure to bromomethane. Available chronic-duration oral studies did not identify targets for bromomethane. Dermal and ocular exposure to

bromomethane vapor or liquid bromomethane can cause erythema and blisters to skin, and damage to eyes.

- **Respiratory Endpoints:** Studies in humans and animals provide evidence that inhalation of bromomethane produces damage to the respiratory tract. Acute exposure of humans has been reported to cause cough, edema, hemorrhagic lesions, and dyspnea. In animals, the most sensitive effect of inhaled bromomethane is damage to the olfactory epithelium.

- **Neurological Endpoints:** Neurological effects have been observed in humans and animals exposed to inhaled bromomethane. In humans, effects include headache, weakness, ataxia, tremors, paralysis, and seizures. Neurological effects in animals exhibit dose and duration dependence, with effects ranging from alterations in neurotransmitter levels to cerebral and cerebellar degeneration. The most sensitive effects of inhaled bromomethane in animals is decreased locomotor activity.

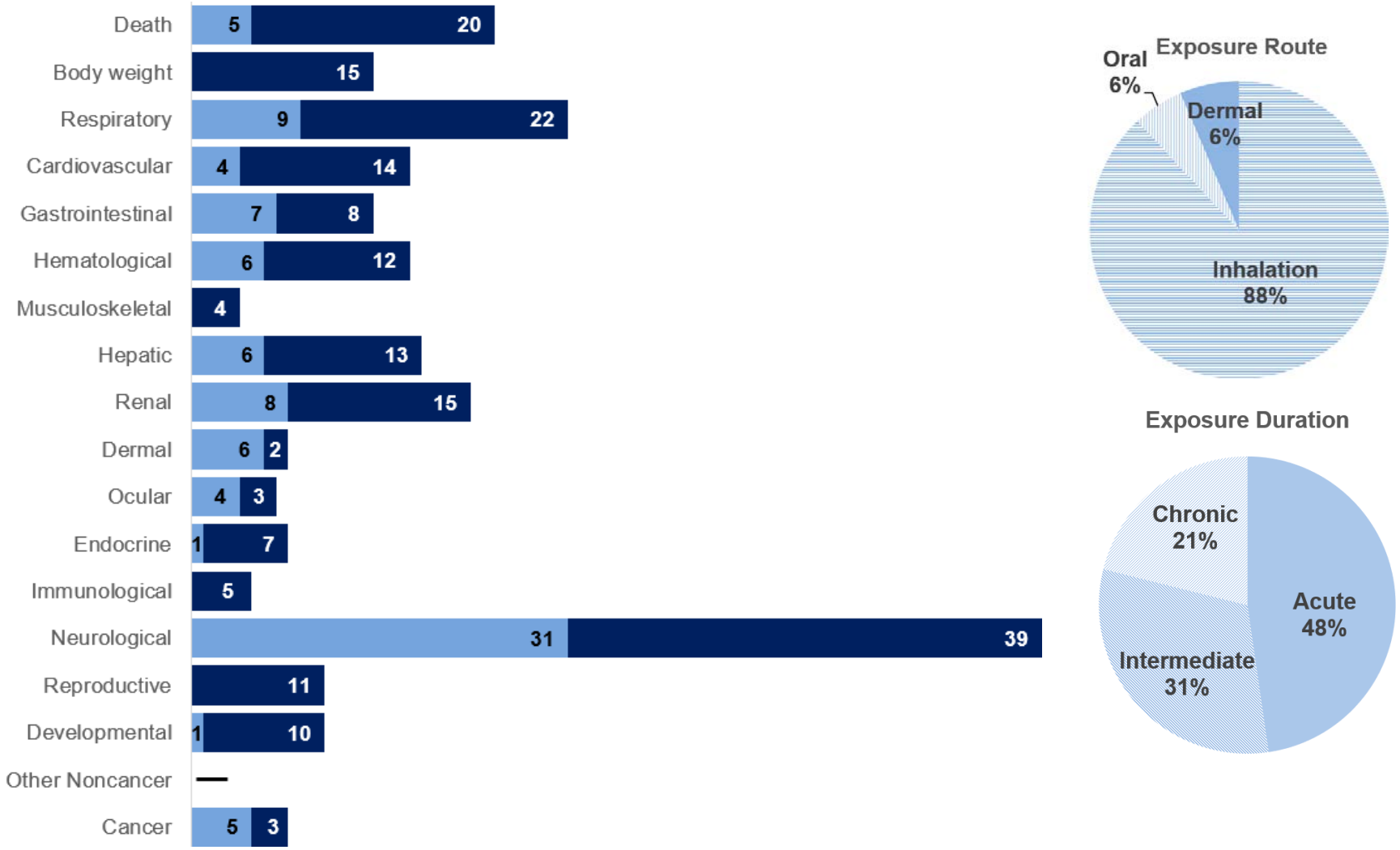
- **Developmental Endpoints:** In animal studies, increased incidences of gallbladder agenesis and fused sternebrae, and decreased fetal weight have been observed in the offspring of rabbits exposed to inhaled bromomethane. However, these effects have not been observed in inhalation studies in other species or in oral exposure studies in animals.

- **Gastrointestinal Endpoints:** Gavage administration of bromomethane to rats produces damage to the gastric epithelium in rats.

- **Other Endpoints:** Inhalation studies in laboratory animals have reported effects to the heart (myocardial fibrosis and degeneration and cardiomyopathy), liver (necrosis), kidneys (nephrosis), and male reproductive system (decreased sperm density and testicular degeneration). However, these effects do not appear to be sensitive targets of bromomethane.

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

Most studies examined the potential respiratory and neurological effects of bromomethane
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 109 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (CD) 15 M, 15 F	6 hours	0, 30, 100, 350	CS, BW, NX, GN, HP	Neuro	100	350		Decreases in motor activity and alterations in FOB performance
EPA 1993									
2	Rat (Fischer-344) 5 M, 5 F	2 weeks 5 days/week 6 hours/day	0, 160	BC, HE, HP	Resp		160		Minimal-mild olfactory epithelium degeneration; loss of olfactory sensory cells
Eustis et al. 1988									
3	Rat (Long-Evans) 15–30 M	2 weeks 4 days/week 4 hours/day	0, 200	CS, HP, OF	Resp		200 M		Marked damage to olfactory epithelium
					Neuro		200 M		Impaired olfactory function
Hastings et al. 1991									
4	Rat (NS) 5 M	8 hours (1 exposure)	0, 16, 31, 63, 125, 250	BI	Neuro	16 M	31 M		Decreased brain neurotransmitters
Honma 1987									
5	Rat (NS) 5 M	8 hours (1 exposure)	0, 63, 125, 188, 250	CS, LE	Death			302 M	LC_{50}
					Neuro			63 M	Impaired reflexes
Honma et al. 1985									
6	Rat (NS) 10 M	5 days 6 hours/day	0, 200	HP, OW	Repro	200 M			
Hurtt and Working 1988									
7	Rat (Fischer-344) 10 M	5 days 6 hours/day	0, 90, 175, 250, 325	HP, LE, CS	Death			325 M	3/5 died
					Resp	90 M	175 M	325 M	Nasal olfactory epithelial degeneration; severe and extensive damage to nasal olfactory epithelium
					Hepatic	250 M	325 M		Focal hepatocellular coagulative necrosis
					Renal	325 M			
					Endocr	90 M	175 M		Microvacuolization of spongiocytes in adrenal cortex

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro	175 M		250 M	Ataxia, cerebellar degeneration
					Repro	250 M	325 M		Delayed spermiation
Hurtt et al. 1987									
8	Rat (NS) 5 M	1–5 days 6 hours/day	0, 90, 200	HP, OF	Resp	90		200	Loss of olfactory epithelium
Hurtt et al. 1988									
9	Rat 40 NS	22 hours (1 exposure)	100–13,000	NS	Death			260	
Irish et al. 1940									
10	Rat (NS) 5–10 M	4 hours	500–900	NS	Death			767 M	25% lethality
Kato et al. 1986									
11	Rat (Long-Evans) M	6 hours	0, 330	HP	Neuro		330 M		Degeneration of neurons in olfactory bulb
Schwob et al. 1999									
12	Rat (Long-Evans) M	6 hours	0, 330	HP, OF	Resp		330 M		Severe damage to nasal olfactory epithelium
					Neuro		330 M		Impaired performance on test of olfactory function
Youngentob and Schwob 2006									
13	Mouse (NS) 6 M	1 hour (1 exposure)	0, 220–1,530	OW, HP, CS	Death			980 M	1/6 died at 980 ppm; LC_{50}=1,160 ppm
					Neuro	560 M	700 M		Hyperactivity
Alexeeff et al. 1985									
14	Mouse (NS) 20 M, 20 F	2 weeks 5 days/week 6 hours/day	0, 160	HP, BC, HE, BW, LE	Death			160	>50% lethality after eight and six exposures in males and females, respectively
					Bd wt		160		26 and 18% decrease in terminal body weights in males and females, respectively
					Resp			160	Congestion, hemorrhage, and thrombi in lungs, nasal olfactory epithelial degeneration and atrophy
					Cardio			160	Cardiomyopathy

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hemato		160		Decreased RBCs, hemoglobin, hematocrit, and increased WBCs; splenic hematopoiesis and red pulp cellular depletion
					Renal			160	Nephrosis
					Endocr		160 F		Adrenal gland x-zone atrophy
					Immuno		160		Thymus atrophy and splenic lymphoid depletion
					Neuro			160	Overt signs of neurotoxicity; neuronal necrosis in the cerebral cortex and cerebellum
					Repro		160 M		Minimal testicular degeneration
Eustis et al. 1988									
15	Mouse (B6C3F1) 10 M, 10 F	2 weeks 5 days/week 6 hours/day	0, 12, 25, 50, 100, 200	CS, BW, HP, LE	Death			200	Deaths in 90% males and 60% females
NTP 1992									
16	Dog (Beagle) 2–3 M, 2–3 F	2–4 days, 7 hours/day	55, 156, 268, 283	CS, BW, HE, OW, GN, HP	Bd wt			283	Weight loss
					Resp	55	156	268	Labored breathing at 156 ppm; pulmonary edema/rales at 268 ppm
					Neuro	55	156	268	Decreased activity, irregular gait post exposure at 156 ppm; extreme or severe delirium at 268 ppm
EPA 2001a									
17	Rabbit (NS) 26 F	13 days GDs 7–19 6 hours/day	0, 20, 40, 80	CS, TG, DX	Neuro	40 F	80 F		Ataxia, lethargy
					Develop	40 F		80 F	Gallbladder agenesis, fused sternebrae
Breslin et al. 1990									
INTERMEDIATE EXPOSURE									
18	Monkey (NS) 4–6 NS	6 months 5 days/week 8 hours/day	33, 66	CS	Neuro	33		66	Paralysis
Irish et al. 1940									

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
19	Rat (Sprague-Dawley) NS	4 weeks 4 days/week 7.5 hours/day	0, 65	NX	Neuro	65			
Anger et al. 1981									
20	Rat (Sprague-Dawley) NS	36 weeks 5 days/week 6 hours/day	0, 55	NX	Neuro	55			
Anger et al. 1981									
21	Rat (NS) 25 M, 25 F	2 generations 5 days/week 6 hours/day	0, 3, 30, 90	OW	Repro	3			
					Develop	3 F 30 M	30 F 90 M		Reduced pup weights
Mayhew et al. 1986, as cited in EPA 1986a									
22	Rat (CD) 15 M, 15 F	6 hours/day, 5 days/week, 13 weeks	0, 30, 70, 140	BW, CS, FI, GN, HP, LE, NX, OW	Death			140 M	2/15 deaths in males exposed to 140 ppm
					Bd wt	30 F 70 M	70 F 140 M		23% decrease in terminal body weight gain along with 9% decrease in food consumption in females, and 37% decrease in terminal body weight gain and 13% decrease in body weight in males
					Resp	70	140		Minimal dysplasia of the olfactory epithelium
					Neuro	30 F 70 M	70 F 140 M		Decreased locomotor activity in females at 70 ppm and 10% decrease in absolute brain weight at 140 ppm; increased landing foot splay, ataxia, and histopathological changes in brain tissue (vacuolization, axonal degeneration, and necrosis in brain tissue) in males that developed convulsions or died
EPA 1994a									

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
23	Rat (Sprague-Dawley) 10 F	6 hours/day 28 days	0, 20, 60, 120	CS, BW, OW, GN, IX	Bd wt	60 F	120 F		12% decrease in terminal body weight
					Immuno	120 F			
EPA 2011									
24	Rat (CD) 24 F	6 hours/day, GDs 6–20 and LDs 5–20	0, 5, 25, 50	CS, BW, GN, HP, LE, NX, OW	Bd wt	5	25		Decreased body weight gain (11–18%) for females on PNDs 7–17; 17% for males on PNDs 13–17
					Neuro	50			No neurological effects in dams (FOB tests)
					Develop	5	25		Decreased motor activity in pups on PND 21; effects were not statistically significant possibly due to high variability in the data
EPA 2019b									
25	Rat (Fischer-344) 5 M, 5 F	3–6 weeks 5 days/week 6 hours/day	0, 160	BW, HE, LE, HP	Death			160	>50% lethality in males after 14 exposures
					Bd wt		160		Decreased terminal body weight, 32% in males and 18% in females
					Resp		160		Olfactory epithelial degeneration and atrophy
					Cardio			160 F	Myocardial degeneration
					Hemato		160 F		Splenic hemosiderosis
					Hepatic		160		Minimal necrosis
					Renal	160			
					Endocr		160		Cytoplasmic vacuolization in adrenal glands
					Immuno		160		Thymus necrosis and atrophy
					Neuro			160	Overt signs of neurotoxicity; neuronal necrosis in cerebral cortex, thalamus, hippocampus
					Repro			160 M	Testicular degeneration
Eustis et al. 1988									
26	Rat (NS) 30 F	19 days GDs 1–19 6 hours/day	20, 70	FX, MX, DX, TG	Repro	70 F			
					Develop	70 F			
Hardin et al. 1981									

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
27	Rat 5 M	3 weeks (continuous)	1, 5, 10	BI	Neuro	5 M	10 M		Decreased neurotransmitters
Honma et al. 1982									
28	Rat (NS) 12 M	3 weeks 5 days/week 4 hours/day	0, 200, 300	CS, HP, BW, NX	Death			300 M	
					Neuro		200 M		Altered behavior
Ikeda et al. 1980									
29	Rat (NS) 20–30 NS	6 months 5 days/week 8 hours/day	33, 66, 100, 200	HP, CS	Death			100	25/30 sacrificed due to morbidity
					Resp	66	100		Mild congestion
Irish et al. 1940									
30	Rat (NS) 10–12 M	6 weeks 5 days/week 4 hours/day	150, 200, 300, 400	HP, BC, BW, CS	Bd wt	150 M	200 M		Decreased body weight (approximately 10% less than control)
					Resp		300 M		Small hemorrhagic lesions in the lung
					Cardio		150 M		Focal fibrosis
					Hemato	400 M			
					Hepatic		300 M		Fatty degeneration
					Renal	400 M			
					Neuro	200 M		300 M	Paralysis
					Develop	300 M		400 M	Testicular atrophy
Kato et al. 1986									
31	Rat (albino) 40 F	6 weeks 5 day/week 7 hours/day	20, 70	DX, TG, OF, MX	Develop	70 F			
NIOSH 1980									
32	Rat (F344) 8 M, 8 F	3 weeks 5 days/week 6 hours/day	0, 30, 60, 120	CS, NX	Neuro	30	60		Decreased startle amplitude
NTP 1992									
33	Rat (F344) 8 M, 8 F	9 weeks 5 days/week 6 hours/day	0, 30, 60, 120	CS, NX	Neuro	120			
NTP 1992									

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
34	Rat (F344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 30, 60, 120	CS, BW, HP, HE, NX	Bd wt	60	120		12–13% decrease body weight gain
					Resp	60	120		Olfactory epithelial dysplasia and cysts
					Cardio	120			
					Hemato	30 F	60 F		Decreased erythrocyte levels
					Hepatic	120			
					Renal	120			
					Neuro	60	120		Altered performance in neurobehavioral tests
NTP 1992									
35	Rat (Sprague-Dawley) 5 M	3 weeks (continuous)	0, 1, 5, 10	HP, BI	Death			10 M	
Sato et al. 1985									
36	Mouse 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 10, 20, 40, 80, 120	NS	Death			120	
					Hemato	120			
					Neuro	40	80	120	Mild limb crossing at twitching at 80 ppm; severe limb crossing and twitching at 120 ppm
					Repro	80	120 M		Decreased sperm density
EPA 1988a									
37	Mouse (B6C3F1) 50 M, 50 F	20 weeks 5 days/week 6 hours/day	100	BW, BC, CS	Death			100	48% of males died
					Bd wt			100	Severe body weight loss
					Hemato	100			
					Neuro			100	Tremors, paralysis
NTP 1987									
38	Mouse (B6C3F1) 8 M, 8 F	13 weeks 5 days/week 6 hours/day	0, 20, 40, 80	CS, NX	Neuro	40	80		Increased activity latency and hotplate latency
NTP 1992									
39	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 10, 20, 40, 80, 120	CS, BW, HE, HP	Bd wt	80 M	120 M		12% decreased body weight gain
					Resp	120			
					Cardio	120			

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hemato	20 M	40 M		Increased RBCs, decreased mean cell volume and mean cell hemoglobin
					Hepatic	120			
					Renal	120			
					Neuro	80		120	Severe curling and crossing of hindlimbs and twitching of forelimbs
NTP 1992									
40	Mouse (B6C3F1) 10 M, 10 F	3 months 5 days/week 6 hours/day	0, 10, 30, 33, 100	CS, BW, HE, HP, NX	Neuro	33 M	100 M		Decreased locomotor activity; increased activity and hot plate latency
NTP 1992									
41	Mouse (B6C3F1) 6–13 M, 6–16 F	6 months 5 days/week 6 hours/day	0, 10, 33, 100	CS, BW, HE, HP, NX	Neuro		10[b]		Decreased locomotor activity
NTP 1992									
42	Guinea pig (NS) 11–16 NS	6 months 5 days/week 8 hours/day	17, 33, 66, 100, 220	NS	Death			100	
					Resp	100	220		Pulmonary congestion, edema, leukocyte infiltration, hemorrhage
					Hepatic	220			
					Renal	220			
Irish et al. 1940									
43	Dog (Beagle) 4 M, 4 F	7 hours/day 5 days/week 5 or 7 weeks	0, 5.3, 11.0/158, 26.0, 53.1, 102.7[c]	CS, BW, FI, HE, BC, UR, OW, HP	Bd wt	102.7 M 11/158[c] F		11/158[c] M	Weight loss (24% less than controls)
					Resp	102.7			
					Cardio	102.7			
					Gastro	102.7			
					Hemato	102.7			
					Musc/skel	102.7			
					Renal	102.7			

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Hepatic	5.3 M 11/158[c] F	11/158[c] M		Increased urinary bilirubin
					Dermal	102.7			
					Ocular	102.7			
					Endocr	102.7			
					Neuro	26	53.1	158	Ataxia, intention tremor, nystagmus, convulsions, minimal vacuoles in cerebellum
					Repro	102.7			
EPA 2001b									
44	Dog (Beagle) 4 M, 4 F	7 hours/day, 5 days/week, 6 weeks	0, 5.3, 10, 20	BW, CS, FI, GN, HP, LE, NX, OW	Bd wt	20			
					Resp	20			
					Cardio	20			
					Gastro	20			
					Musc/skel	20			
					Hepatic	20			
					Renal	20			
					Endocr	20			
					Immuno	20			
					Neuro	10 F 5.3 M	20 F 10 M		Absence of proprioceptive placing
					Repro	20			
EPA 2002									
45	Rabbit (NS) 15 F	15 days GDs 1–15 6 hours/day	20, 70	DX, TG	Death			70 F	
					Develop	20 F			No information reported on developmental effects at 70 ppm
Hardin et al. 1981									
46	Rabbit (NS) 42–58 NS	6 months 5 days/week 8 hours/day	17, 33, 66	HP, CS	Death			66	14/42 died
					Resp	17	33		Pneumonia
					Cardio	66			
					Hepatic	66			

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal	66			
					Neuro	17		33	Paralysis
Irish et al. 1940									
47	Rabbit (NS) 24 F	24 days GDs 1–24 7 hours/day	20, 70	TG, FX	Repro	20 F			
					Develop	20 F			
NIOSH 1980									
48	Rabbit (NS) 6 M	8 months 4 days/week 7.5 hours/day	27	NX	Neuro	27 M			No decrease in nerve conduction velocity
Russo et al. 1984									
CHRONIC EXPOSURE									
49	Rat (F344/DuCrj) 50 M, 50 F	2 years 5 days/week 6 hours/day	0, 4, 20, 100	CS, BW, HP	Resp	4	20		Inflammation of nasal epithelium
					Cardio	100			
					Hepatic	100			
					Renal	100			
					Neuro	100			
Gotoh et al. 1994									
50	Rat (NS) 90 M, 90 F	128 weeks 5 days/week 6 hours/day	0, 3.1, 29.6, 89.1	HP, GN, BC, UR	Death			89.1	Early mortality
					Bd wt	89.1			
					Resp		3.1[d]		Very slight or slight basal cell hyperplasia of nasal olfactory epithelium
					Cardio	29.6		89.1	Thrombi in heart, cartilaginous metaplasia, moderate-severe myocardial degeneration
					Gastro	29.6	89.1		Hyperkeratosis of esophagus
					Hemato	89.1			
					Renal	89.1			
Reuzel et al. 1987, 1991									

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
51	Mouse (Crj:BDF1) 50 M, 50 F	2 years 5 days/week 6 hours/day	0, 4, 16, 64	CS, BW, HP	Resp	64			
					Cardio	64			
					Hepatic	64			
					Renal	64			
					Neuro	16	64		Cerebellum atrophy
Gotoh et al. 1994									
53	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week 6 hours/day	0, 10, 33	BC, CS	Hemato	33			
					Neuro	10	33		Abnormal posture
NTP 1987									
53	Mouse (B6C3F1) 86 M, 86 F	12–18 months 5 days/week 6 hours/day	0, 10, 33, 100	CS, BW, HP, OF	Neuro		10 F		Decreased locomotor activity
NTP 1992 (Animals in the 100 ppm group were exposed for 20 weeks and allowed to recover until the end of the study.)									
54	Mouse (B6C3F1) 86 M, 86 F	2 years 5 days/week 6 hours/day	0, 10, 33, 100	CS, BW, HP, OF	Death			100	Decreased survival
					Bd wt	33	100		Decreased body weight gain
					Resp	33	100		Olfactory epithelial necrosis and metaplasia
					Cardio	33	100		Myocardial degeneration and cardiomyopathy
					Musc/skel	33	100		Sternum dysplasia
					Hepatic	33			
					Renal	33			

Table 2-1. Levels of Significant Exposure to Bromomethane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro	10	33	100	Overt signs of neurotoxicity at 33 ppm; cerebellar and cerebral degeneration at 100 ppm

NTP 1992 (Animals in the 100 ppm group were exposed for 20 weeks and allowed to recover until the end of the study.)

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration inhalation Minimal Risk Level (MRL) of 0.02 ppm based on a minimal LOAEL adjusted for intermittent exposure ($LOAEL_{adj}$), and converted to a human equivalent concentration ($LOAEL_{HEC}$) for extrarespiratory effects by multiplying the $LOAEL_{adj}$ by the default blood:gas partition coefficient of 1. The $LOAEL_{HEC}$ of 1.8 ppm was divided by a total uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).
[c]The following dosing protocol was used (all exposures were 7 hours/day, 5 days/week). Control (0 ppm): half of the group was exposed for 5 weeks and the remaining half was exposed for 2 additional weeks; 5.3 ppm: exposure for 7 weeks; 11/158 ppm: 5-week exposure to 11 ppm, followed by exposure to 158 ppm for 6 days followed by a 2-day recovery (no rationale was provided for the change in dose after 5 weeks of exposure); 26.0, 53.1, and 102.7 ppm: 5-week exposure.
[d]Used to derive a chronic-duration inhalation MRL of 0.001 ppm based on a minimal LOAEL of 3 ppm adjusted for intermittent exposure ($LOAEL_{adj}$), and converted to a human equivalent concentration ($LOAEL_{HEC}$) by multiplying the $LOAEL_{adj}$ by the RGDR for extrathoracic respiratory effects. The $LOAEL_{HEC}$ of 0.108 ppm was divided by a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Bd wt or BW = body weight; BC = blood chemistry; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; FOB = functional observational battery; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LC_{50} = lethal concentration, 50% kill; LD = lactation day; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OF = organ function; OW = organ weight; PND = postnatal day; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RGDR = regional gas dose ration; TG = teratogenicity; UR = urinalysis; WBC = white blood cell

Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation

Acute (≤14 days)

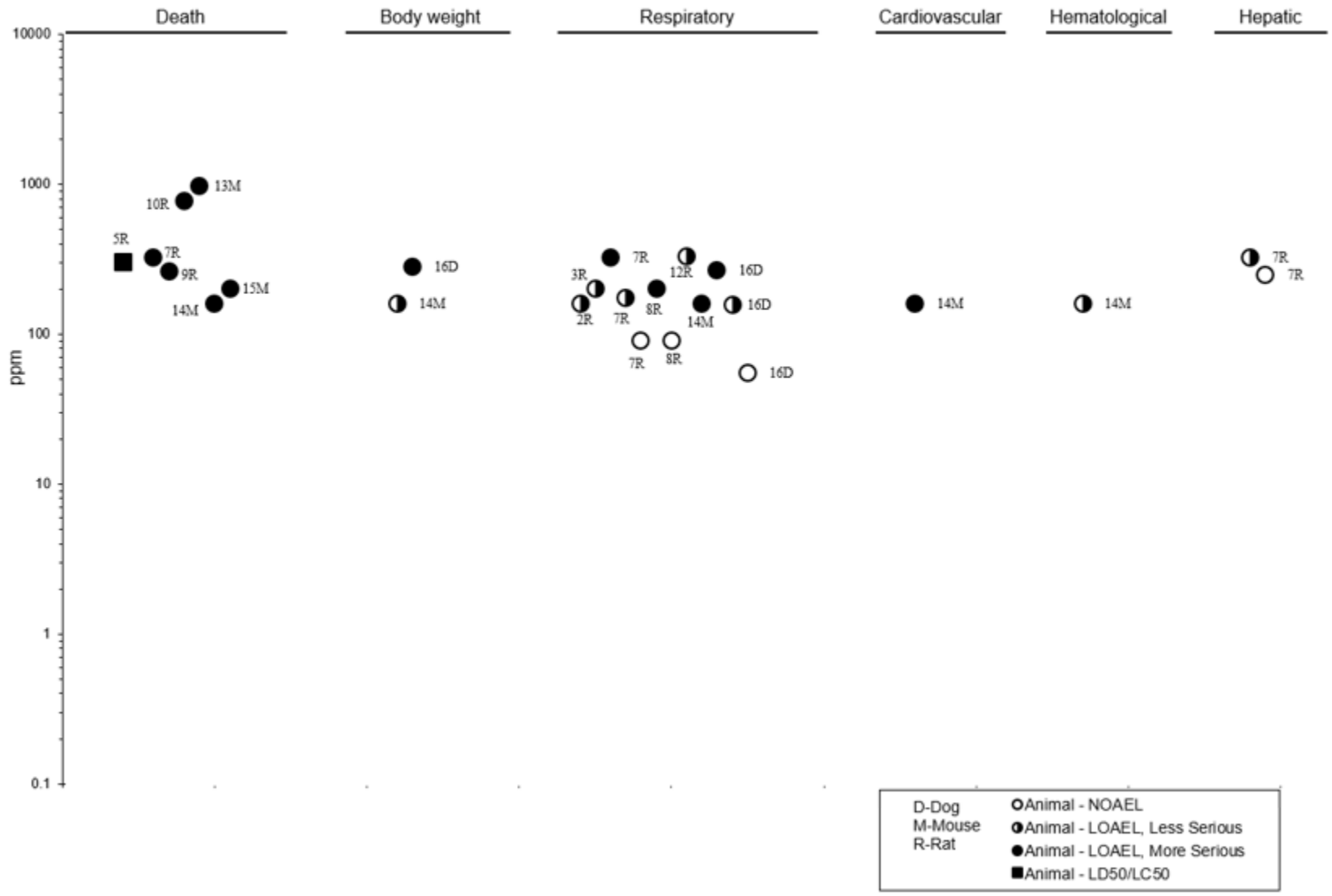


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation

Acute (≤14 days)

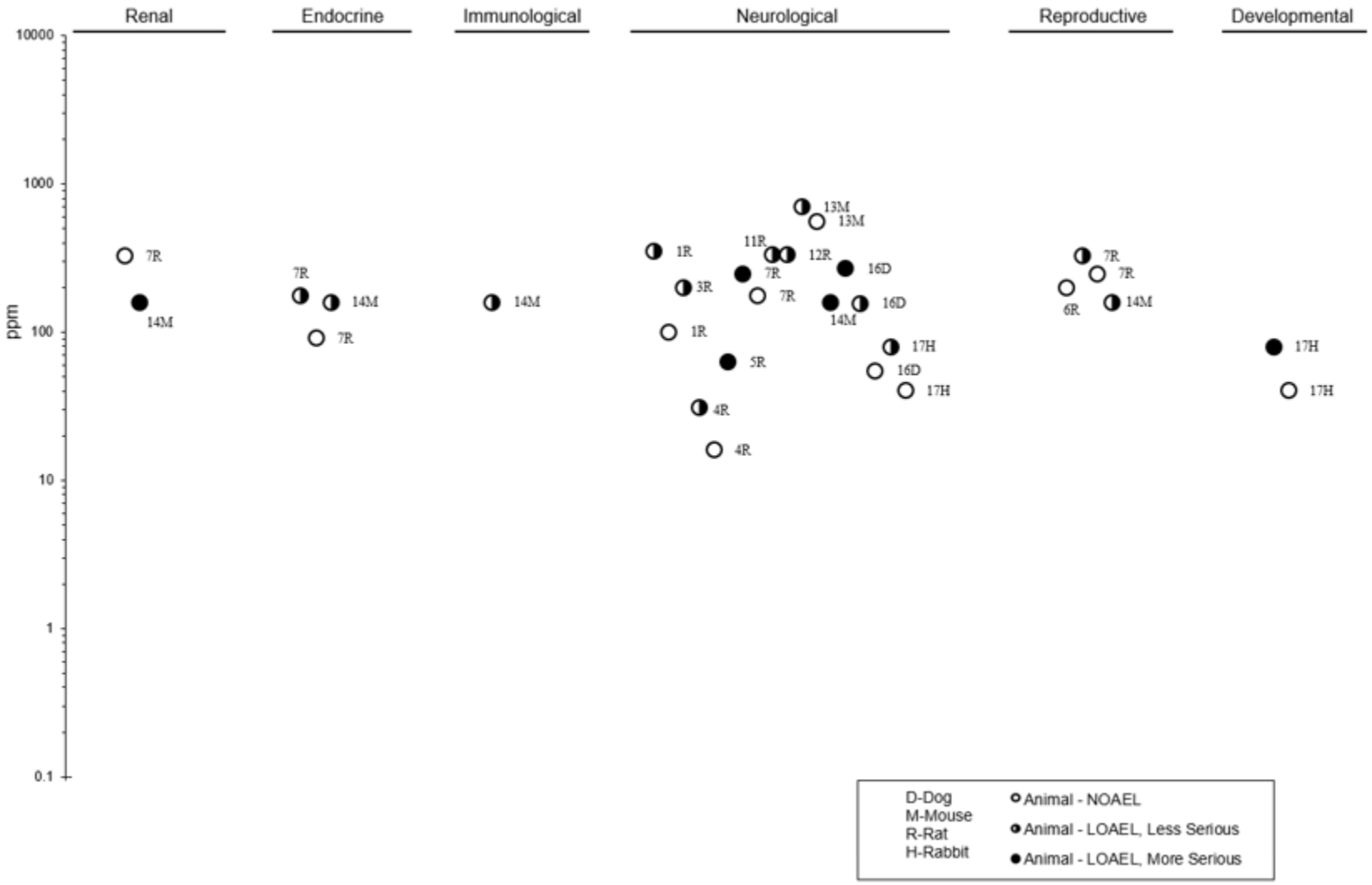


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

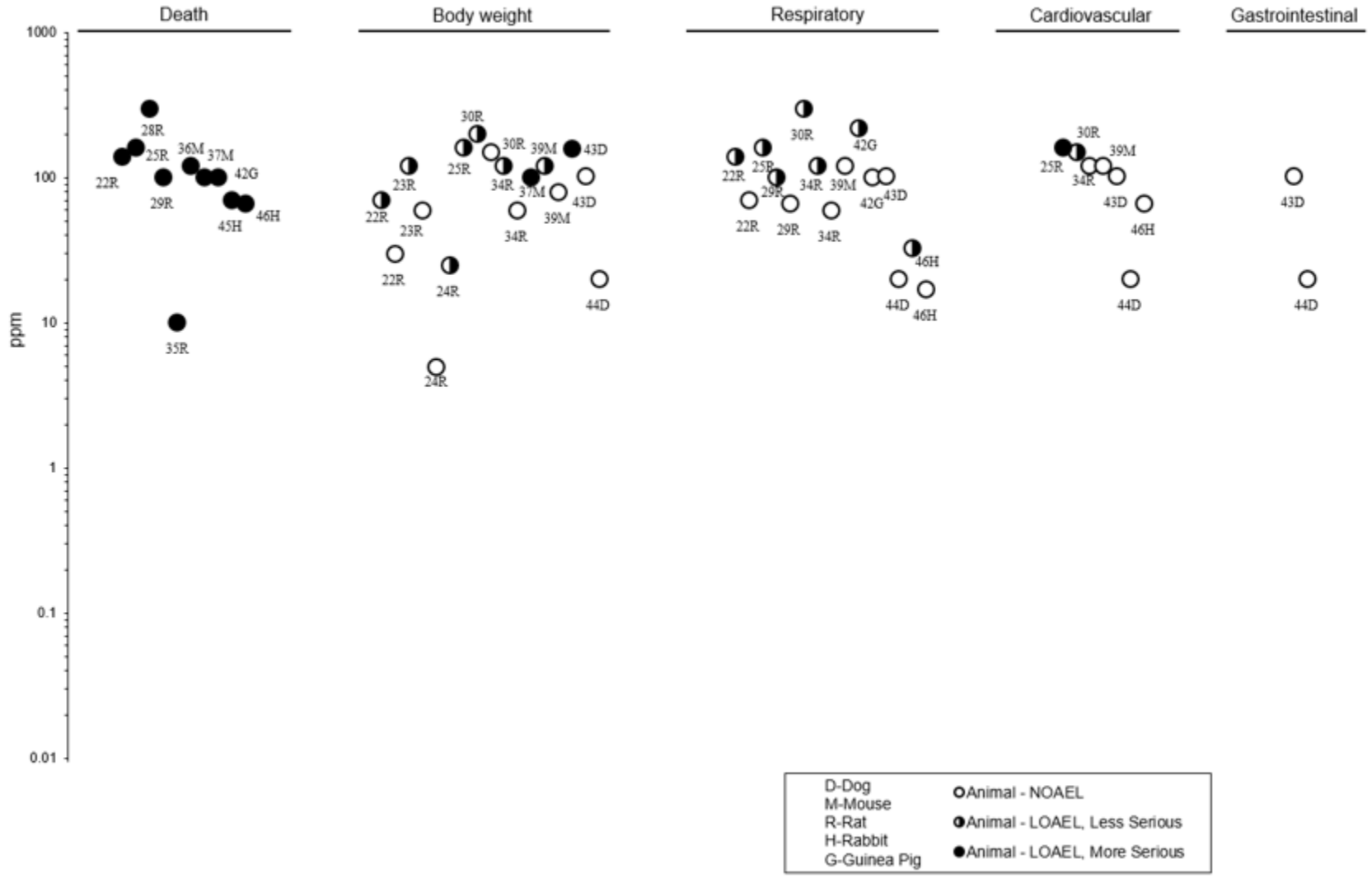


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

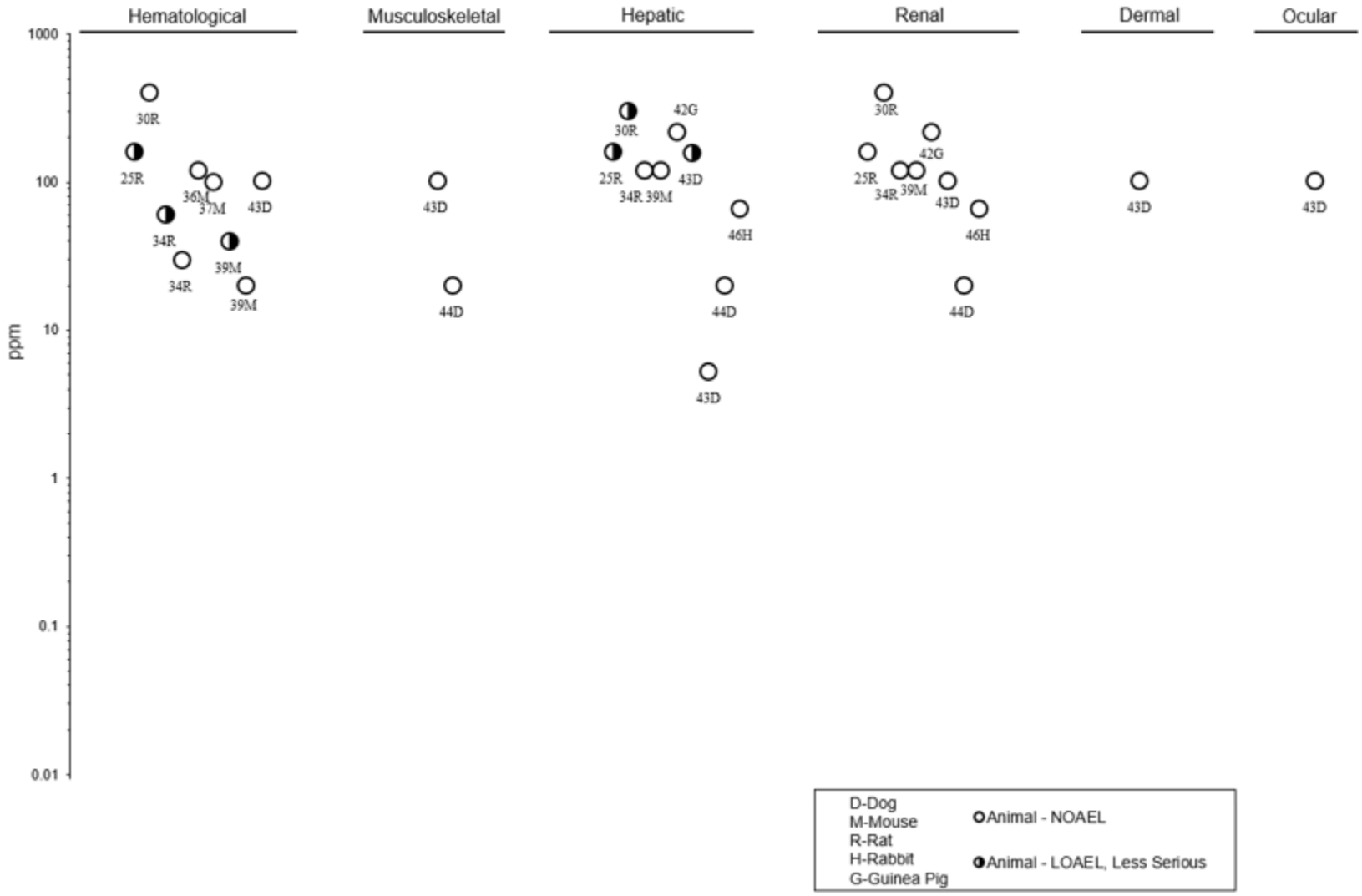


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

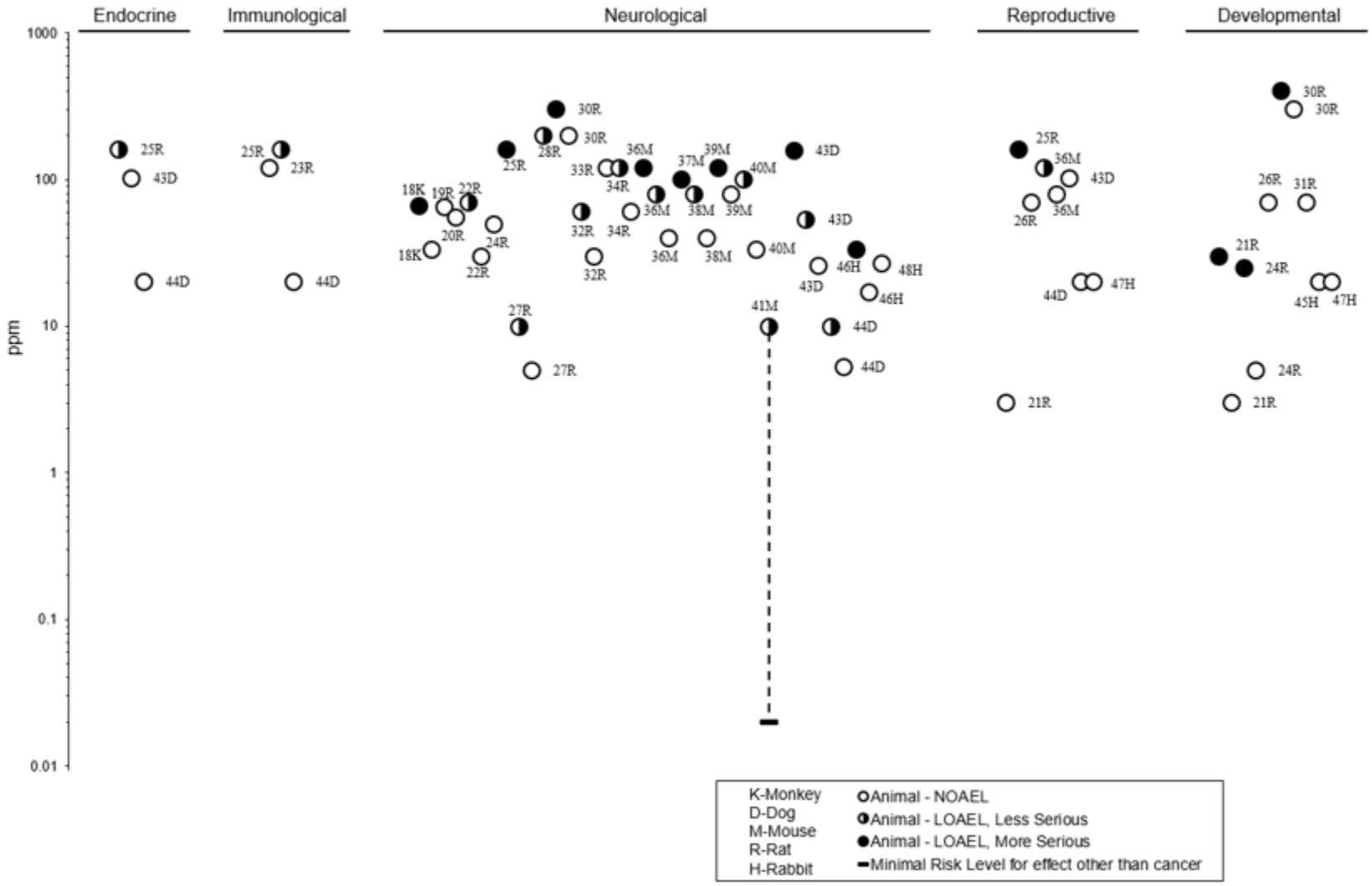


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Chronic (≥365 days)

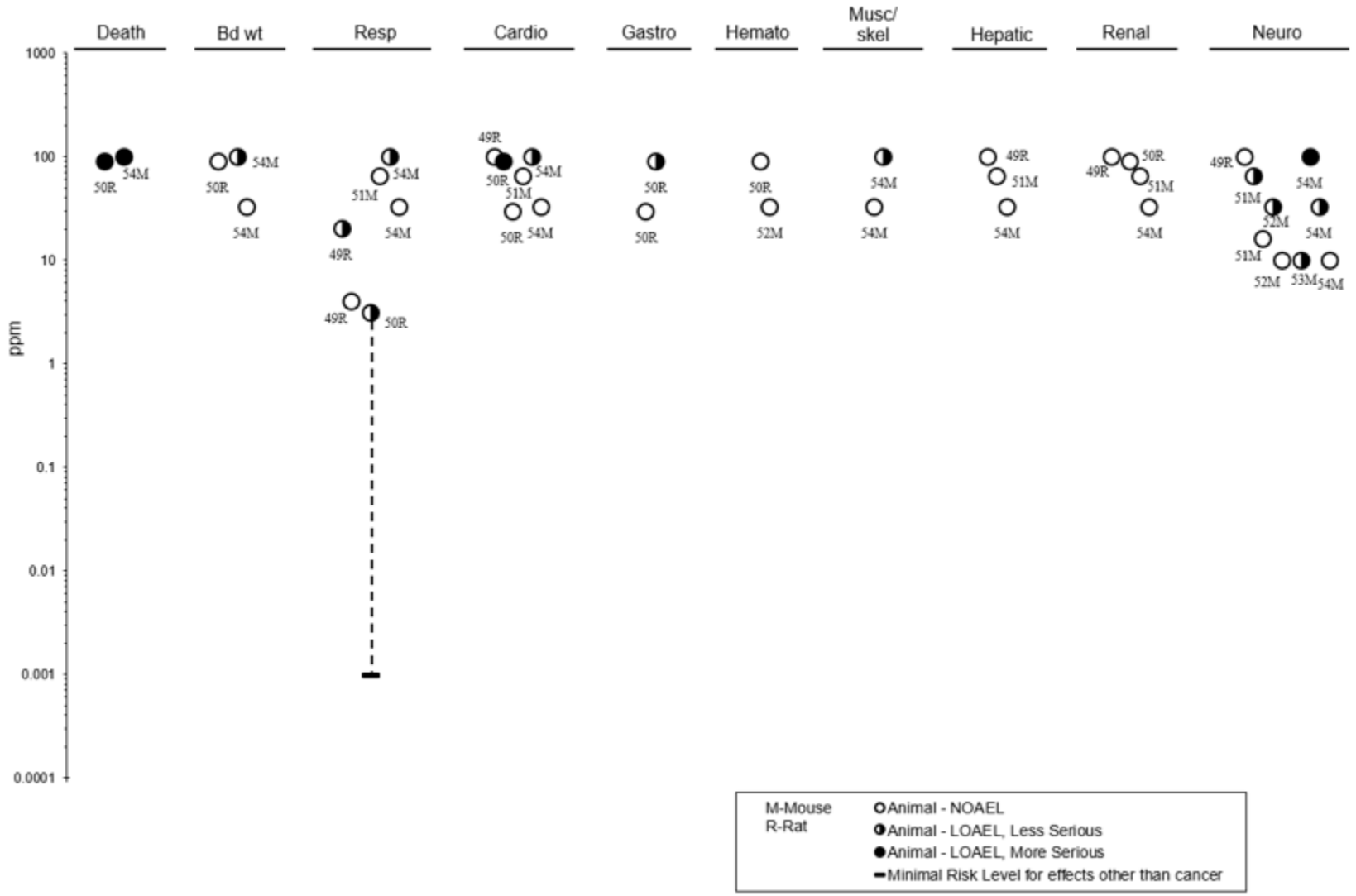


Table 2-2. Levels of Significant Exposure to Bromomethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Crj:CD (SD)) 24 F	GDs 6–15 (GO)	0, 3, 10, 30	DX	Gastro	10 F	30 F		Erosion and thickened wall of the non-glandular portion of the stomach
					Develop	30 F			
Kaneda et al. 1998									
2	Rabbit (Kbl:JW)	GDs 6–18 (GO)	0, 1, 3, 10	DX	Develop	10 F			
Kaneda et al. 1998									
INTERMEDIATE EXPOSURE									
3	Rat (NS) 9–14 M	13–25 weeks 5 days/week (G)	0, 50	HP	Gastro			50 M	Fibrosis, inflammation, hyperplasia
Boorman et al. 1986									
4	Rat (NS) 10 M, 10 F	13 weeks 5 days/week (G)	0, 0.4, 2, 10, 50	GN, HP, BC	Resp	50			
					Gastro	0.4	2	50	Hyperplasia and focal hyperemia at 2 mg/kg/day; ulcers at 50 mg/kg/day
					Hemato	10	50		Slight anemia
					Hepatic	50			
					Neuro	50			
Danse et al. 1984									
5	Rat (Sprague-Dawley) 15 M, 15 F	4 weeks *ad libitum* (F)	0, 0.009, 0.085, 0.835, 7.98	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd wt	7.98			Decreased body weight gain was observed, but is not considered adverse because food consumption was also decreased
					Resp	7.98			
					Cardio	7.98			
					Gastro	7.98			
					Hemato	7.98			
					Musc/skel	7.98			
					Hepatic	7.98			
					Renal	7.98			

Table 2-2. Levels of Significant Exposure to Bromomethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Endocr	7.98			
					Neuro	7.98			
					Repro	7.98			
EPA 1996									
CHRONIC EXPOSURE									
6	Rat (Sprague-Dawley) 50 M, 50 F	24 months (F)	M: 0.02, 0.11, 2.20, 11.1; F: 0, 0.03, 0.15, 2.92, 15.12	CS, BW, FI, HE, BC, UR, OW, GN, HP	Bd wt	11.1 M			Decreased body weight gain was observed, but is not considered adverse because food consumption was also decreased
					Resp	11.1 M			
					Cardio	11.1 M			
					Hemato	11.1 M			
					Musc/skel	11.1 M			
					Renal	11.1 M			
					Ocular	11.1 M			
					Endocr	11.1 M			
EPA 1999									
7	Dog (Beagle) 4 or 8 M, 4 or 8 F	1 year *ad libitum* (F)	M: 0, 0.06, 0.15, 2.28; F: 0, 0.07, 0.12, 0.27	BC, BW, FI, GN, HE, HP, OP, UR	Resp	0.27			
					Cardio	0.27			
					Gastro	0.27			
					Musc/skel	0.27			
					Hepatic	0.27			
					Dermal	0.27			
					Ocular	0.27			
					Endocr	0.27			
					Immuno	0.27			

Table 2-2. Levels of Significant Exposure to Bromomethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	0.27			
					Repro	0.27			
Wilson et al. 2000									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmological; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis

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

Acute (≤14 days)

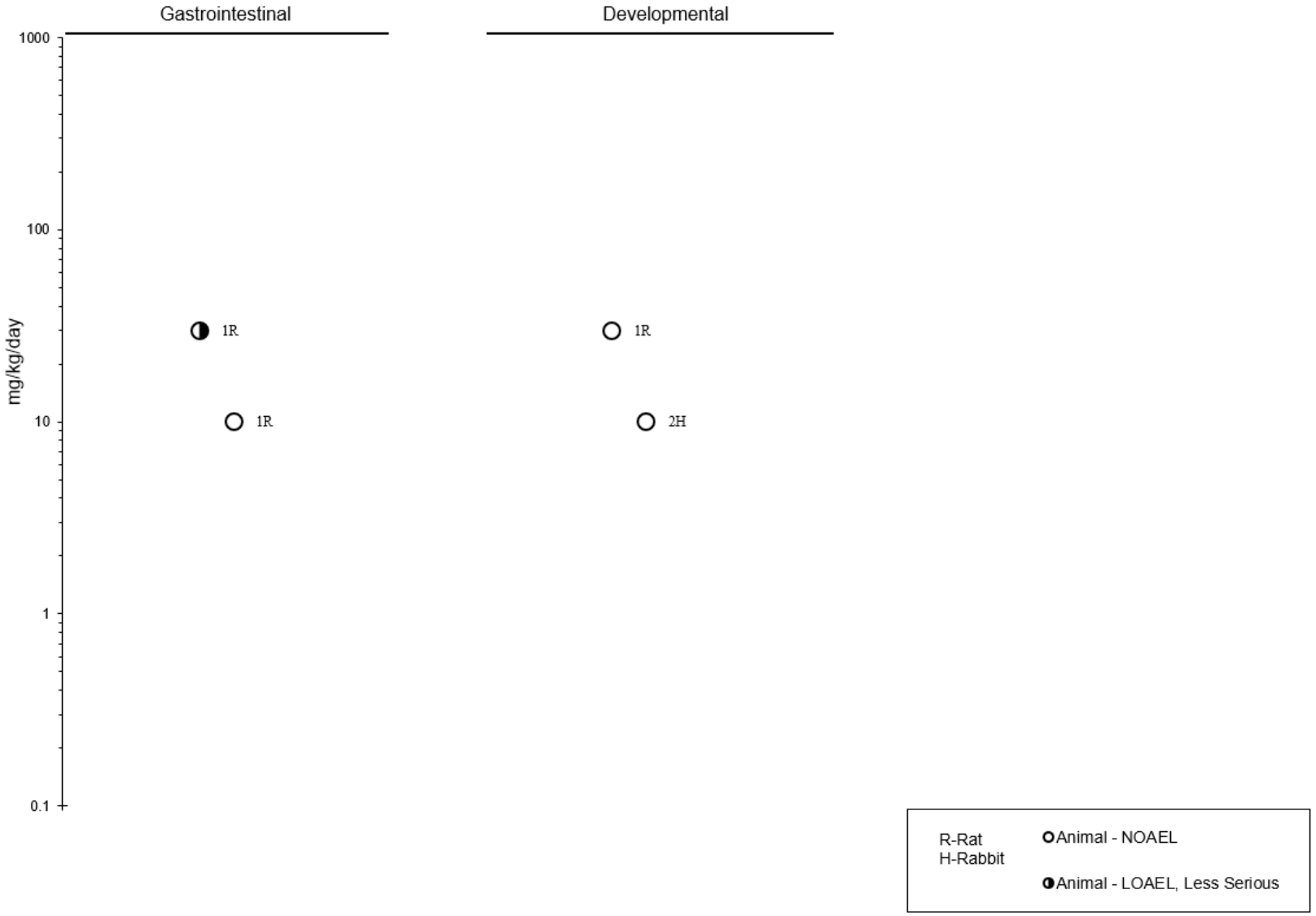


Figure 2-3. Levels of Significant Exposure to Bromomethane – Oral

Intermediate (15-364 days)

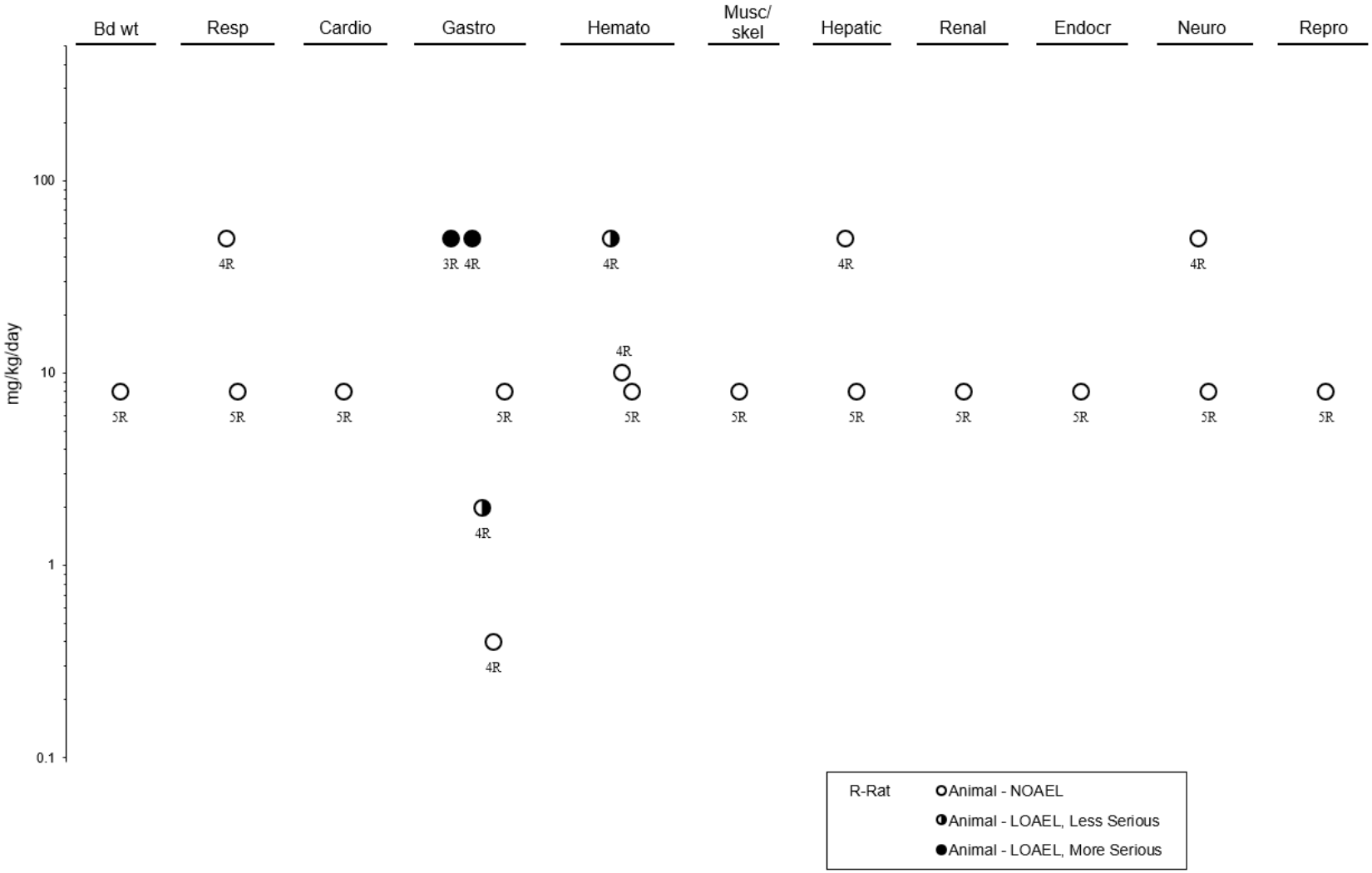
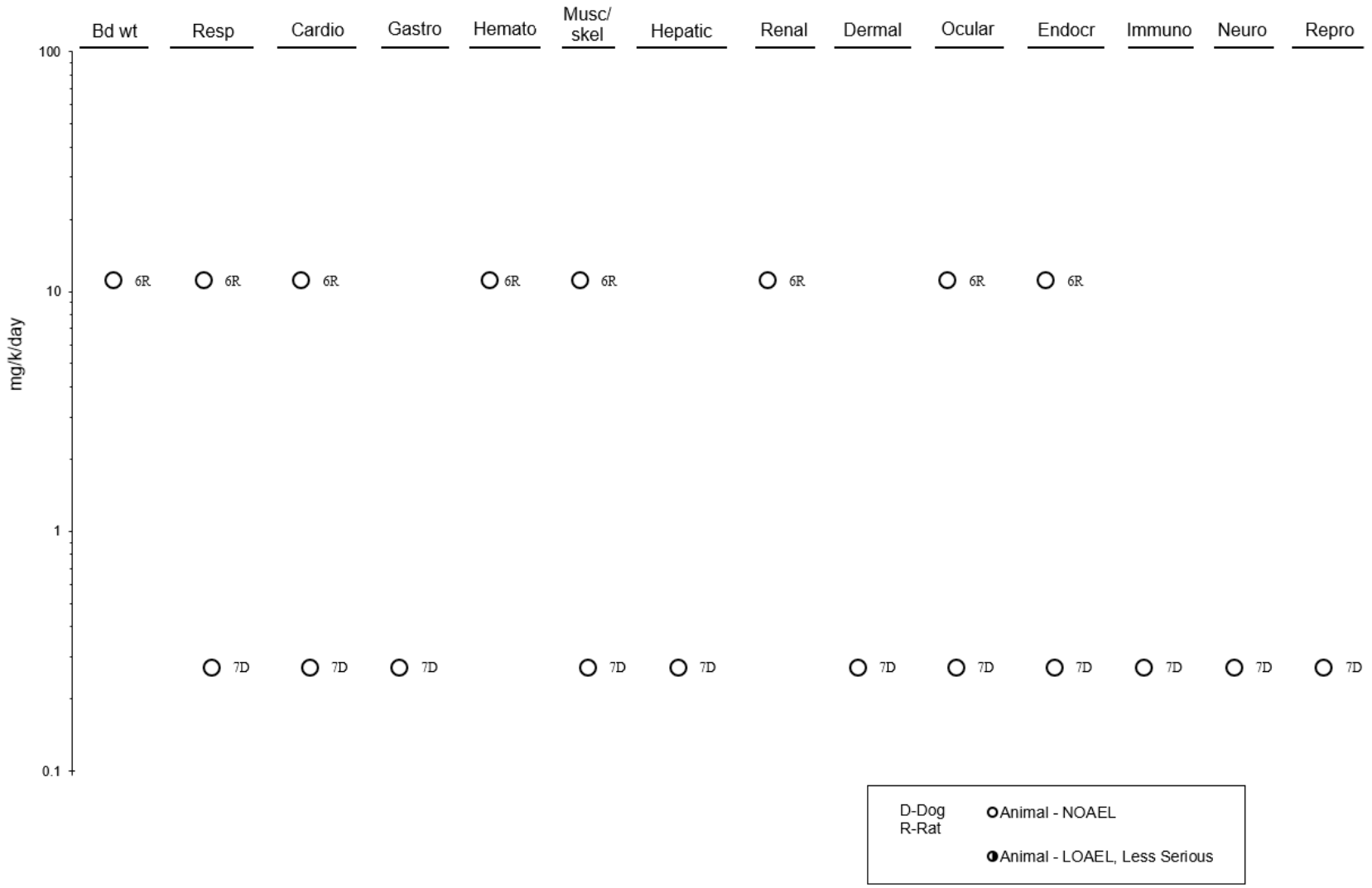


Figure 2-3. Levels of Significant Exposure to Bromomethane – Oral

Chronic (≥365 days)



2.2 DEATH

There are many reports of humans who have died following acute inhalation exposure to bromomethane. Most cases involved accidental exposures associated with manufacturing or packaging operations, use of or leaking fire extinguishers containing bromomethane, or fumigation activities (Alexeeff and Kilgore 1983). Death is not immediate, but usually occurs within 1–2 days of exposure (Langard et al. 1996; Marraccini et al. 1983; Prain and Smith 1952); deaths have also been reported a number of days after the exposure (Behrens and Dukes 1986). The cause of death is not certain, but is probably due to neurological and lung injury. Fatal exposure levels in humans are usually not known, but limited data suggest that the value depends, in part, on exposure duration. No studies were located regarding lethality in humans after oral exposure to bromomethane.

Inhalation studies in animals indicate that acute inhalation exposures to levels of 160–980 ppm may be lethal (Alexeeff et al. 1985; Eustis et al. 1988; Honma et al. 1985; Hurtt et al. 1987; Irish et al. 1940; Kato et al. 1986; NTP 1992). Several studies reveal that there is an extremely narrow margin between lethal and nonlethal exposures. For example, Kato et al. (1986) found no deaths in rats exposed to 700 ppm for 4 hours, but 100% lethality in animals exposed to 800 ppm, with 25% lethality at 767 ppm. Similarly, Irish et al. (1940) found 100% survival in rats exposed to 100 ppm for 24 hours and 100% lethality at 220 ppm. In repeated inhalation exposure studies, no deaths were observed in rats exposed to 120 ppm bromomethane for 13 weeks (NTP 1992), but 50% mortality was observed following 3 weeks of exposure to 160 ppm (Eustis et al. 1988). Species and sex differences in the lethality of bromomethane have been found (Eustis et al. 1988). Deaths were observed in 50% of the male mice, female mice, and male rats after 8, 6, or 14 exposures to 160 ppm, respectively; no deaths were observed in similarly exposed female rats. Intermediate-duration inhalation exposures of animals can lead to death after exposure to levels at concentrations of 70–300 ppm in rats, mice, and/or rabbits (EPA 1988a; Eustis et al. 1988; Hardin et al. 1981; Ikeda et al. 1980; Irish et al. 1940; NTP 1987, 1992; Reuzel et al. 1987; Sato et al. 1985).

No deaths or alterations in survival were observed in rats chronically exposed to 15.12 mg/kg/day microencapsulated bromomethane in the diet (EPA 1999) or in dogs exposed to bromomethane in feed at doses up to 0.28 mg/kg/day for 1 year (Wilson et al. 2000).

2.3 BODY WEIGHT

Several inhalation studies in animals indicate that exposure to bromomethane decreases body weight gain or produces weight loss. In acute exposure studies, decreases in body weight gain were observed in mice exposed to 160 ppm for 2 weeks (Eustis et al. 1988) and 13% weight loss was observed in dogs exposed to 283 ppm for 2 days associated with extreme toxicity, emesis, heavy salivation, and dehydration (EPA 2001b). No alterations in body weight gain were observed in mice exposed to 100 ppm for 2 weeks (NTP 1992). In intermediate-duration studies, body weight decreases were observed in rats and mice. In rats, terminal body weights were decreased in by 37% in males exposed to 140 ppm and by 23% in females exposed to 70 ppm for 13 weeks (EPA 1994a). Small decreases in body weight gain and/or terminal body weights were observed in rats exposed to 200 ppm for 3 or 6 weeks (Ikeda et al. 1980; Kato et al. 1986), in rats exposed to 120 ppm for 4 weeks (EPA 2011), in rats and mice exposed to 120 ppm for 13 weeks (NTP 1992), and in mice exposed to 100 ppm for 20 weeks and allowed to recover for over 80 weeks (NTP 1992). In contrast, weight loss was noted in mice exposed to 100 ppm for 13 weeks (NTP 1992), 100 ppm for 20 weeks (NTP 1987), and in dogs exposed to 102.7 ppm for 5 weeks (EPA 2001b); additionally, a 32% decrease in body weight gain was observed in rats exposed to 160 ppm for 3–6 weeks (Eustis et al. 1988). A decrease in maternal body weight gain was observed in rabbits exposed to 80 ppm on gestation days 7–19; this concentration was also associated with severe neurological effects and likely a decrease in food intake (Breslin et al. 1990); however, no decreases in maternal weight gain were observed when the experiment was repeated. In chronic-duration studies, decreases in body weight gain were observed in mice exposed to 100 ppm for 2 years (NTP 1992), but were not observed in rats exposed to concentrations as high as 89.1 ppm for 128 weeks (Reuzel et al. 1987, 1991).

Dietary exposure studies in rats observed decreased body weight gain; however, because these decreases were accompanied by decreased food consumption, they are not considered adverse. In a 4-week study of rats exposed to 7.98 mg/kg/day in the diet as microencapsulated bromomethane, mean body weight gain was decreased by 14% in males during the first week of exposure and by 33% in females during weeks 1–2, but not during other weeks (EPA 1996). These changes were accompanied by decreased food intake. Decreases in body weight gain were observed in the first 12–18 months of exposure to 11.1 and 15.12 mg/kg/day microencapsulated bromomethane in male and female rats, respectively, in the diet for 2 years; however, decreased food consumption was also decreased during that time (EPA 1999). No effects on body weight were observed in male or female beagle dogs given bromomethane in the diet for 52 weeks at doses up to 0.28 mg/kg/day (Wilson et al. 2000).

2.4 RESPIRATORY

Observations in humans exposed to inhaled bromomethane indicate that the respiratory tract, particularly the lungs, is a target of bromomethane toxicity. The human data do not allow for a concentration-response assessment since most reports did not include exposure levels; however, it can be assumed that the severity of the lesions increased with exposure concentration. Lung edema is the most common effect, and is often accompanied by focal hemorrhagic lesions (Greenberg 1971; Marraccini et al. 1983; Miller 1943; Prain and Smith 1952; Wyers 1945). This injury can severely impair respiratory function and lead to hypoxia, cyanosis, and complete respiratory failure (Greenberg 1971; Hine 1969; O'Neal 1987). There is also evidence that bromomethane is a respiratory irritant based on reports of sore throat and a burning sensation in the nose and throat (Bishop 1992; Hine 1969); this likely occurs at lower concentrations than the severe lung effects. A study of bromomethane applicators (69% did not use protective equipment) reported a 36% incidence of dyspnea, cough, and phlegm (Akca et al. 2009).

Inhalation studies in laboratory animals suggested that the nasal cavity, particularly the olfactory epithelium, is the most sensitive target in the respiratory tract. In acute exposure studies, degeneration of the olfactory epithelium was observed in rats exposed to ≥160 ppm (Eustis et al. 1988; Hastings et al. 1991; Hurtt et al. 1987, 1988; Reed et al. 1995; Youngentob and Schwob 2006) and in mice at 160 ppm (Eustis et al. 1988). These studies demonstrate that the severity and extent of the damage increased with concentration. A 5-day exposure to 175 ppm resulted in moderate olfactory epithelium degeneration in 50–80% of the tissue and exposure to 325 or 330 ppm resulted in severe degeneration in 80–95% of the olfactory epithelium (Hurtt et al. 1987; Youngentob and Schwob 2006). Although the severity of the olfactory epithelial degeneration appears to decrease with exposure duration in acute studies, there is some evidence of a shift in the type of lesions. Moderate to marked olfactory epithelium degeneration was observed after a 3-day exposure to 160 ppm. After 10 days, the severity of the degeneration was scored as minimal to mild; however, there was a loss of olfactory sensory cells and respiratory epithelial metaplasia (Eustis et al. 1988). Several studies demonstrated that the marked damage to the olfactory epithelium can occur in mice and rats after a single 4–8-hour exposure to ≥180 ppm bromomethane (Hastings et al. 1991; Holbrook et al. 2014; Huard et al. 1998; Hurtt et al. 1988; Reed et al. 1995). With continued exposure, there is evidence of regeneration of the olfactory epithelium after 3 or 4 days of exposure (Hastings et al. 1991; Hurtt et al. 1988) and recovery 10 weeks post-exposure (Hastings et al. 1991; Hurtt et al. 1988). Upon examination of the type of olfactory epithelial cells damaged by bromomethane, Huard et al. (1998) found that neurons and sustentacular cells were completely destroyed by exposure to 330 ppm bromomethane for 6 hours; most of the Bowman’s ducts were also eliminated.

However, three proliferative cell populations—Bowman's duct/gland cells, horizontal basal cells, and globose basal cells—were spared and could regenerate the olfactory epithelium.

Intermediate- and chronic-duration inhalation studies suggest that rats may be more sensitive to the nasal effects of bromomethane than mice. A 13-week exposure to 120 ppm resulted in increases in the incidence of olfactory epithelium dysplasia and cysts in rats, but no nasal effects in mice (NTP 1992). Dysplasia of the olfactory epithelium due to local irritation was also observed in male and female rats exposed to 140 ppm bromomethane for 13 weeks (EPA 1994a). In rats, a 29-month exposure resulted in basal cell hyperplasia in the olfactory epithelium (Reuzel et al. 1987, 1991); the severity of the lesion was scored as very slight at 3.1 ppm, slight at 29.6 ppm, and slight to moderate at 89.1 ppm. This study did not find nasal lesions in rats exposed for 12 or 24 months. Another study (Gotoh et al. 1994) reported no nasal lesions in rats exposed to 4 ppm for 2 years, inflammation in males at 20 ppm and in females at 100 ppm, and necrosis and metaplasia of the olfactory epithelium in males at 100 ppm. In contrast, no nasal effects were observed in mice exposed to 33 or 100 ppm for 2 years (Gotoh et al. 1994; NTP 1992). In the NTP (1992) study, olfactory epithelium necrosis (males only) and metaplasia were observed in mice exposed to 100 ppm for 20 weeks and allowed to recover for the remainder of the 2-year study (NTP 1992). Degeneration of the olfactory epithelium was also observed in dogs exposed to 11.0 ppm for 4 weeks followed by 158 ppm for 6 days, followed by a 2-day recovery (EPA 2001b); no lesions were observed in dogs exposed to 102.7 ppm for 4 weeks (EPA 2001b). In addition to the lesions observed in the olfactory epithelium, several studies have also reported focal or multifocal loss of olfactory sensory cells (Eustis et al. 1988; Hurtt et al. 1988) and a loss of olfactory function.

Labored breathing was observed in dogs exposed to 156 ppm for 4 days and pulmonary edema and rales were observed at 268 ppm (EPA 2001a). Lung congestion, hemorrhage, and thrombi were observed in mice acutely exposed to a 160 ppm bromomethane (Eustis et al. 1988); this concentration also resulted in deaths. Intermediate-duration exposure in rats resulted in pulmonary hemorrhage at 10 ppm (Sato et al. 1985) and hemorrhagic lesions at 400 ppm (Kato et al. 1986). Lung congestion was noted in rats exposed to 100 ppm and rabbits exposed to 66 ppm (Irish et al. 1940); however, the study provided limited incidence data. However, other intermediate-duration studies in rats and mice did not find lung effects at exposure levels as high as 120 ppm (NTP 1992) and chronic exposure studies in rats and mice have not reported lung effects at 89.1–100 or 33–64 ppm, respectively (Gotoh et al. 1994; NTP 1992; Reuzel et al. 1987).

Oral exposure of animals to bromomethane does not appear to produce adverse effects in the respiratory tract. In animals, no histological evidence of lung injury was detected in rats exposed to oral doses of 50 mg/kg/day for 13 weeks (Danse et al. 1984). Slight atelectasis and interstitial pneumonia were observed in some animals exposed to oral doses of 10 or 50 mg/kg/day, but this was judged to be due to inadvertent inhalation exposure that occurred during oral dosing (Danse et al. 1984). In a 2-year study in rats (EPA 1999) and 1-year study in beagle dogs (Wilson et al. 2000), doses up to 11.1 in males and 15.12 in females (equivalent to 0.28 mg/kg/day bromomethane), respectively, did not result in alterations in lung weight or histopathology of nasopharyngeal tissues, trachea, or lung. Similarly, a dose of 7.98 mg/kg/day for 4 weeks in rats resulted in no exposure-associated findings (EPA 1996).

2.5 CARDIOVASCULAR

Some cardiovascular effects, such as high blood pressure and minute myocardial hemorrhages, have been reported in cases of individuals exposed to inhaled bromomethane (Bishop 1992; O'Neal 1987; Prockop and Smith 1986; Viner 1945); the effects have not been consistently found and it is not known if these effects are related to the bromomethane exposure or were pre-existing conditions. However, the findings are supported by several studies in mice and rats that indicate that the heart is susceptible to injury. Effects that have been reported at exposure levels of 89.1–150 ppm include fibrosis (Kato et al. 1986), myocardial degeneration (Eustis et al. 1988; NTP 1992; Reuzel et al. 1987, 1991), cardiomyopathy (NTP 1992), and cardiac thrombi (Reuzel et al. 1987). No histological alterations were observed in the hearts of dogs exposed to 102.7 ppm for 5 weeks (EPA 2001b).

Neither heart weight nor histopathology of heart or abdominal aorta were altered by treatment of beagle dogs with bromomethane in feed at doses up to 0.28 mg/kg/day for 1 year (Wilson et al. 2000), or rats exposed to 7.98 mg/kg/day for 4 weeks (EPA 1996) or male and female rats exposed to doses of 11.1 and 15.12 mg/kg/day, respectively, as microencapsulated bromomethane in the diet for 2 years (EPA 1999).

2.6 GASTROINTESTINAL

Several case reports have noted nausea, vomiting, and/or diarrhea in individuals acutely exposed to inhaled bromomethane (Deschamps and Turpin 1996; Herzstein and Cullen 1990; Hustinx et al. 1993; Kulkarni et al. 2015; Langard et al. 1996; O'Malley et al. 2011; Yamano et al. 2001); it is not known if the nausea and vomiting were neurological effects or due to gastrointestinal irritation.

In animals, exposure to inhaled bromomethane typically is not associated with gastrointestinal effects; however, oral exposure studies show that bromomethane produces damage to the gastrointestinal tract. Gastrointestinal effects have not been noted in most inhalation studies in animals, but Alexeeff et al. (1985) reported an unusual increase in hemorrhagic lesions of the colon in mice exposed to high, lethal concentrations (1,490 ppm) of bromomethane, Hurtt et al. (1987) reported diarrhea in rats exposed to 250 ppm, and Reuzel et al. (1987, 1991) noted an increased incidence of hyperkeratosis of the esophagus and stomach in rats exposed to 89.1 ppm. This effect is probably mediated by transport of bromomethane from the lungs to the throat by mucociliary clearance (Reuzel et al. 1987).

Studies in gavaged animals show that repeated administration of bromomethane to rats can result in irritation and hyperplasia of the epithelium in the forestomach (Boorman et al. 1986; Danse et al. 1984; Kaneda et al. 1998). In rats exposed to 30 mg/kg/day bromomethane in corn oil by gavage on days 6–15 of gestation, erosion and thickening of the wall of the non-glandular stomach or adhesion of the stomach to the spleen, liver, or diaphragm were observed (Kaneda et al. 1998). These effects were not observed in rabbits similarly exposed at doses up to 10 mg/kg/day (Kaneda et al. 1998). Adhesion of the stomach to the liver, spleen, or diaphragm and frank ulceration of the stomach were also observed in rats exposed to 50 mg/kg/day bromomethane by gavage for 5 days/week for 13–25 weeks (Boorman et al. 1986). Microscopic evaluation showed inflammation, fibrosis, acanthosis, and pseudoepitheliomatous hyperplasia of the forestomach. Following a 4-week recovery period in rats exposed for 13 weeks, epithelial hyperplasia had regressed, although fibrotic lesions or adhesions, which developed during exposure, remained. As compared to rats exposed for 13 weeks, the severity and incidence of hyperplasia was increased in rats exposed for 25 weeks; the incidence of fibrosis was increased, although the severity was decreased.

Dose-dependent gastrointestinal lesions were observed in rats administered bromomethane at doses of 2, 10, and 50 mg/kg/day by gavage for 90 days (Danse et al. 1984). In the 2 mg/kg/day group, mild focal hyperemia of the forestomach was observed. In rats administered 10 and 50 mg/kg/day, hyperkeratosis and decreased surface area due to adhesions were observed, with severity increasing with dose. At 50 mg/kg/day, frank ulcerations were observed in the forestomach. Lesions appeared to be the result of a direct irritant effect of bromomethane on the epithelium. Boorman et al. (1986) conducted a response study with the observations that epithelial hyperplasia increased with exposure duration from 13 to 25 weeks, but regressed when exposure through 13 weeks was stopped, although fibrotic lesions or adhesions that developed during exposure remained. The possible relationship between this hyperplastic response and cancer of the forestomach is discussed in Section 2.18. In contrast, dietary exposure to

bromomethane did not result in gastrointestinal lesions in beagle dogs exposed to 0.28 mg/kg/day bromomethane for 1 year (Wilson et al. 2000) or rats exposed to 7.98 mg/kg/day for 4 weeks (EPA 1996) or male and female rats exposed to up to 11.1 and 15.12 mg/kg/day microencapsulated bromomethane, respectively, for 2 years (EPA 1999).

2.7 HEMATOLOGICAL

Hematological effects have not been observed in humans exposed to inhaled bromomethane (Johnstone 1945; Kantarjian and Shaheen 1963; Longley and Jones 1965; O'Neal 1987; Viner 1945; Wyers 1945). Inconsistent results have been observed regarding hematological effects in animals following inhalation exposure. Decreased erythrocyte, hematocrit, and hemoglobin levels and increased leukocyte levels were observed in female mice exposed to 160 ppm for 8 days; no effects were observed in males (Eustis et al. 1988). A 13-week study found decreases in erythrocyte levels in female rats exposed to 60 or 120 ppm and decreases in hematocrit and hemoglobin levels in female rats exposed to 120 ppm; however, only minimal decreases were observed (approximately 5%) (NTP 1992). A related effect of splenic hemosiderosis was observed in rats exposed to 160 ppm bromomethane for 6 weeks (Eustis et al. 1988). In contrast, a 13-week mouse study found increases in erythrocyte levels and decreases in mean cell volume and mean cell hemoglobin in males exposed to ≥40 ppm and increases in hemoglobin levels in males at 120 ppm (NTP 1992). The biological significance of these findings is not clear. Other studies have not found significant hematological effects (EPA 1988a, 1994; Kato et al. 1986; Reuzel et al. 1987, 1991).

Oral exposure of animals does not appear to produce adverse effects to the hematological system. Slight anemia was observed in rats exposed to doses of 50 mg/kg/day for 13 weeks, but this was judged to be secondary to the pronounced lesions of the forestomach (Danse et al. 1984). No evidence of other hematological effects was detected at doses up to 10 mg/kg/day. Bromomethane in feed at doses up to 0.28 mg/kg/day for 1 year in dogs, or 7.98 mg/kg/day for 4 weeks in rats or 11.1 and 15.12 mg/kg/day in male and female rats, respectively, for 2 years did not result in effects on hematological alterations in dogs or rats, respectively (EPA 1996, 1999; Wilson et al. 2000).

2.8 MUSCULOSKELETAL

There are limited data on the toxicity of bromomethane to the musculoskeletal system. NTP (1992) reported a dose-related increase in the incidence of dysplasia in the sternum of mice exposed to inhaled

bromomethane at a concentration of 100 ppm for 20 weeks. Bromomethane in feed at doses up to 0.28 mg/kg/day for 1 year (Wilson et al. 2000) or 7.98 mg/kg/day for 4 weeks (EPA 1996) did not result in microscopic lesions in bone or skeletal muscle.

2.9 HEPATIC

Case reports of humans exposed to bromomethane vapors indicated that the liver may become swollen and tender in some cases (Hine 1969); more severe liver effects, including congestion, fatty degeneration, or atrophy, have been reported in lethal cases (Miller 1943; O'Neal 1987; Prain and Smith 1952). In other cases, no significant liver injury was detected (Greenberg 1971; Hine 1969; Marraccini et al. 1983). Similar results have been reported in rats and mice exposed to inhaled bromomethane, with mild signs of liver injury (edema, focal hemorrhages, minimal necrosis) being noted in some studies at levels of 160–1,200 ppm (Alexeeff et al. 1985; Eustis et al. 1988; Hurtt et al. 1987; Irish et al. 1940; Kato et al. 1986); no hepatocellular lesions were observed at 66 ppm (Irish et al. 1940). No liver effects were observed in rat and mouse chronic exposure studies at concentrations as high as 120 ppm (Gotoh et al. 1994; NTP 1992; Reuzel et al. 1987, 1991) or in dogs exposed to ≤102.7 ppm for 5 weeks (EPA 2001b).

In animals exposed to oral bromomethane, histological signs of liver damage were not detected in rats given doses up to 50 mg/kg/day for 90 days (Danse et al. 1984) or to 7.98 mg/kg/day for 4 weeks (EPA 1996). Exposure of beagle dogs to 0.28 mg/kg/day bromomethane in feed for 1 year or of male and female rats to 11.1 and15.12 mg/kg/day microencapsulated bromomethane in feed, respectively, for 2 years did not result in treatment-related serum chemistry changes or effects on liver weight or histopathology (EPA 1999; Wilson et al. 2000).

2.10 RENAL

Adverse renal effects are often reported in humans exposed to high levels of bromomethane vapor. Common effects noted in case reports include congestion, anuria or oliguria, proteinuria, and histological alterations in the kidney (Hine 1969; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Viner 1945; Wyers 1945). However, there are many cases where renal effects were minimal or absent (Hine 1969; Johnstone 1945; Longley and Jones 1965). Although two laboratory animal studies reported kidney effects—enlarged and paled kidney in mice exposed to 900 ppm for 1 hour (Alexeeff et al. 1985); and nephrosis in mice exposed to 160 ppm for 2 weeks (Eustis et al. 1988) and minimal nephrosis in rats exposed for 3–6 weeks (Eustis et al. 1988), most intermediate- and chronic-duration studies in rats and

mice did not find renal effects (EPA 2001b; Gotoh et al. 1994; NTP 1992). A developmental study in rats, with inhalation exposure of dams for 6 weeks, showed a slightly increased incidence of interstitial nephritis at 70 ppm, the highest concentration tested (Sikov et al. 1981 [MRID00102990], as cited in EPA 2018a). However, the incidence did not reach statistical significance and EPA (2018a) did not consider the incidence during gestation to be "significant enough to determine a LOAEL," but it might be a threshold effect. Renal effects reported by Sikov et al. (1981 [MRID00102990], as cited in EPA 2018a) are not included in Table 2-1 (Levels of Significant Exposure to Bromomethane – Inhalation) because the primary study report was not available for review.

Decreased absolute, but not relative, kidney weights were observed in beagle dogs given bromomethane in feed at doses up to 0.28 mg/kg/day for 52 weeks, but there were no treatment-related effects on serum chemistry, urinalysis, or kidney histopathology (Wilson et al. 2000). No renal effects were observed in rats exposed to 7.98 mg/kg/day for 4 weeks (EPA 1996) or male and female rats exposed to 11.1 and 15.12 mg/kg/day, respectively, in the diet for 2 years (EPA 1999).

2.11 DERMAL

Dermal effects are associated with direct exposure of skin to bromomethane vapor or liquid, but not with oral exposure. Bromomethane vapor is irritating to the skin, and humans who are exposed to bromomethane in air may experience signs of skin irritation. Direct dermal contact with bromomethane can lead to severe injury to the skin. Symptoms usually do not appear immediately, but develop a few hours after exposure termination. Early signs typically include a burning, tingling, or itching sensation, with erythema, edema, numbness, pain, and large blisters that resemble second-degree burns developing somewhat later (Butler et al. 1945; Hezemans-Boer et al. 1988; Horiuchi et al. 2008; Watrous 1942; Wyers 1945). Injury is usually mild on exposed skin areas where rapid evaporation can occur and is more severe in moist or covered regions where evaporation is retarded and the liquid can remain on the skin longer (Watrous 1942; Zwaveling et al. 1987). Effects generally begin to subside within 5–10 days after exposure termination (Watrous 1942), and recovery is usually complete within about 1 month post-exposure (Butler et al. 1945; Zwaveling et al. 1987).

The exposure levels leading to dermal effects of this sort are rarely known. Most cases involve people doused with liquid bromomethane (Longley and Jones 1965; Watrous 1942) or exposed to very high vapor levels (Hezemans-Boer et al. 1988; Zwaveling et al. 1987). Numerous case reports of humans exposed to lower levels of airborne bromomethane did not include descriptions of dermal effects, even

though the level of inhalation exposure caused profound or even fatal neurological or respiratory effects (e.g., Greenberg 1971; Hine 1969; Marraccini et al. 1983).

In rats, a 30-second exposure to liquefied bromomethane applied to a 12 cm^2 area of shaved skin resulted in slight edema and small ecchymoses (Yamamoto et al. 2000). A 1–5-minute exposure resulted in necrotic changes 12 hours postexposure. Histological examination of the skin showed a necrotized epidermis 6–72 hours postexposure and complete re-epithelialization 1 week postexposure. In all layers of the dermis, degeneration of the vascular wall, which progressed to necrosis and hemorrhaging, was observed. The severity of the epidermal and dermal damage was exposure duration-related.

No studies were located regarding dermal or ocular effects following systemic absorption of bromomethane in animals or humans. No microscopic lesions were noted in the skin of beagle dogs exposed to bromomethane in the diet (up to 0.28 mg/kg/day) for 52 weeks (Wilson et al. 2000).

2.12 OCULAR

Bromomethane vapor is irritating to the eyes, and humans who are exposed to bromomethane in air may experience conjunctivitis, erythema, rashes, edema of the eyelids, exfoliation, lesions, or even blisters (Langard et al. 1996; O'Neal 1987; Prain and Smith 1952; Wyers 1945). However, eye irritation has not been observed in animals exposed to bromomethane vapor or dietary bromomethane. Ophthalmoscopic examination did not reveal alterations in dogs exposed to 102.7 ppm bromomethane for 5 weeks (EPA 2001b). In beagle dogs given bromomethane in feed at doses up to 0.28 mg/kg/day for 52 weeks, there were no effects on ophthalmology or histopathology of eyes (with optic nerves) (Wilson et al. 2000). No alterations were noted in the ophthalmoscopic examination in male and female rats exposed to up to 11.1 and 15.12 mg/kg/day, respectively, in the diet for 2 years (EPA 1999).

2.13 ENDOCRINE

A cohort study evaluated potential associations between occupational pesticide exposure and subclinical hypothyroidism in 679 male pesticide workers residing in Iowa and North Carolina (Lerro et al. 2018). Exposures to pesticides were self-reported, with exposures reported as “intensity-weighted days;” however, no quantitative estimates of exposure were reported. It is likely that workers were exposed to multiple chemicals, although this was not explicitly stated in the study report; results were not adjusted for multiple exposures. The risk of subclinical hypothyroidism was not increased in bromomethane

workers, with an odds ratio (OR) of 0.45 (95% confidence interval [CI] 0.11, 1.81) for the highest intensity exposure. No additional information regarding potential endocrine effects of bromomethane in humans was identified.

In rats, histological alterations consisting of microvacuolation of spongiocytes were noted in the adrenal cortex following exposure to 175 or 250 ppm bromomethane for 4–5 days (Hurtt et al. 1987); at 350 ppm, lipid droplet accumulation in the parenchymal cells and intrasinusoidal accumulation of erythrocytes were observed. Minimal to slight intracytoplasmic vacuoles were also observed in the zona fasciculata of the adrenal glands in dogs exposed to 11.0 ppm for 5 weeks and 159 ppm for 5 days, but not in dogs exposed to 102.7 ppm for 5 weeks (EPA 2001b).

Exposure of rats to bromomethane in feed at 7.98 mg/kg/day for 4 weeks (EPA 1996) or of beagle dogs to 0.28 mg/kg/day bromomethane in feed for 1 year did not result in endocrine changes (as measured by weight of thyroid and parathyroid and histopathology of thyroid, parathyroid, adrenal glands, pancreas, and pituitary gland) (EPA 1996; Wilson et al. 2000).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation or oral exposure to bromomethane. Data from animal studies are limited to inhalation exposure. Eustis et al. (1988) reported thymus necrosis and atrophy in rats and mice exposed to 160 ppm for 6 or 2 weeks, respectively; splenic lymphoid depletion was also observed in mice. In a study submitted to EPA, no alterations in sheep red blood cell antibody formation were observed in rats exposed to concentrations as high as 120 ppm for 28 days (EPA 2011).

2.15 NEUROLOGICAL

Adverse effects on the neurological system occur following inhalation exposure of humans and animals; however, there is no evidence of neurological toxicity following oral exposure of animals. Inhalation exposure to bromomethane frequently leads to a spectrum of neurological effects in humans. Initial symptoms typically include headache, dizziness, nausea/vomiting, confusion, weakness, numbness, slurred speech, and visual disturbances (Akca et al. 2009; Anger et al. 1986; Deschamps and Turpin 1996; Herzstein and Cullen 1990; Hine 1969; Hustinx et al. 1993; Johnstone 1945; Kantarjian and Shaheen 1963; Kulkarni et al. 2015; Marraccini et al. 1983; O’Neal 1987; Prain and Smith 1952; Rathus and

Landy 1961; Watrous 1942). Other effects that can develop include slurred speech, lack of inhibition, agitation, and confusion (Bishop 1992; Greenberg 1971; Hustinx et al. 1993; Johnstone 1945; Kulkarni et al. 2015; O'Neal 1987; Prain and Smith 1952). In severe cases, these effects may progress to ataxia, tremor, seizures, and coma (Balagopal et al. 2011; Behrens and Dukes 1986; Bishop 1992; de Souza et al. 2013; Deschamps and Turpin 1996; Geyer et al. 2005; Greenberg 1971; Hustinx et al. 1993; Johnstone 1945; Kulkarni et al. 2015; Longley and Jones 1965; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Prockop and Smith 1986; Rathus and Landy 1961; Viner 1945; Wyers 1945; Yamano and Nakadate 2006; Yamano et al. 2001). In most cases of acute exposure, the effects did not occur immediately, but developed after a lag of several hours (Clarke et al. 1945); some cases have reported effects developing several weeks after exposure (Herzstein and Cullen 1990). If death does not ensue, symptoms usually decrease in severity over the course of several weeks to several months post-exposure, although frequently, they do not disappear completely (Bishop 1992; Chavez et al. 1985; de Souza et al. 2013; Greenberg 1971; Hine 1969; Johnstone 1945; Kantarjian and Shaheen 1963; Longley and Jones 1965; Prockop and Smith 1986). A study of fumigators involved in fumigation jobs using sulfuryl fluoride or bromomethane for at least 6 months did not find significant alterations in nerve conduction velocity tests or neurobehavioral tests among workers with high bromomethane exposure, as compared to a referent group (Calvert et al. 1998a); exposure levels were not reported. Because there were only 28 workers with high bromomethane exposure, the statistical power of this study was fairly low.

Quantitative data on the exposure levels leading to neurological effects in humans are limited. A single exposure study reported neurological effects in workers exposed to 4,400 ppm bromomethane for approximately 1 hour (Deschamps and Turpin 1996); although the workers wore respirators, the bromomethane saturated the respirator cartridge within a few minutes. Early studies indicated that workplace exposure to concentrations of 100–500 ppm could lead to visual disturbances, speech disturbances, mental confusion, and numbness of extremities (Johnstone 1945) and exposure to <35 ppm resulted in headache, nausea/vomiting, numbness, and vertigo (Watrous 1942). Anger et al. (1986) reported an increased incidence of neurological symptoms (muscle ache, muscle fatigue) and poorer performance on tests of memory and finger sensitivity in a group of fumigators who used bromomethane for at least 1 year. Although the study authors estimated an exposure level of 2.3 ppm, exposure levels were not determined for these workers; the value of 2.3 ppm was taken from personal monitoring data collected in different populations of fumigators. The study authors estimated exposures to be 2.3 ppm for field fumigators and 169 ppm for study structural fumigators; however, actual exposures in this study are unknown. Therefore, the outcomes observed cannot quantitatively be related to exposure levels. In addition, several confounding issues complicate interpretation of study results: (1) workers were also

exposed to sulfuryl fluoride and chloropicrin; (2) the control group was comprised of workers who were more sedentary than fumigators; (3) it was not clear how many workers were involved in structural fumigation versus field fumigation; (4) several demographic differences were noted between groups, including racial/ethnic mix, physical demands of job-related activities, and self-reported alcohol consumption, prescription drug use, and illegal drug use; and (5) workers self-selected for participation in the study. It is noted that the study accounted for potential confounders by dividing workers into separate groups based on the percentage of time they used bromomethane or sulfuryl fluoride and statistical adjustments were made for some variables including age, alcohol consumption, and race.

Two studies evaluated potential associations between neurodevelopment in children and exposure to bromomethane. A longitudinal birth cohort study examined the relationship between residential proximity to four agricultural fumigants (bromomethane, chloropicrin, metam sodium, and 1,3-dichloropropene) and IQ and behavior in 285 children at age 7 years (Gunier et al. 2017). Participants lived in the Salinas Valley, California, and lived within 8 km of fumigant use. Quantitative estimates of exposure were not reported. In children residing in the area from birth to age 7 years, a 10-fold increase in bromomethane use was associated with a 2.6-point decrease (95% CI: -5.2, 0.0) in Full-Scale IQ. No association was observed between bromomethane exposure and attention problems or hyperactivity, as assessed by both parents and teachers. A population-based, case-control study examining associations between prenatal and infant exposure to pesticides and autism spectrum disorder in children did not find an association for bromomethane (von Ehrenstein et al. 2019). The study was conducted in 2,961 children with a diagnosis of autism spectrum disorder, identified through records from the California Department of Developmental Services. Exposure data were obtained from the data from the California state mandated Pesticide Use Report. Participants were considered as exposed based on proximity to pesticide application. No quantitative exposure estimates were reported. ORs (95% Cis) for autism spectrum disorder during pregnancy and the first year of life were 1.12 (0.88, 1.42) and 1.09 (0.86, 1.39), respectively.

Inhalation studies in animals confirm that the central nervous system is a sensitive target of bromomethane toxicity; the effects include alterations in neurotransmitter levels, impaired performance on neurobehavioral tests, overt signs of toxicity, and histological lesions. A series of studies conducted by Honma and associates measured neurotransmitter levels in a number of sections of the brains of rats following a single 8-hour exposure (Honma 1987; Honma et al. 1987) or 3-week continuous exposure (Honma et al. 1982). An 8-hour exposure to 31 ppm resulted in significant decreases in norepinephrine levels in the hypothalamus (Honma 1987; Honma et al. 1987); at 100 ppm, decreases in dopamine and

serotonin were observed in the striatum, and norepinephrine levels were decreased in the striatum, hypothalamus, frontal cortex, and midbrain. Continuous exposure to 10 ppm for 3 weeks also resulted in decreases in norepinephrine levels in the hypothalamus (Honma et al. 1982).

Several studies have reported alterations in neurological function in rats, mice, and rabbits exposed for acute, intermediate, and chronic durations. An 8-hour exposure to bromomethane resulted in decreased locomotor activity at 188 ppm, decreased body temperature at 125 ppm, and increased sleep potency of thiopental at 63 ppm (Honma et al. 1985). In rats exposed to 350 ppm for 6 hours, a decrease in motor activity and a number of alterations in performance on functional observational battery (FOB) tests were observed; FOB alterations included inactivity, decreased rearing, uncoordinated righting response, and decreased hindlimb grip strength (EPA 1993). These alterations were observed 1-day post-exposure, but were not observed 8 or 15 days post-exposure. Intermediate- and chronic-duration studies reported alterations in performance on neurobehavioral performance tests (NTP 1992). The observed effects included decreases in locomotor activity, increases in hotplate latency, decreases in startle response latency and amplitude, decreases in forelimb grip strength, increases in hindlimb grip strength, and impaired performance on the rotarod test (Ikeda et al. 1980; NTP 1992). NTP (1992) classified the severity of neurobehavioral effects as mild. Of these effects, exposure-related decreases in locomotor activity was the most sensitive effect, with a LOAEL value of 10 ppm in male and female mice exposed for 6 months and in female mice exposed for 9 months; a NOAEL was not identified (NTP 1992). Decreased locomotor activity was observed in female rats exposed to 70 ppm for 13 weeks, with a NOAEL of 30 ppm; at week 13, total cumulative movements were significantly decreased by 37 and 34% at exposures of 70 and 140 ppm, respectively. EPA (1994a) noted that the largest decreases in locomotor activity were observed during the first half of the 90-minute testing session, but that no statistically significant differences were observed when epoch data were compared. In males, convulsions with death, altered FOB tests (increased landing foot splay and incidence of uncoordinated righting), and histopathological alterations in the brain (vacuolization, axonal degeneration, and necrosis) accompanied by convulsions and death were observed at 140 ppm, with a NOAEL of 70 ppm (EPA 1994a). A study in rabbits also found decreases in sciatic and ulnar nerve conduction velocity and decreases in eye blink reflex following a 4-week exposure to 65 ppm (Anger et al. 1981); no alterations in nerve conduction velocity were observed in rats similarly exposed to 65 ppm for 4 weeks or to 55 ppm for 36 weeks (Anger et al. 1981) or in rabbits exposed to 27 ppm for 8 months (Russo et al. 1984). A 6-week dog study (EPA 2002) did not find alterations in performance on FOB tests or locomotor activity.

Numerous studies have reported overt signs of neurotoxicity in rats, mice, dogs, rabbits, and monkeys following acute, intermediate, or chronic exposure to bromomethane. Commonly reported effects included decreased locomotor activity, abnormal gait, tremors, paralysis, convulsions, delirium, and limb crossing and twitching (Alexeeff et al. 1985; Breslin et al. 1990; EPA 1988a, 2001a; Eustis et al. 1988; Hurtt et al. 1987; Irish et al. 1940; NTP 1992). The lowest LOAELs for overt signs of neurotoxicity in mice following acute-, intermediate-, and chronic-duration exposure were 12 ppm (NTP 1992), 53.1 ppm (EPA 2001b), and 33 ppm (NTP 1992), respectively. Although 12 ppm was identified as a LOAEL for neurological signs in mice following acute exposure, there is some uncertainty due to the vague reporting of the clinical signs; NTP (1992) reported that trembling, jumpiness, and paralysis were observed in all groups and that the effects were most pronounced at ≥50 ppm. However, no incidence data were provided and it is not known if all of these effects were observed at all bromomethane concentrations. Neurological signs (lack of interest when approached, considered to be decreased activity) were observed in 2/8 dogs exposed to 53.1 ppm 7 hours/day, 5 days/week for 5 weeks, with more rapidly appearing and severe neurological effects (tremor) at 103 ppm (Newton et al. 1994a, 1994b [MRID 443386801 and 443386802, respectively], as cited in EPA 2001b). After lower and longer exposures of 5 ppm for 34 exposures over 7 weeks, during a neurological examination, 2/8 female dogs were unresponsive and motionless and another dog appeared depressed, no effects were noted in the remaining six dogs exposed to 5.3 ppm for 7 weeks. Following the same protocol using 11 ppm exposures for 7 weeks and then increasing to 158 ppm resulted in rapid onset of severe neurological effects (two exposures produced decreased activity; six exposures resulted in tremors, prostration, ataxia, intention tremor, nystagmus, marked depression, opisthotonus, paddling gait of all limbs, vacuolization of the cerebellar granular layer in 8/8 dogs, olfactory epithelial degeneration in 8/8 dogs, and intracytoplasmic vacuolization of the adrenals in 4/4 dogs) (EPA 2001b). In a subsequent study, no overt signs of neurotoxicity were observed in eight dogs exposed to 20 ppm for 6 weeks (EPA 2002). Histological examinations of the brain found cerebellar degeneration in rats exposed to 250 ppm for 5 days (Hurtt et al. 1987), neuronal necrosis in the cerebrum and cerebellum in mice exposed to 160 ppm for 2 weeks and in rats exposed to 160 ppm for 2.5 weeks (Eustis et al. 1988), edema, congestion/hyperemia, and necrosis in the cortex in rats exposed to 400 ppm for 6 weeks (Kato et al. 1986), vacuoles in the granular layer of the cerebellum of dogs exposed to 11.0 ppm for 5 weeks followed by 158 ppm for 5 days (EPA 2001b), and cerebellar and cerebral degeneration in rats exposed to 325 ppm for 4 days (Hurtt et al. 1987) and in mice exposed to 100 ppm for 20 weeks and allowed to recover for the remaining duration of the 2-year study (NTP 1992). The histological alterations observed in the intermediate-duration studies occurred at or near lethal concentrations. In chronic-duration studies, slight atrophy in the cerebellum was observed in mice

exposed to 64 ppm for 2 years (nonlethal concentration) (Gotoh et al. 1994), but not in rats exposed to 89.1 or 100 ppm (Gotoh et al. 1994; Reuzel et al. 1987, 1991).

A developmental study in rats indicates that bromomethane produces neurotoxicity in offspring (Beck 2004 [MRID 46665001], as cited in EPA 2019b). Dams were exposed to 0, 5, 25, or 50 ppm bromomethane on gestation days 6–20 and again on lactation days 5–20; neurotoxicity assessments (FOB testing, acoustic startle response, locomotor activity, and learning and memory testing) were conducted in offspring on postnatal days 21, 26, 62, and 72. The only adverse neurological effects observed were decreases in total and ambulatory activities in the 25 and 50 ppm exposure group on postnatal day 21. EPA (2019b) noted that these decreases did not reach statistical significance, possibly due to high variability in the data. In the 25 ppm group, total and ambulatory activities were reduced 26 and 31% from control values, respectively. In the 50 ppm group, total and ambulatory activities were 40 and 45% from control values, respectively. EPA (2019b) noted that these reductions were not statistically significant, reportedly due to large variability in the data.

Several studies have also examined the effect of bromomethane on the olfactory system. As discussed in Section 2.4 (Respiratory), exposure to bromomethane can result in significant damage to the nasal olfactory epithelium. Bromomethane exposure can also result in damage to the neurons in the olfactory bulb; a 6-hour exposure to 330 ppm bromomethane resulted in death of 90–98% of the neurons (Schwob et al. 1999; Youngentob and Schwob 2006). As with the nasal olfactory epithelium, damage to the olfactory bulb was repaired. Glial cell proliferation was observed 1 day post-exposure and new olfactory neurons appeared by post-exposure day 3; at 6–8 weeks post-exposure, the population of reinnervated fibers was similar to controls (Schwob et al. 1999). Damage to the olfactory epithelium and neurons in the olfactory bulb resulted in severe impairment of olfaction in rats exposed to 200 ppm for 4 hours (Hastings et al. 1991) and rats exposed to 330 ppm for 6 hours (Youngentob and Schwob 2006). Although there was continued exposure in the Hastings et al. (1991) study, olfactory performance improved and was similar to controls by exposure day 4; the investigators noted that the recovery of olfactory function did not appear to be correlated with regeneration of the olfactory epithelium, which occurred at a much slower rate. Youngentob and Schwob (2006) showed that rats were still able to perceive odors (rats were able to correctly identify 45% of the odors compared to 20% chance performance), but there was a significant shift in odor quality perception, which was not correlated with a decrease in identification performance. These results suggest that a few neurons for some odor receptors are retained, allowing the animal to identify an odor, whereas some odor receptors may be completely eliminated. The study also found that there was a large degree of variation in the location of the damaged

tissue between individual rats and that there was a significant relationship between individual odorant identification performance and the extent and location of the damaged tissue. In a study examining the recovery of olfactory neurons after bromomethane damage in mice exposed for 8 hours to 180 ppm, regenerated olfactory sensory neurons remained functionally impaired when observed 3 months later, because the innervation of the olfactory bulb by regenerated P2 olfactory sensory neurons was erroneous (Holbrook et al. 2014). Instead of one receptor innervating one glomerulus (as in normal epithelium), several P2 axons innervated multiple glomeruli, and these axons were not believed to be synaptically connected to the glomeruli (Holbrook et al. 2014).

An oral dietary study that exposed rats to 7.98 mg/kg/day bromomethane for 4 weeks reported no neurological effects based on brain weight and pathological assessment of the brain, peripheral nerves, spinal cord, pituitary, and optic nerve (EPA 1996).

Several mechanisms have been proposed to explain the neurotoxicity of bromomethane. One possible mechanism involves binding to proteins involved in oxidative reactions and energy production (reviewed by de Souza et al. 2013). Humans exposed to high levels of bromomethane exhibit MRI abnormalities that are characteristic of energy deprivation syndrome (e.g., de Souza et al. 2013; Geyer et al. 2005); the alterations included T2 signal abnormalities and fluid-attenuated inversion recovery sequences in the cerebellar dentate nuclei, periaqueductal region, dorsal midbrain and pons, and inferior olives symmetrically. These abnormalities consist of strikingly symmetric changes in the periventricular, cerebellar, and brainstem areas of the brain, locations that are particularly susceptible to damage from energy deprivation (reviewed by de Souza et al. 2013). In addition, several metabolites of bromomethane, including methanethiol and formaldehyde, are highly reactive compounds capable of inhibiting cellular respiration (reviewed by de Souza et al. 2013). Bromomethane has also been shown to rapidly inhibit creatine kinase in the brain (Hyakudo et al. 2001). Creatine kinase maintains cellular energy homeostasis by catalyzing the conversion of creatine and ATP to phosphocreatine and ADP (reviewed by de Souza et al. 2013). Inhibition of tyrosine hydroxylase activity by bromomethane may be the mechanism by which the dopaminergic system is perturbed (reviewed by de Souza et al. 2013). Furthermore, S-methylcysteine formed during the metabolism of bromomethane is structurally analogous to the neurotransmitter γ-amino butyric acid, and has been shown to exert neurotoxic effects on the rat hippocampus (reviewed by Bulathsinghala and Shaw 2014).

Glutathione depletion induced by bromomethane could also contribute to neurotoxicity. Lower glutathione levels and reduced glutathione-S-transferase activity were observed in the brains of rats

exposed to bromomethane by inhalation for 5 days (Davenport et al. 1992). Under conditions of acute-duration, high-level exposures, however, glutathione appears to detoxify bromomethane. For example, when glutathione levels were depleted with buthionine sulfoximine prior to exposing rats to bromomethane, an increase in toxicity was observed (reviewed by WHO 1995). In addition, Tanaka et al. (1988) observed an alleviation of bromomethane effects on sleep and wakefulness as well as an increase in the subcutaneous LD_{50} of bromomethane when rats were pretreated with glutathione. Further, humans with a congenital deficiency in glutathione transferase suffered more severe effects of bromomethane exposure, further supporting a detoxifying action of glutathione conjugation under conditions of acute exposure (reviewed by de Souza et al. 2013).

Bromomethane also alters neurotransmitter levels in the brain. Reduced levels of dopamine and norepinephrine were observed in the brains of rats after exposure to bromomethane (Honma et al. 1987). In addition, tyrosine hydroxylase activity was inhibited by exposure to bromomethane (Honma 1987). Inhibition of tyrosine hydroxylase activity by bromomethane may be the mechanism by which the dopaminergic system is perturbed (reviewed by de Souza et al. 2013). Furthermore, S-methylcysteine formed during the metabolism of bromomethane is structurally analogous to the neurotransmitter, γ-amino butyric acid, and has been shown to exert neurotoxic effects on the rat hippocampus (reviewed by Bulathsinghala and Shaw 2014).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects of bromomethane in humans after inhalation or oral exposure, or in animals following oral exposure. In male animals, effects on the testes (delayed spermiation, minimal tubular degeneration, atrophy) have been observed in rats and mice exposed to 160–405 ppm for 1–6 weeks (Eustis et al. 1988; Hurtt et al. 1987; Kato et al. 1986) and decreases in sperm density were observed in mice exposed to 120 ppm for 13 weeks (EPA 1988a). However, exposure of male rats to 70 ppm for 5 days did not interfere with normal reproductive function and impregnation success (NIOSH 1981), and no histopathological alterations were observed in male rats exposed to 200 ppm for 5 days (Hurtt and Working 1988). No effects on reproductive function in females have been observed in rats or rabbits exposed to levels up to 70 ppm before and during gestation (NIOSH 1980), even though these levels produced maternal toxicity. No histological alterations were observed in reproductive tissues of dogs exposed to ≤102.7 ppm for 5 weeks (EPA 2001b). No organ weight or histological changes in reproductive tissues of rats were observed following dietary exposure to 7.99 mg/kg/day for 4 weeks (EPA 1996).

2.17 DEVELOPMENTAL

One epidemiology study evaluated the potential association between residential proximity to bromomethane application and developmental outcomes (Gemmill et al. 2013). Moderate or high bromomethane use during the second trimester was inversely associated with birth weight (not significant in moderate use group), birth length, and head circumference (not significant in high use group). These associations were found in women living within a 3-, 5-, or 8-km radius from the source. Two additional epidemiology studies in children examining neurodevelopmental outcomes are reviewed in Section 2.15 (Neurological).

An inhalation developmental study in rats reported slight, but statistically significant, delays in sexual maturation (Beck 2004 [MRID 46665001], as cited in EPA 2019b). In offspring of dams exposed to 50 ppm bromomethane for 6 hours/day on gestation days 6–20 and lactational days 5–20, preputial separation and vaginal opening were delayed by 1.4 and 1.6 days, respectively. No effects were observed following exposure to 5 ppm. Increased incidences of a malformation (gallbladder agenesis) and a minor variation (fused sternebrae) and decreased fetal body weights were observed in offspring from rabbits exposed to 80 ppm during gestation (Breslin et al. 1990); marked maternal toxicity (lethargy, ataxia, lateral recumbency, and decreased body weight) were also observed at this exposure level and the observed developmental effects may have been secondary to the maternal toxicity. No decreased weights were observed in F0 generation females or in F1 generation pups in a multigeneration study in rats exposed up to 90 ppm, but a 21% non-dose-related reduction was reported for F2 generation female pups exposed to either 30 or 90 ppm, and pup weight was decreased in F2 generation males exposed to 90 ppm (Mayhew et al. 1986, as cited in EPA 1986a). In contrast, studies in rats and rabbits indicate that inhalation exposure to levels up to 70 or 20 ppm, respectively, for 7 hours/day during gestation does not result in any statistically significant developmental effects, (Hardin et al. 1981; Sikov et al. 1980, as summarized in NIOSH 1980). For rabbits, inhalation exposure up to 20 ppm for 15 days also produced no developmental effects; however, developmental toxicity could not be assessed in the 70 ppm group due to extreme maternal mortality starting on gestation day 15 (Hardin et al. 1981).

Developmental toxicity was assessed in rats and rabbits administered bromomethane via gavage in corn oil on gestation days 6–15 or 6–18, respectively (Kaneda et al. 1998). No significant alterations in resorptions or fetal deaths, number of live fetuses, sex ratio, or fetal body weights were observed in rats exposed to ≤30 mg/kg/day or rabbits exposed to ≤10 mg/kg/day. An increase in fetuses having

25 presacral vertebrae was observed in rats exposed to 30 mg/kg/day; however, there were no significant differences in the number of litters with this variation and it was not considered exposure-related. No alterations in the occurrence of external, visceral, or skeletal malformations or variations were observed in the rabbits.

2.18 CANCER

The U.S. Department of Health and Human Services (NTP 2016) has not categorized the carcinogenicity of bromomethane. IARC (2016) classified bromomethane as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). EPA (IRIS 2002) has determined that bromomethane is classified as a Group D carcinogen (not classifiable as to human carcinogenicity).

The carcinogenic potential of bromomethane has not been formally investigated in epidemiological studies of occupationally-exposed workers; however, some information is available from epidemiological studies. Wong et al. (1984) studied the incidence of cancer in a cohort of workers exposed to a wide variety of brominated chemicals, and noted that two men who died of testicular cancer had both been exposed to organic bromides, including bromomethane. However, since there are numerous risk factors for testicular cancer, and since the workers may have been exposed to other chemicals, this observation is not sufficient to indicate that bromomethane is carcinogenic. Several studies have evaluated the potential association between bromomethane and increased risk of prostate cancer. Utilizing the Agricultural Health Study cohort of male pesticide applicators, Alavanja et al. (2003) found elevated ORs for prostate cancer (adjusted for age and family history of prostate cancer) among applicators with the two highest cumulative exposure quintiles for bromomethane (OR 2.73, 95% CI 1.18–6.33 and OR 3.47, 95% CI 1.37–8.76, respectively). A nested case-control study of predominantly Hispanic farm workers did not find an association between bromomethane exposure and prostate cancer (Mills and Yang 2003). For the highest estimated exposure quartile (estimate not reported), the OR was 1.59 (95% CI 0.77–3.30); no trend was observed over increasing exposure quartiles (p=0.25). A second case control study examined residents in California's Central Valley and assessed potential exposure to bromomethane using pesticide use near the subject's residence (Cockburn et al. 2011). An increase in the risk of prostate cancer was observed among exposed residents (OR 1.62; 95% CI 1.02–2.59). However, when the cases were categorized based on low and high exposure, no significant differences were found between the two groups (p=0.10). In a follow-up study of the Agricultural Health Study cohort, no significant association between increasing bromomethane exposure and increasing risk of prostate cancer was found (Barry et al. 2012); the relative risk (RR) for workers with the highest intensity weight lifetime days of exposure was

0.99 (95% CI 0.72–1.36). However, there was a nonsignificant increase in the relative risk among bromomethane applicators with a family history of prostate cancer (RR 1.46, 95% CI 0.97–2.20). The Barry et al. (2012) study found an increased risk of stomach cancer among applicators with high bromomethane use (RR 3.13; 95% CI 1.25–7.80; RR 3.33, 95% CI 1.30–8.51 with a 15-year lag), as compared to applicators with no use of bromomethane. A nested case-control study of Hispanic agricultural workers did not find an association between ever using bromomethane and gastric cancer (OR 1.01; 95% CI 0.57–1.74) (Mills and Yang 2007). However, among workers with the highest potential exposure, there was an increased risk (OR 2.38; 95% CI 1.06–5.37) when compared to workers with the lowest risk, but not with workers with no bromomethane exposure (OR 1.33; 95% CI 0.67–2.67). Although these occupational studies provide some suggestive associations between increased cancer risk and exposure to bromomethane, the studies are inadequate for establishing causality; none of the studies measured actual bromomethane exposure levels and workers were likely exposed to multiple pesticides.

The potential carcinogenesis of bromomethane has been evaluated in laboratory animals following inhalation and oral exposure. No evidence of carcinogenic effects was detected in mice exposed to 33 ppm for 2 years (NTP 1992), in mice exposed to 100 ppm for 20 weeks and allowed to recover for the remainder of the 2-year study (NTP 1992), or in rats exposed to 89.1 ppm for 29 months (Reuzel et al. 1987, 1991). No tumors were identified in beagle dogs exposed to bromomethane in feed for 1 year (Wilson et al. 2000). Danse et al. (1984) reported an increased incidence of forestomach lesions, which were interpreted as squamous cell carcinomas, in rats administered 50 mg/kg bromomethane via gavage 5 days/week for 13 weeks. However, histological diagnosis of epithelial carcinomas in the presence of marked hyperplasia is difficult (Wester and Kroes 1988). After reevaluation of the histological slides, a panel of scientists from the National Toxicology Program (NTP) concluded that there was no evidence of a neoplastic response in this study, but rather only hyperplasia and inflammation (IRIS 2002). This is consistent with the observation that the hyperplasia of the forestomach produced by 13 weeks of exposure to bromomethane regressed when exposure ended (Boorman et al. 1986). Longer-term (25 weeks) oral exposure of rats to 50 mg/kg/day of bromomethane led to a severely dysplastic and hypermetabolic forestomach lesion in 1 rat (out of 15 exposed) that was judged to be a very early carcinoma; however, the regression of hyperplasia after exposure ended argued against the carcinogenic potential of bromomethane.

2.19 GENOTOXICITY

Bromomethane has produced positive results in a number of mutagenicity test systems, both *in vitro* (Table 2-3) and *in vivo* (Table 2-4). This effect does not appear to require metabolic activation, which is consistent with the fact the bromomethane is a direct-acting alkylating agent that can methylate DNA (Ikawa et al. 1986; Starratt and Bond 1988). This property suggests that bromomethane might be carcinogenic, but this has not been established.

Table 2-3. Genotoxicity of Bromomethane *In Vitro*

Species (test system)	Endpoint	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Escherichia coli Sd-4	Gene mutation	No data	+	Djalali-Behzad et al. 1981
E. coli WP2 her (gene reversion)	Gene mutation	+	+	Moriya et al. 1983
Salmonella typhimurium (TA100, TA1535) (gene reversion)	Gene mutation	+	+	Moriya et al. 1983
S. typhimurium (TA98, TA1537, TA1538) (gene reversion)	Gene mutation	–	–	Moriya et al. 1983
S. typhimurium (TA100) (desiccator system)	Gene mutation	No data	–	Simmon and Tardiff 1978
S. typhimurium (TA100) (desiccator system)	Gene mutation	+	+	NTP 1992
S. typhimurium (TA98) (plate test)	Gene mutation	–	–	Kramers et al. 1985
S. typhimurium (TA100) (plate test)	Gene mutation	+	+	Kramers et al. 1985
Klebsiella pneumonia (ur^- pro^-) (fluctuation test)	Gene mutation	No data	+	Kramers et al. 1985
Eukaryotic organisms:				
Mouse lymphoma cells (L5178YTK+/-) (forward mutation)	Gene mutation	No data	+	Kramers et al. 1985
Syrian hamster embryo cells	Enhanced transformation by Sa7 adenovirus	No data	–	Hatch et al. 1983

Table 2-3. Genotoxicity of Bromomethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Human peripheral lymphocytes	Sister chromatid exchanges	No data	+	Tucker et al. 1986
Rat liver cells	Unscheduled DNA synthesis	No data	–	Kramers et al. 1985
Human embryonic intestinal cells	Unscheduled DNA synthesis	–	–	NIOSH 1981

– = negative result; ± = weakly positive; DNA = deoxyribonucleic acid

Table 2-4. Genotoxicity of Bromomethane *In Vivo*

Species (test system)	Endpoint	Results	Reference
Nonmammals			
Drosophila melanogaster Berlin-K wild type (sex linked recessive lethal test)	Gene mutation	+	Kramers et al. 1985
D. melanogaster (somatic wing spot assay)	Recombinogenic activity	+	Katz 1987
D. melanogaster Oregon-K wild type (sex-linked recessive lethal test)	Gene mutation	–	NIOSH 1981
Mammals			
Human (lymphocytes)	Gene (*hprt*) mutation	–	Calvert et al. 1998b
Human (lymphocytes)	Kinetochore-negative micronuclei induction	–	Calvert et al. 1998b
Human (lymphocytes)	Kinetochore-positive micronuclei induction	–	Calvert et al. 1998b
Human (oropharyngeal cells)	Micronuclei inductions	+	Calvert et al. 1998b
Sprague-Dawley rat (bone marrow cells)	Chromosomal aberrations	−	NIOSH 1981
B6C3F1 mouse (bone marrow cells)	Sister chromatid exchange	+	NTP 1992
Sprague-Dawley rat	Dominant lethal	–	NIOSH 1981
B6C3F1 mouse	Sperm abnormality	−	NIOSH 1981
F344 rat (testes)	DNA alkylation	+	MRID4318201, as cited in EPA 2018a
CBA mouse (liver and spleen cells)	DNA alkylation	+	Djalali-Behzad et al. 1981
F344 rats (liver, lung, stomach, and forestomach)	DNA adduct formation	+	Gansewendt et al. 1991
F344 rat (bone marrow cells)	Micronuclei inductions	+	Ikawa et al. 1986

Table 2-4. Genotoxicity of Bromomethane *In Vivo*

Species (test system)	Endpoint	Results	Reference
BDF_1 mouse (bone marrow cells)	Micronuclei inductions	+	Ikawa et al. 1986
B6C3F1 mouse (peripheral erythrocytes)	Micronuclei inductions	+	NTP 1992

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

The *in vivo* genotoxicity of bromomethane was evaluated in bromomethane fumigation workers (Calvert et al. 1998b). Increases in micronuclei were observed in oropharyngeal cells (p=0.08). Increases in kinetochore-positive micronucleated lymphocytes (p=0.06 in smokers and 0.08 in nonsmokers) were found, but this association was not found when workers were divided into two groups based on the number of hours since recent bromomethane exposure. No alterations in lymphocyte hrpt Vf formation were observed (p=0.73). In animals, the frequency of bone marrow cells with chromosomal aberrations was not increased in rats exposed to 70 ppm for 5 days (NIOSH 1981), but was increased several-fold in rats exposed to 140 ppm for 14 days (Ikawa et al. 1986). Inhalation exposure of rats to 250 ppm bromomethane 6 hours/day for 5 days resulted in DNA alkylation in testicular cells; mortality and neurotoxicity were also observed at this exposure level (MRID4318201, as cited in EPA 2018a). Djalali-Behzad et al. (1981) found that inhalation exposure of mice to bromomethane for 4 hours led to alkylation of DNA in liver and spleen, although the levels were quite low. In contrast to these positive findings, no genotoxic effects could be detected in sperm from rats or mice exposed to 70 ppm bromomethane for 5 days, using either the dominant lethal or recessive lethal tests, or by direct examination of the sperm (NIOSH 1981). These studies indicate that bromomethane does have genotoxic potential, but that effects may be minimal and difficult to measure following brief or low dose exposure.

Additionally, inhalation and oral studies in rats (Gansewendt et al. 1991) and inhalation and intraperitoneal studies in mice (Djalali-Behzad et al. 1981) demonstrate that bromomethane is an alkylating agent resulting in the formation of DNA adducts: 3-methyl-adenine, 7-methyl-guanine, and O^6-methyl-guanine. In the rats, the methylated guanines were preferentially found in the stomach and forestomach following inhalation or oral exposure.

2.20 MECHANISMS OF TOXICITY

Several mechanisms have been proposed regarding the neurotoxicity of bromomethane; these are discussed in Section 2.15.

Little information is available regarding the mechanisms of toxicity for bromomethane. However, general cellular mechanisms may play a role in the toxicity of bromomethane. Bromomethane may be directly toxic to cells via its ability to bind lipids and proteins (reviewed by de Souza et al. 2013). In addition, bromomethane has been shown to deplete glutathione in several tissues (reviewed by WHO 1995). In rats exposed to bromomethane by inhalation, increased glutathione-S-transferase activity was observed in the lungs (Jaskot et al. 1988).

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

3.1 TOXICOKINETICS

- Absorption:
  - Respiratory tract: Bromomethane is well absorbed from the respiratory tract. A small study in humans estimated that approximately 52–55% of the inhaled dose was absorbed. Studies in animals estimate a fractional absorption from the respiratory tract of 27–48%.
  - Gastrointestinal tract: The estimated fractional absorption of oral bromomethane in a single study in rats was ≥97%.
  - Dermal: Bromomethane is absorbed following dermal exposure, although quantitative estimates of absorption were not identified.

- Distribution: Based on inhalation exposure studies in laboratory animals, bromomethane undergoes wide distribution throughout the body, including the central nervous system.

- Metabolism: Bromomethane undergoes extensive metabolism. Metabolites include bromide ion, methanol (which can be further metabolized to formaldehyde, formate, and carbon dioxide), S-methyl derivatives, and glutathione conjugates.

- Excretion: Excretion of bromomethane occurs mainly by expiration of carbon dioxide or by urinary excretion of nonvolatile metabolites (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Small amounts of bromomethane undergo biliary excretion and are excreted in the feces.

3.1.1 Absorption

In a small human study, bromomethane uptake was 55.4% and 52.1% when the subjects inhaled 0.018 ppm bromomethane through the nose or mouth, respectively (ARB 1988). A study in nine fumigators accidentally exposed to bromomethane found elevated serum bromide levels 4 hours after exposure (Hustinx et al. 1993). Studies in rats suggest that exposure to airborne bromomethane is rapidly absorbed and distributed (Andersen et al. 1980; Bond et al. 1985; Gargas and Andersen 1982; Jaskot et al. 1988; Medinsky et al. 1985). Andersen et al. (1980) and Gargas and Andersen (1982) suggested that bromomethane absorption followed a rapid first-order uptake kinetics with no measurable saturable kinetics based on studies in rats exposed to 100–10,000 ppm bromomethane for 2 hours. Gas uptake

constants of 0.44 $(kg\text{-}hour)^{-1}$ (Andersen et al. 1980) and 0.55 $(kg\text{-}hour)^{-1}$ (Gargas and Andersen 1982) were calculated from these data. Gargas and Andersen (1982) estimated a first-order rate constant of 0.32 $(kg\text{-}hour)^{-1}$. In contrast, Medinsky et al. (1985) reported nonlinear uptakes, with saturation at ≥170 ppm. Fractional absorption was 48% at 1.6 and 9.0 ppm, 38% at 170 ppm, and 27% at 310 ppm in rats exposed for 6 hours. At high bromomethane levels (310 ppm), the total amount absorbed appears to reach a maximum (62 mg/kg), suggesting that some aspect of uptake (perhaps glutathione availability) becomes limiting (see Section 3.1.3). The first-order rate constant for bromomethane was estimated to be 1.6 $(kg\text{-}hour)^{-1}$. Medinsky et al. (1985) suggested that the higher concentrations tested in the Gargas and Andersen (1982) study may have resulted in glutathione depletion shortly after exposure was initiated and that the glutathione availability was a rate-limiting factor in bromomethane uptake; this is supported by the much higher rate constant estimated in the Medinsky et al. (1985) study compared to the Gargas and Andersen (1982) study. In dogs, an uptake of 39.5% was estimated following a 3-hour exposure to 0.174–0.361 ppm bromomethane (ARB 1986).

No studies were located regarding bromomethane absorption after oral exposure of humans. In rats given a single oral dose of ^{14}C-labeled bromomethane dissolved in corn oil, only about 3% of the label was excreted in the feces (Medinsky et al. 1984). This indicates that at least 97% of the dose was absorbed from the gastrointestinal tract.

No quantitative studies were located regarding bromomethane absorption across the skin of humans. Yamamoto et al. (2000) reported a rapid increase in plasma bromide levels in rats dermally exposed to liquid bromomethane for 0.5–5 minutes.

3.1.2 Distribution

Most information regarding distribution of bromomethane was obtained from inhalation exposure studies in laboratory animals. In rats exposed to ^{14}C-bromomethane in air, radioactive label was widely distributed throughout the body (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Levels were somewhat higher in lungs, adrenals, liver, and kidneys than in other tissues (Bond et al. 1985; Jaskot et al. 1988). The form of the label was not studied by these researchers, but is probably mostly metabolites. However, Honma et al. (1985) showed that low levels of parent bromomethane can be detected for up to 24 hours after an 8-hour exposure to 250 ppm bromomethane. The study found that the highest levels of bromomethane were in the adipose tissue, followed by the blood, muscles, brain, kidneys, and liver. Bromomethane levels in the adipose tissue and blood rapidly declined post-exposure; the levels were

decreased by half within the first 30 minutes. The elimination of bromomethane from the brain and liver was slower. A similar distribution pattern was found when bromine (rather than bromomethane) levels were measured. A similar tissue distribution pattern was observed in rats exposed to 250–1,000 ppm bromomethane for 2 hours (Honma et al. 1985), with the exception that bromomethane levels were higher in the liver than in the brain immediately following exposure. Kato et al. (1986) noted concentration-specific differences in bromine tissue distribution in rats 5 days following a 6-week exposure to 200–400 ppm (4 hours/day, 5 days/week). At 200 ppm, the ratio of bromine concentrations in the kidneys, spleen, and liver was 1:0.87:0.16; at 400 ppm, the ratio was 1:0.76:0.56.

In rats exposed to a very high bromomethane concentration (2,000 ppm for 1 hour), there was a rapid increase in relative plasma bromine levels and then a rapid decrease. Using a two-compartment model, a half-time of 9.1 days was calculated for plasma bromine levels (Hori et al. 2002). In rats exposed to 300 ppm bromomethane 6 hours/day for 3 days, a plasma bromine half-time of 5.4 days was calculated (Hori et al. 2002).

Bromomethane's relative hydrophobicity suggests that it can cross the blood-brain barrier (de Souza et al. 2013), which is supported by the elevated brain bromomethane levels measured in the Honma et al. (1985) rat study.

In rats given oral doses of ^{14}C-bromomethane, label was distributed widely throughout the body, with highest levels in liver and kidneys (Medinsky et al. 1984).

In rats dermally exposed to liquid bromomethane, plasma bromide levels rapidly increased in proportion to the exposure duration with peak levels observed 1 hour after a 0.5-, 1-, 3-, or 5-minute exposure (Yamamoto et al. 2000). The plasma bromide levels gradually decreased and returned to baseline levels 4–8 weeks postexposure. Yamamoto et al. (2000) estimated plasma bromide ion half-times (assuming a two-compartment model) of 6.3, 6.5, 5.3, and 5.0 days following the 0.5-, 1-, 3-, and 5-minute exposures, respectively.

3.1.3 Metabolism

Bromomethane undergoes initial metabolism primarily by nucleophilic displacement of the bromide ion. When the attacking species is water, the products are methanol and bromide ion:

$$HOH + CH_3Br \rightarrow CH_3OH + H^+ + Br^-$$

The amount of bromomethane broken down by this reaction in the body is not known, but increased levels of both methanol and bromide have been detected in exposed animals (Gargas and Andersen 1982; Honma et al. 1985). Elevated bromine levels were found in the blood, kidneys, and liver of rats shortly after termination of an 8-hour exposure to 250 ppm (Honma et al. 1985). The peak levels of bromine occurred 4–8 hours after exposure, as compared to the peak levels of bromomethane, which occurred after 1 hour of exposure. Oxidation of methanol leads to formaldehyde and formate, which may enter the one-carbon metabolic pool, be oxidized to carbon dioxide and water, or undergo further reactions in the oxalate or tricarboxylic acid cycles to form amino acids such as cysteine or homocysteine (Bulathsinghala and Shaw 2014). Bromomethane may also react with organic thiols (R-SH) to yield S-methyl derivatives:

$$R\text{-}SH + CH^3Br \rightarrow R\text{-}SCH^3 + H^+ + Br^-$$

This has been shown to result in formation of S-methylcysteine derivatives in hemoglobin of mice exposed to bromomethane (Iwasaki 1988b), and by analogy with methyl chloride (Kornbrust and Bus 1983), is likely to result in formation of S-methyl glutathione (Medinsky et al. 1985). Conjugation with glutathione is supported by the finding of decreased glutathione concentrations in the liver, kidneys, lungs, and brains of mice exposed to bromomethane for 1 hour (Alexeeff et al. 1985). Further metabolism of S-methyl derivatives such as those mentioned above produces methanethiol via intermediates S-methylcysteine and methylthioacetic acid (Bulathsinghala and Shaw 2014). Methanethiol undergoes additional metabolism to formaldehyde and formate, subsequently following the pathways described above. Ultimately, the formation of carbon dioxide accounts for 40–50% of the administered dose and other unidentified nonvolatile metabolites account for about 20–25% of the administered dose (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985).

3.1.4 Excretion

No studies were located regarding excretion of bromomethane in humans after inhalation or oral exposure. In animals exposed to bromomethane vapors, excretion occurs mainly by expiration of carbon dioxide or by urinary excretion of nonvolatile metabolites (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Only small amounts are excreted in the feces. Very little parent bromomethane is exhaled (Jaskot et al. 1988; Medinsky et al. 1985), and tissue levels of parent bromomethane decrease with a half-life of only about 15–30 minutes (Honma et al. 1985; Jaskot et al. 1988). Half-lives for clearance of

metabolites from the body and most tissues range from 2 to 10 hours (Honma et al. 1985; Jaskot et al. 1988).

A significant fraction (about 25–30%) of ^{14}C-radiolabeled bromomethane ($^{14}CH^{3}Br$) remains in tissues after 24–72 hours and a small portion is excreted (7% via exhaled air in 32 hours). The greater excretion rate of $^{14}CO_2$ (43% in exhaled air, 21% in urine, and 2% in feces) indicates rapid metabolism and longer-term retention of bromide ion (Jaskot et al. 1988; Medinsky et al. 1985). This rapid excretion of $^{14}CO_2$ presumably represents turnover of various intracellular metabolites or adducts, although this has not been established. The half-life of bromine in the blood, kidneys, and liver was approximately 5 days in rats exposed to 250 ppm bromomethane for 8 hours (Honma et al. 1985). Following a 1-hour exposure to 220–1,530 ppm bromomethane, 95% of the bromide was eliminated from the blood, kidneys, liver, lungs, and brain of mice after 2.5 days. Saturation of the detoxification mechanism by inhaled bromomethane (which can affect excretion) was proposed by the study authors (Alexeeff et al. 1985).

One study in animals indicates that the rate and pattern of excretion of ^{14}C-label following oral exposure to ^{14}C-bromomethane is similar to that following inhalation exposure: 32% was exhaled as carbon dioxide, 43% was excreted in the urine, 4% of unmetabolized parent compound was exhaled, 2% was excreted in the feces, and 14% remained in the body after 72 hours (95% of the radiolabel was recovered) (Medinsky et al. 1984). In rats with cannulated bile ducts, 46% of the administered dose was excreted in the bile, with much lower amounts exhaled as CO_2 (12%) and excreted in urine (7%) (Medinsky et al. 1984). Given the low fecal excretion seen in rats without bile duct cannulation, these experiments suggest that bromomethane metabolite(s) excreted in bile are reabsorbed and further metabolized prior to excretion in urine or as exhaled CO_2.

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

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

No PBPK models were identified for bromomethane.

3.1.6 Animal-to-Human Extrapolations

In several species, including humans, similar target tissues have been found, namely the respiratory tract and the nervous system. Although the target tissues were similar across species, dose-response differences were noted in several animal studies. Irish et al. (1940) exposed rats, rabbits, and monkeys to the same bromomethane concentrations for 6 months. The respective NOAEL and LOAEL values for neurotoxicity were 66 and 100 ppm (convulsions) for rats, 17 and 33 ppm (paralysis) for rabbits, and 33 and 66 ppm (paralysis) for monkeys. NTP (1992) also noted species-differences in the neurotoxicity of bromomethane; exposure to 120 ppm resulted in alterations in performance on neurobehavioral tests without overt signs of toxicity in rats and severe curling and crossing of hindlimbs and twitching of forelimbs in mice. Although mice were more sensitive to the neurotoxicity of bromomethane, the respiratory tract was more sensitive in rats than in mice. Olfactory epithelial dysplasia was observed in rats exposed to 120 ppm for 13 weeks; no nasal effects were observed in mice also exposed to 120 ppm for 13 weeks (NTP 1992). Reliable dose-response data are not available for humans that would allow for a comparison of adverse effect levels with animal data. In the absence of these data, it is assumed that humans would be as sensitive as animals to the neurological and respiratory toxicity of bromomethane.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

There are limited data on the toxicity of bromomethane in children. One case report discussed effects observed in an infant accidentally exposed to bromomethane (Langard et al. 1996). Vomiting and severe diarrhea were reported in the infant who died; the cause of death was determined to be acute pneumonia due to aspiration. Vomiting, as well as eye, throat, and mouth irritation, was reported in the parents.

A study in rabbits found increased incidences of a minor malformation and minor variation and decreases in body weights in the offspring of rabbits exposed via inhalation (Breslin et al. 1990). However, other studies in rats and rabbits have not reported developmental effects following inhalation exposure during gestation (Hardin et al. 1981; NIOSH 1980) or oral exposure (Kaneda et al. 1998).

It may be expected that the young, the elderly, and people with lung, kidney, or neurological disease might be more readily affected than healthy adults. In addition, humans with a congenital deficiency in glutathione transferase suffered more severe effects of bromomethane exposure, further supporting a detoxifying action of glutathione conjugation under conditions of acute exposure (reviewed by de Souza et al. 2013). Studies in animals reveal that there are differences in sensitivity between species (such as respiratory toxicity, neurotoxicity, and mortality) (e.g., Gotoh et al. 1994; Irish et al. 1940), and some studies have noted small differences in sensitivity between males and females (Eustis et al. 1988). It is not known if these differences apply to humans.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to bromomethane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of

the U.S. population to environmental chemicals using biomonitoring; see CDC (2018), http://www.cdc.gov/exposurereport/. If available, biomonitoring data for bromomethane from this report are discussed in Section 5.6, General Population Exposure.

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

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

3.3.1 Biomarkers of Exposure

Measurement of parent bromomethane (e.g., in expired air, blood, or urine) has not been investigated as a possible biomarker of exposure in humans, mainly because studies in animals suggest that bromomethane is cleared so rapidly (half-lives of 15–30 minutes) that this is unlikely to be useful for monitoring environmental exposures. Similarly, methanol and other organic metabolites are also cleared with short half-lives (Honma et al. 1985; Jaskot et al. 1988), so they are also unlikely to be useful in biomonitoring.

In contrast, the bromide ion level in blood or serum has been used as a biomarker of bromomethane exposure. The relationship between bromide ion concentrations and the severity of effects in exposed people was investigated by Alexeeff and Kilgore (1983), who assembled and evaluated data from a large number of case reports. Serum bromide levels are usually below 15 ppm in unexposed people. In bromomethane-exposed people, levels up to 80 ppm may occur without any obvious clinical signs, while levels of 150–400 ppm are observed in people with moderate to severe symptoms. Bromide is cleared from blood with a half-life of about 12 days in healthy people, and half-lives of 3–15 days have been

observed in bromomethane-exposed people (Alexeeff and Kilgore 1983). Consequently, the correlation between serum bromide levels and severity of effects is most apparent within the first 1–2 days of exposure, and there may be little correlation later. Bromide ion is cleared mainly by excretion in the urine, and may be a candidate biomarker of bromomethane exposure. Tanaka et al. (1991) observed a significant correlation ($r=0.596$, $p<0.01$) between bromine levels in urine and personal air samples for bromomethane (concentrations ranging up to 390 ppm) in a group of 41 plant fumigators wearing gas masks with respirator canisters. The authors postulated three potential routes of exposure to bromomethane in the workers, including dermal absorption, leakage through an incomplete seal of the gas mask, and breakthrough in the respiratory canister (Tanaka et al. 1991). Further investigation is needed to better establish whether urinary bromine is a reliable biomarker of exposure to bromomethane.

Formation of stable methylated adducts such as S-methylcysteine in hemoglobin is known to occur in animals following inhalation exposure to bromomethane (Iwasaki 1988a, 1988b), and has been demonstrated *in vitro* using both human and mouse hemoglobin (Bamgbose and Bamgbose 2008), but the potential use of this endpoint for biomonitoring in humans has not been fully explored.

Neither elevated serum bromide levels nor formation of methylated adducts are, by themselves, specific for bromomethane exposure. For example, increased bromide levels could result from exposure to bromide in the diet or ingestion of bromate- or bromide-containing medicines, and increased methyl adducts might result from exposure to other methyl halides, various methyl nitrosamines, or other alkylating agents. However, the combination of these two methods (i.e., a finding of increased bromide and increased methylation) would strongly indicate that bromomethane exposure had occurred.

3.3.2 Biomarkers of Effect

As discussed in Chapter 2, the effects that are most often observed in humans exposed to bromomethane vapor are central nervous system injury (disturbed vision, tremor, convulsions, coma), lung irritation (edema, impaired respiration), and renal injury (oliguria or anuria). Of these, neurological or neurobehavioral signs often appear to be the most sensitive indication of effect, since preclinical symptoms can be observed in humans exposed to low levels of bromomethane in the workplace (Anger et al. 1986; Kishi et al. 1988; Verberk et al. 1979). Of course, positive findings for endpoints of this sort (headache, weakness, ataxia, nausea, double vision, abnormal electroencephalogram) are not specific indicators of bromomethane exposure, since other chemicals or diseases may produce similar neurological changes.

3.4 INTERACTIONS WITH OTHER CHEMICALS

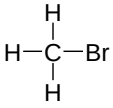
No studies were located regarding the interaction of bromomethane with other chemicals. Since it seems likely that cellular glutathione may serve a protective function by reacting with bromomethane (Kornbrust and Bus 1983), other chemicals (electrophilic xenobiotics, reactive intermediates) that lead to decreases in glutathione levels might increase the toxicity of bromomethane, but this has not been investigated. Similarly, bromomethane might be expected to have additive or synergistic interactions with other alkylating agents, but this has not been investigated.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

Table 4-1. Chemical Identity of Bromomethane

Characteristic	Information	Reference
Chemical name	Bromomethane	Windholz 1983
Synonym(s) and registered trade name(s)	Methyl bromide; monobromomethane; methyl fume; Embafume; Terabol	EPA 1986b; IRIS 2002
Chemical formula	CH_3Br	Windholz 1983
Chemical structure		Windholz 1983
CAS Registry Number	74-83-9	Sax and Lewis 1987

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-2. Physical and Chemical Properties of Bromomethane

Property	Information	Reference
Molecular weight	94.94	HSDB 2014
Color	Colorless	HSDB 2014
Physical state	Gas	HSDB 2014
Melting point	-93.68°C	HSDB 2014
Boiling point	3.5°C	HSDB 2014
Density at 20°C[a]	3.97 at 20°C (gas); 1.73 at 0°C (liquid)	HSDB 2014
Odor	Usually odorless; sweetish chloroform-like odor at high concentrations	HSDB 2014
Odor threshold:		
Water	No data	
Air	80 mg/m^3 (20 ppm)	Ruth 1986

Table 4-2. Physical and Chemical Properties of Bromomethane

Solubility:		
Water at 20°C	15.2 g/L at 25°C 18.5 g/L at 20°C 13.4 g/L at 25°C	HSDB 2014
Organic solvents	Readily soluble in lower alcohols, ethers, esters, ketones, halogenated hydrocarbons, aromatic hydrocarbons, and carbon disulfide; freely soluble in benzene, carbon tetrachloride, and carbon disulfide; miscible in ethanol and chloroform	HSDB 2014
Partition coefficients:		
Log K_{ow}	1.19	HSDB 2014
Log K_{oc}	0.95–1.3	Yates et al. 2003
Vapor pressure at 20°C	1,420 mmHg	HSDB 2014
Henry's law constant at 25°C	0.00734 atm m^3/mole	HSDB 2014
Autoignition temperature	Nonflammable	EPA 1986b
Flashpoint	Nonflammable	EPA 1986b
Flammability limits	Nonflammable	EPA 1986b
Conversion factors[b]	1 ppm=3.88 mg/m^3 1 mg/m^3=0.26 ppm	
Explosive limits	Nonflammable	EPA 1986b

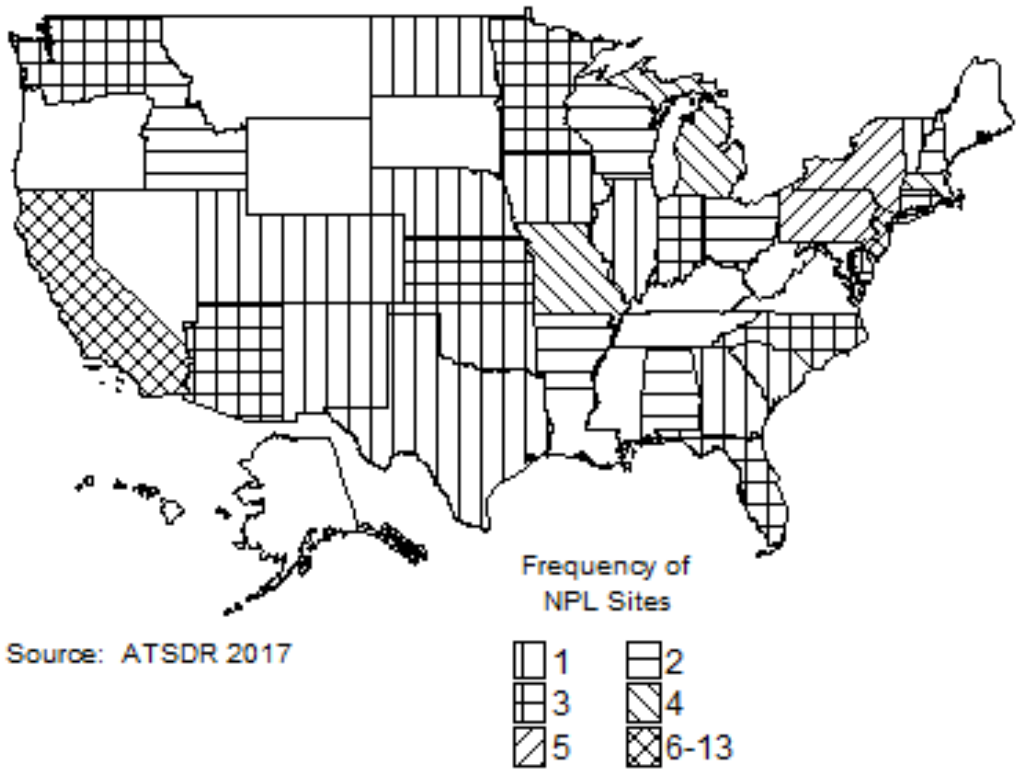
[a]Density of vapor relative to air.
[b]Based on the following formulas: ppm = (mg/m^3) (24.45)/ (molecular weight), and mg/m^3 = (ppm) (molecular weight)/ 24.45.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Bromomethane has been identified in at least 94 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which bromomethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

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



- The most likely route of human exposure is by inhalation because bromomethane exists as a gas at room temperature. Exposure to higher levels of inhaled bromomethane is more likely to occur in occupational settings; exposure of the general population is by bromomethane in ambient air.

- The general population is not likely to be exposed to bromomethane via the oral route; however, exposure to a small amount of bromomethane could occur via contaminated water or food.

- Bromomethane is a naturally occurring component of the environment, with oceans representing the largest natural source.

- Anthropogenic emissions of bromomethane recently have been markedly reduced due to restriction of bromomethane as a fumigant. Currently, the largest anthropogenic emission sources of bromomethane are biomass burning in agriculture and the use of biofuels.

- Bromomethane readily volatilizes into air from water and soil, with volatilization increasing with temperature.

- In air, the main degradation pathway for bromomethane is reaction with photochemically-generated hydroxyl radicals.

- Bromomethane degrades in water through a combination of abiotic (e.g., hydrolysis) and biotic processes.

- In soil, bromomethane degrades by three principle mechanisms: hydrolysis, methylation by organic matter, and biological oxidation by soil microorganisms.

Bromomethane is a naturally occurring component of the environment, with oceans representing the largest natural source (Butler and Rodriguez 1996). In the past, the primary anthropogenic source of bromomethane in the environment was from its use as a fumigant in fields and greenhouses to control a variety of pests and, to a lesser extent, by automobile exhaust. From 1995 to 1998, the use of bromomethane as a fumigant accounted for approximately 40% of all identified sources; however, by 2012, this use accounted for only about 10% of all sources of bromomethane (UNEP 2015). The use of bromomethane as a fumigant has declined about 80% since the mid-1990s. Today, the largest source of anthropogenically generated bromomethane arises from biomass burning and the use of biofuels (UNEP 2015).

Bromomethane has a high potential for volatilization and tends to partition to the atmosphere where it is slowly degraded. Bromomethane that has not degraded in the troposphere will gradually diffuse into the stratosphere where it will slowly degrade due to direct photolysis from high-energy UV radiation, which releases free bromine radicals, and contributes to the catalytic removal of stratospheric ozone. Because of

its ozone-depletion and global warming potential, the United States and most other nations have gradually phased out its agricultural use as a fumigant. Bromomethane may only currently be used in the United States for two critical use exemptions and for quarantine and preshipment (QPS) purposes (EPA 2016a).

Levels of bromomethane in the troposphere have been decreasing at a rate of approximately 0.2–0.4 ppt per year due to the phase out of its use as an agricultural fumigant (WMO 2011). The 2008 annual mean levels of bromomethane were estimated to range from 7.3 to 7.5 ppt (WMO 2011). Prior to the widespread use of bromomethane as a fumigant, it was estimated that natural background levels in the atmosphere were approximately 5.3 ppt (UNEP 2015). Levels can be several orders of magnitude greater where it was applied as a fumigant. For example, bromomethane levels >12 mg/m^3 (3 ppm) were observed 4 hours postapplication above a field located in California in which it was applied (Yates et al. 1997).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Bromomethane is produced by reaction of methanol with hydrobromic acid, followed by distillation of the product (IARC 1986; Windholz 1983). Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of bromomethane in 2017 (TRI17 2019). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Bromomethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	1,000	9,999	1, 12, 13
AR	1	1,000,000	9,999,999	1, 2, 3, 4, 5, 9
CA	2	10,000	9,999,999	2, 3, 4, 7, 9
FL	1	100,000	999,999	7, 9
GA	1	100,000	999,999	7, 9
IL	1	100	999	1, 5
LA	1	1,000	9,999	1, 5, 13
MO	2	1,000	999,999	1, 5, 6
NC	1	100,000	999,999	7, 9
ND	1	1,000	9,999	12

Table 5-1. Facilities that Produce, Process, or Use Bromomethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
NE	1	1,000	9,999	12
OH	1	1,000	9,999	12
SC	2	0	9,999	1, 5
TN	1	0	99	1, 5
TX	1	0	99	1, 5, 12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI17 2019 (Data are from 2017)

According to the National Pesticide Information Retrieval System, there are nine companies in the United States manufacturing bromomethane (NPIRS 2016). Several of these products are mixtures of bromomethane with another pesticide. The companies, their bromomethane containing products, and the active ingredients are provided in Table 5-2. EPA also monitors the amount of bromomethane produced and used annually in the United States and releases data regarding its inventory for that calendar year. Because not all of the bromomethane that is produced is consumed annually, there may be a surplus at the end of the year. Data from 2003 to 2014 are provided in Table 5-3. Numerous countries have also phased out the use of bromomethane. Global production of bromomethane for all uses was estimated at 24,866 metric tons in 2013, which is nearly a 70% decrease in production from the early 1990s (UNEP 2015).

Table 5-2. U.S. Companies Manufacturing Bromomethane

Company	Registered product	Active ingredients
Albermerle Corp.	M-B-R 98 Technical. EPA registration number 3377-27	98% bromomethane
Great Lakes Chemical Corp.	MEH-O-GAS 100. EPA registration number 5785-11	100% bromomethane
	TERR-O-GAS 70 preplant soil fumigant. EPA registration number 5785-19	70% bromomethane, 30% chloropicrin
	TERR-O-GAS 98. EPA registration number 5785-22	98% bromomethane, 2% chloropicrin
	TERR-O-GAS 67. EPA registration number 5785-24	67% bromomethane, 33% chloropicrin

Table 5-2. U.S. Companies Manufacturing Bromomethane

Company	Registered product	Active ingredients
	TERR-O-GAS 57. Preplant soil fumigant. EPA registration number 5785-28	57% bromomethane, 43% chloropicrin
	TERR-O-GAS 75. EPA registration number 5785-40	75% bromomethane, 25% chloropicrin
	METH-O-GAS Q. EPA registration number 5785-41	100% bromomethane
	TERR-O-GAS 80. EPA registration number 5785-47	80% bromomethane, 20% chloropicrin
	TERR-O-GAS 50. EPA registration number 5785-48	50% bromomethane, 50% chloropicrin
	Methyl bromide. EPA registration number 5785-51	100% bromomethane
	67-63 EPA registration number 5785-52	67% bromomethane, 33% chloropicrin
	98-2 EPA registration number 5785-56	98% bromomethane
Soil Chemicals Corp.	PIC-BROM 33. EPA registration number 8536-5	67% bromomethane, 32.8% chloropicrin
	PIC-BROM 55. EPA registration number 8536-6	45% bromomethane, 54.7% chloropicrin
	PIC-BROM 43. EPA registration number 8536-7	43% bromomethane, 56.7% chloropicrin
	PIC-BROM 59. EPA registration number 8536-9	50% bromomethane, 49.7% chloropicrin
	PIC-BROM 25. EPA registration number 8536-11	75% bromomethane, 24.9% chloropicrin
	Methyl bromide 100. EPA registration number 8536-15	100% bromomethane
	Methyl bromide 98. EPA registration number 8536-19	98% bromomethane
	PIC-BROM 67. EPA registration number 8536-20	33% bromomethane, 66% chloropicrin
	Methyl bromide quarantine fumigant. EPA registration number 8536-29	100% bromomethane
ICP-IL America, Inc.	METABROM 100. EPA registration number 8622-16	100% bromomethane
	METABROM Q. EPA registration number 8622-55	100% bromomethane
Trical Inc.	TRI-CON 57/43. EPA registration number 11220-4	57% bromomethane, 43% chloropicrin
	TRI-CON 67/33. EPA registration number 11220-7	67% bromomethane, 33% chloropicrin
	TRI-CON 75/25. EPA registration number 11220-8	75% bromomethane, 25% chloropicrin
	TRI-CON 50/50. EPA registration number 11220-10	50% bromomethane, 50% chloropicrin
	TRI-CON 45/55. EPA registration number 11220-11	45% bromomethane, 54.7% chloropicrin
	Methyl bromide 89.5. EPA registration number 11220-17	89.5% bromomethane, 10.5% chloropicrin
	MBC concentrate soil fumigant. EPA registration number 11220-32	98% bromomethane

Table 5-2. U.S. Companies Manufacturing Bromomethane

Company	Registered product	Active ingredients
Bromine Compounds LTD	Methyl bromide 100. EPA registration number 15298-4	100% bromomethane
Shadow Mountain Products Corp.	TRI-CON 80/20. EPA registration number 58266-1	80% bromomethane, 19.9% chloropicrin
Triest AG Group, Inc.	MBC soil fumigant. EPA registration number 87994-1	68.6% bromomethane
	MBC-33. EPA registration number 87994-2	67% bromomethane, 32.8% chloropicrin
Mebrom Corp.	MEBROM 100. EPA registration number 89816-2	100% bromomethane
	MEBROM 70-30. EPA registration number 89816-3	70% bromomethane, 30% chloropicrin

Source: NPIRS 2016

Table 5-3. Bromomethane Inventory in the United States from 2003 to 2014

Year	Amount of inventory at the end of the year (metric tons)
2003	16,422
2004	12,994
2005	9,974
2006	7,941
2007	6,458
2008	4,271
2009	3,064
2010	1,803
2011	1,249
2012	627
2013	357
2014	158

Source EPA 2016c

5.2.2 Import/Export

In 1990, the world consumption of bromomethane was >6.7×10^7 kg (WHO 1994). Global bromomethane sales for 1984 to 1990 totaled 389,814 tons, ca. 3.9×10^8 kg (WHO 1995). According to Chemical Data Reporting Submissions Database (EPA 2016e), one reporting facility, a confidential manufacturing company, reported 0 pounds of imports for 2012. Two reporting facilities, Albemarle Corporation and Chemtura Corporation, reported import volumes as 'withheld' for 2012 through 2015 (EPA 2016e). More detailed data regarding the import and export of bromomethane were not located.

5.2.3 Use

In the past, the primary use of bromomethane was as a soil or space fumigant for the control of insects (insecticide), fungi (fungicide), and rodents (EPA 1986b; IARC 1986). It also had previous applications as an acaricide, antimicrobial, herbicide, and nematicide. Space fumigation was usually performed by enclosing the structure in a sealed tent and releasing bromomethane gas inside, while soil fumigation was usually performed by injecting bromomethane into the soil underneath a nonporous covering. Bromomethane was used in pre-planting soil fumigation, quarantine and commodity fumigation, and structural fumigation (WHO 1995). Bromomethane is classified as an 8A fumigant by the Insecticide Resistance Action Committee; it is a non-specific (multi-site) inhibitor (IRAC 2019). Bromomethane was also used in fire extinguishers in Europe from the 1920s through the 1940s (WHO 1995; IARC 1986; O'Neil et al. 2014), but never gained widespread use as a fire extinguishing agent in the United States (Alexeeff and Kilgore 1983). In the 1960s, use of bromomethane in fire extinguishers was stopped after causing fatal accidents (WHO 1995). Bromomethane has been used in ionization chambers; wool degreasing; oil extraction of nuts, seeds, and flowers; as a soil or space fumigant for insects, fungi, and rodents; and as a methylating agent in the chemical industry (Larrañaga et al. 2016; O'Neil et al. 2014). Bromomethane has also been used for the disinfection of potatoes, tomatoes, and other crops (Larrañaga et al. 2016). EPA has restricted the use of bromomethane to critical uses (EPA 2016a).

Because bromomethane is considered an ozone-depleting substance, the EPA phased out its use under the Clean Air Act in 2005; however, some critical use exemptions are still allowed to eliminate quarantine pests and for agricultural use where there are no technically or financially feasible alternatives (EPA 2014a, 2016a). The application of bromomethane is deemed critical if two strict criteria are met: a lack of bromomethane availability would result in a significant market disruption and no feasible alternative substances are available (EPA 2016a). Only two critical use exemptions were approved by the EPA for 2016: strawberry farmers in the state of California and dry cure pork producers (EPA 2016a, 2016b). The EPA denied critical use exemptions in 2016 for Michigan cucurbit, eggplant, pepper, and tomato growers; Florida eggplant, pepper, strawberry, and tomato growers; the California Association of Nursery and Garden Centers; California stone fruit, table and raisin grape, walnut, and almond growers; ornamental growers in California and Florida; and the U.S. Golf Course Superintendents Association (EPA 2015a). For 2016, the EPA is allowing the production and import of 141 metric tons of bromomethane for these two critical uses (EPA 2016b). A separate exemption under the Clean Air Act exists for the production and consumption of bromomethane for QPS purposes in order to prevent the

spread of quarantine pests that may cause disease or result in significant environmental problems (e.g., fumigation of logs to control wood-boring pests from imported wood products). Since 1999, global consumption of bromomethane for QPS has remained steady at approximately 10,000 metric tons annually; however, non-QPS consumption of bromomethane has decreased from approximately 50,000 metric tons in 1999 to <3,000 metric tons in 2013 (UNEP 2015).

5.2.4 Disposal

National or local regulations must be observed when disposing of bromomethane (WHO 1994). For large quantities, controlled incineration is recommended; incineration is hazardous for untrained personnel and therefore, only minimal amounts should be released into well-ventilated outdoor air (WHO 1994). Incineration requires dilution with additional fuel. Safe, efficient methods for loading this toxic gas into the combustion chamber must be employed. If an appropriate combustion chamber is unavailable, clearly labeled waste containers must be returned to the supplier (UN Hazard Class 2.3, UN Subsidiary Risks 6.1; National Fire Protection Association Code: Health 3; Flammability 1; Instability 0) (NOAA 2019; WHO 1994). Spills may accumulate in lowered spaces as this gas is heavier than air; disposal of spills by trained experts includes personal protection requiring complete protective clothing and self-contained breathing apparatus; ventilation is critical, and a direct water jet should never be used on spills containing bromomethane (WHO 2009). Disposal of fumigant products containing bromomethane, equipment wash-waters, or rinsate must not contaminate or be released to water as this pesticide is toxic to mammals and birds (EPA 2008a).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in

solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 294,930 pounds (~133.78 metric tons) of bromomethane to the atmosphere from 19 domestic manufacturing and processing facilities in 2017, accounted for about 99.98% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). These releases are summarized in Table 5-4.

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Bromomethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	41,653	0	0	0	0	41,653	0	41,653
AL	2	20,000	0	10	0	0	20,010	0	20,010
CA	2	639	0	0	0	0	639	0	639
FL	1	608	0	0	0	0	608	0	608
GA	1	10,601	0	0	0	0	10,601	0	10,601
IL	1	11,345	0	0	0	0	11,345	0	11,345
LA	1	0	0	0	0	0	0	0	0
MO	2	891	0	0	0	0	891	0	891
NC	1	3,000	0	0	0	0	3,000	0	3,000
ND	1	2,383	0	0	0	0	2,383	0	2,383
NE	1	7,350	0	0	0	0	7,350	0	7,350
OH	1	0	0	0	0	0	0	0	0
SC	2	102,966	0	0	0	0	102,966	0	102,966
TN	1	93,494	15	0	31	0	93,540	0	93,540

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Bromomethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
TX	1	0	0	0	0	0	0	0	0
Total	19	294,930	15	10	31	0	294,986	0	294,986

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI17 2019 (Data are from 2017)

Since bromomethane is highly volatile, nearly all environmental releases of bromomethane are into the air. EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. The NEI database derives emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. In 2011, approximately 5,596 metric tons of bromomethane were emitted to the environment in the United States according to data submitted to the NEI (EPA 2015b). For 2013, the United Nations Environmental Program (UNEP) estimated that total anthropogenic global emissions of bromomethane from non-QPS usage (e.g., agricultural soil fumigation practices) amounted to 1,673 metric tons and QPS emissions were 7,108 metric tons (UNEP 2015). The largest QPS emission (3,874 metric tons) was estimated to arise from usage on timber and wood packaging, followed by emissions on durable goods, preplant fumigation, and perishable items (UNEP 2015).

Use of bromine-containing additives (ethylene dibromide) in leaded gasoline results in the release of bromomethane in exhaust fumes (about 70–220 μg/m^3 of exhaust) (Harsch and Rasmussen 1977), and this may have been a significant source of bromomethane release in the past. Combustion of unleaded gasoline releases much less bromomethane (about 4–5 μg/m^3), so current emissions from this source are presumably much lower than previously, and are likely to decrease further as leaded gasoline continues to be phased out.

Due to the phase-out of leaded gasoline and the restrictions on bromomethane use as a fumigant, anthropogenic emissions of bromomethane are lower than the amount produced from natural sources. Currently, the largest estimated anthropogenic emission sources of bromomethane are biomass burning in agriculture and the use of biofuels (UNEP 2015). The ocean is both a major source and a sink for bromomethane. Estimates suggest that about 56 Gg (56,000 metric tons) of bromomethane are emitted from the ocean and uptake is about 77 Gg (77,000 metric tons) annually, resulting in a net sink of about 21 Gg (21,000 metric tons) (Baker et al. 1999). Others have offered slightly different estimates, but still concluded that the ocean acts as a net sink for bromomethane (Butler and Rodriguez 1996; WMO 2011). Approximately 10–40 Gg (10,000–40,000 metric tons) of bromomethane are released each year from the burning of biomass (Butler and Rodriguez 1996; WMO 2011). Coastal salt marshes have also been identified as a natural terrestrial source of bromomethane, with emissions of about 14 Gg (14,000 metric tons) annually, and the production of bromomethane and methyl chloride was demonstrated in laboratory studies using a variety of terrestrial plants and wood rot fungi (Rhew et al. 2003). A summary of all of the different sources and sinks of bromomethane were presented by the World Meteorological Organization in its 2010 Scientific Assessment of Ozone Depletion. The UNEP (2015) Report of the Methyl Bromide Technical Options Committee also provides a comprehensive review on the emissions of this substance from both anthropogenic and natural sources. Estimates of the various sources for two different temporal periods are provided in Table 5-5.

Table 5-5. Estimated Anthropogenic and Natural Sources of Bromomethane (Gg/Year) 1996–1998 and 2008

Sources[a]	1996–1998 (Gg/year)	Range (Gg/year)	2008 (Gg/year)	Range (Gg/year)
Fumigation-dispersive (soils)	41.5	28.1–55.6	6.7	4.6–9.0
Fumigation quarantine and preshipment	7.9	7.4–8.5	7.6	7.1–8.1

Table 5-5. Estimated Anthropogenic and Natural Sources of Bromomethane (Gg/Year) 1996–1998 and 2008

Sources[a]	1996–1998 (Gg/year)	Range (Gg/year)	2008 (Gg/year)	Range (Gg/year)
Ocean	42	34–49	42	34–49
Biomass burning	29	10–40	29	10–40
Leaded gasoline	5.7	4.0–7.4	<5.7	No data
Temperate peatlands	0.6	-0.1–1.3	0.6	-0.1–1.3
Rice paddies	0.7	0.1–1.7	0.7	0.1–1.7
Coastal salt marshes	7	0.6–14	7	0.6–14
Based on California salt marshes	14	7–29	14	7–29
Based on Scottish salt marshes	1	0.5–3.0	1	0.5–3.0
Based on Tasmania salt marshes	0.6	0.2–1.0	0.6	0.2–1.0
Mangroves	1.3	1.2–1.3	1.3	1.2–1.3
Shrublands	0.2	0–1	0.2	0 to 1
Rapeseed	4.9	3.8–5.8	5.1	4.0–6.1
Fungus (litter decay)	1.7	0.5–5.2	1.7	0.5–5.2
Fungus (leaf-cutter ants)	0.5	No data	0.5	No data

[a]Potential terrestrial sources (tropical trees, temperate woodlands, tropical ferns, and abiotic decomposition) were not quantified.

Source: WMO 2011

5.3.2 Water

Estimated releases of 15 pounds (~0.01 metric tons) of bromomethane to surface water from 19 domestic manufacturing and processing facilities in 2017, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs) (TRI17 2019). These releases are summarized in Table 5-4.

Some bromomethane may leach from fumigated soil into surface water (EPA 1986b; IARC 1986). Most of this would be expected to quickly volatilize into air, although some could migrate downward into groundwater where evaporation is not significant.

5.3.3 Soil

Estimated releases of 31 pounds (~0.02 metric tons) of bromomethane to soil from 19 domestic manufacturing and processing facilities in 2017, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). An additional 10 pounds (~0.005 metric tons), accounted for <1% of the total environmental emissions, were released via underground injection (TRI17 2019). These releases are summarized in Table 5-4.

Soil fumigation was the primary use of bromomethane in the United States, historically accounting for approximately 65% of total consumption (EPA 1987; IARC 1986). However, the use of bromomethane applied to soils as a fumigant has been decreasing rapidly since the late 1990s. Soil fumigation of California strawberry crops is still allowed for 2016 and the EPA is allowing 141 metric tons of bromomethane to be used for this and one other critical use exemption (EPA 2016b).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Bromomethane is a readily volatile compound, with a boiling point of 3.6°C (Windholz 1983) and a vapor pressure at 20°C of 1,420 mmHg (EPA 1982). Consequently, bromomethane has a strong tendency to volatilize into air from other media (soil, water). Because bromomethane is quite soluble in water (approximately 13–18 g/L) (EPA 1986b), some bromomethane in air may partition into clouds and rain, where it may be redeposited to the earth by wet deposition.

Anderson et al. (1996) used soil column studies to assess the volatilization rate of bromomethane applied as a pressurized liquid to the surface of a sandy clay loam (53% sand, 29% silt, 17% clay, 3.1% organic matter, pH 6.6) as a function of temperature and moisture content. The results indicated that volatilization of bromomethane from the soil surface was rapid and positively correlated with increasing temperature and moisture content. At a constant soil moisture tension of 0.3 bar, 27.3, 30.4, and 50.9% of the applied bromomethane was volatilized after 3 hours at temperatures of 15, 25, and 35°C, respectively. After 119 hours, 32.2, 35.2, and 54.4% of the applied bromomethane was lost to volatilization at 15, 25, and 35°C, respectively. At a constant incubation temperature of 25°C, 4.0, 28.7, 28.0, and 66.3% of the applied bromomethane was volatilized at 3, 1, 0.3, and 0.03 bar tension, respectively, after 2 hours. After 72 hours, 4.1, 28.9, 34.7, and 66.7% was volatilized at 3, 1, 0.3, and 0.03 bar tension, respectively

(Anderson et al. 1996). Volatilization of bromomethane from three soils consisting of different organic matter content showed large variations in the amounts volatilized versus the amounts degraded (Gan et al. 1996, 1997). Forty mL of bromomethane gas was injected to a depth of 30 cm into packed columns of low organic matter containing soils: a Greenfield sandy loam (0.92% organic matter) or a Carsitas loamy sand (0.22% organic matter). Similar experiments were conducted using Linne clay loam with greater organic matter content (2.99% organic matter). Cumulative volatilization losses from the two low organic matter containing soils were approximately 90%; however, only 44% of the applied bromomethane was volatilized from the Linne clay loam, with about half being degraded. Only about 10% degradation occurred in the two low organic matter containing soils. Additional experiments were conducted to determine the effect of moisture content on the rate of volatilization. Increasing the volumetric moisture content of the Greenfield sandy loam from 0.058 to 0.180 cm^3/cm^3 resulted in a 17% decrease in the amount of bromomethane that was volatilized (Gan et al. 1996). It was concluded that as the moisture content increased, the effective diffusion coefficient of bromomethane in the soil decreased, resulting in a lower surface volatilization flux and greater degradation (Gan et al. 1996, 1997); these results are in contrast to the findings of Anderson et al. (1996). Similarly, it was observed that soils with higher bulk density tended to have lower volatilization rates since the effective diffusion coefficient of bromomethane and other gasses in these soils are lower as compared to soils with lower bulk density.

It is common practice to cover treated fields with tarps immediately following fumigation in order to limit volatilization loss of the fumigant and maximize the impact of fumigant vapors on the treated soils. Historically, high-density polyethylene (HDPE) tarps were used in agriculture as the standard barrier film; however, HDPE is semi-permeable to gases such as bromomethane and other fumigants. The development of high barrier totally impermeable film tarps (TIF) (HDPE-based films containing multilayer polymers composed of ethylene vinyl alcohol) or virtually impermeable films (VIF) (HDPE or low-density polyethylene [LDPE] films containing nylon or vinyl polymers) have shown better performance at reducing volatilization losses of bromomethane and other fumigants (Fennimore and Ajwa 2011; Freeman 2015). Volatilization losses from soil columns treated with bromomethane and methyl iodide were monitored using HDPE tarps or high-barrier TIF tarps, or left completely uncovered following fumigation (Gan and Yates 1996; Gan et al. 1997). In each experiment, it was observed that greater volatilization losses occurred in soils that were left uncovered and contained the lowest amounts of organic matter. The authors also observed that under similar conditions, a greater percentage of methyl iodide was volatilized as compared to bromomethane due to the relatively slow rate of degradation of methyl iodide when compared to bromomethane (Gan and Yates 1996; Gan et al. 1997). Using a Greenfield sandy loam with approximately 0.92% organic matter, the cumulative volatilization loss of

bromomethane injected as a cooled liquid to a depth of 30 cm below the surface was 75, 68, and 45% for an uncovered soil column, a soil column covered with HDPE, and a soil column covered with a TIF tarp, respectively (Gan et al. 1997). Volatilization was significantly decreased in similar experiments using soils containing a higher percentage of organic matter. For example, only 30% of the applied bromomethane was volatilized from a nursery potting soil containing 9.60% organic matter and covered with a HDPE film. Packed soil column experiments using a low organic Arlington sandy loam (0.92% organic matter, pH 7.2) indicated that approximately 88% of the injected bromomethane was volatilized if the soil surface was left uncovered (Gan et al. 2000). Volatilization losses were 83 and 55% of the nominal concentration when the soil columns were covered with a HDPE tarp and a high-barrier TIF tarp, respectively (Gan et al. 2000). The addition of soil amendments rich in organic matter was also shown to reduce volatilization losses of bromomethane by enhancing the rate of degradation (Gan et al. 1998). Applying 5% composted manure to soil columns treated with bromomethane reduced volatilization approximately 12% as compared to unamended soil columns (Gan et al. 1998).

Majewski et al. (1995) monitored postapplication volatilization losses of a bromomethane/chloropicrin (67%/33%) fumigant in field experiments in Monterey County, California in which bromomethane was injected into the soil and then the fields were either left uncovered or were covered with tarps (Majewski et al. 1995). The fumigant was injected to a depth of 25–30 cm in pressurized liquid form at an application rate of 392 kg/ha to fields located approximately 6 km away from one another. One field was immediately covered with a high-barrier TIF plastic tarp, while the other field was left uncovered. Both fields were Salinas clay loam with similar physical properties and moisture content. The primary difference between the properties of the soils was that the non-tarped field contained a greater content of organic carbon (2.30%) than the tarped field (1.40%) and possessed higher clay content, but a lower silt content. Cumulative volatilization losses of bromomethane were approximately 22 and 32% at 5 and 9 days postapplication, respectively, for the tarp-covered field, while the cumulative volatilization loss of bromomethane from the uncovered field was about 89% 5 days postapplication (Majewski et al. 1995). The maximum volatilization flux of bromomethane from the covered field occurred about 20 hours postapplication and was 91 µg/m^2-second, while the maximum volatilization flux from the uncovered field was about 4 times greater and occurred at <3 hours postapplication.

Field studies conducted in California demonstrated the effectiveness of deep injection depths, irrigation, and postapplication tarping practices at reducing bromomethane volatilization from treated fields (Wang et al. 1997). Bromomethane was injected into Arlington fine sandy loam (64% sand, 29% silt, 7% clay) in experimental plots constructed at the University of California Agricultural Experimental Station in

Riverside, California. When bromomethane was applied as a gas at an injection depth of 25 cm, cumulative volatilization losses were 87, <42, and 59% for uncovered plots, plots that were immediately irrigated and covered by HDPE tarps, and non-irrigated plots covered by HDPE tarpaulins, respectively. At a deeper injection depth of 60 cm, the volatilization losses decreased to 60, 15, and <15% for uncovered plots, HDPE covered plots, and plots covered by a Hytibar plastic tarp, respectively.

Bromomethane, either as a gas or dissolved in water, has relatively low affinity for soils (Brown and Rolston 1980; Fuhr et al. 1948). K_{oc} values in the ranges of 1–10 (EPA 1986b; Roy and Griffin 1985) and 9–22 (Yates et al. 2003) suggest that this compound possesses high mobility and could ultimately leach into groundwater. However, the rapid volatilization and degradation rates of bromomethane in soil will reduce the potential of this chemical to leach. The lack of detection of bromomethane in groundwater (see Section 5.5.2 water monitoring data) strongly suggests that although bromomethane is very mobile in soils, it is either volatilized or degraded before migrating to lower soil horizons and contaminating groundwater.

Bromomethane is not expected to bioconcentrate in aquatic organisms because of its low octanol/water partition coefficient (K_{ow}) (estimated to be about 13) (EPA 1979a). The bioconcentration factor (BCF) for bromomethane has not been measured experimentally. However, based on an empirical relation between the BCF and the K_{ow} (Neely et al. 1974), the estimated BCF for bromomethane is about 3. This low estimated BCF indicates that bromomethane is not likely to bioconcentrate in aquatic organisms (EPA 1986b).

5.4.2 Transformation and Degradation

Air. The main degradation pathway for bromomethane in the troposphere is reaction with photochemically-generated hydroxyl radicals. The rate constant for this reaction has been measured to be 4.02×10^{-14} cm^3/molecule-second at 25°C (Atkinson 1989), which corresponds to an atmospheric half-life of about 266 days, assuming a hydroxyl radical concentration of 1.5×10^6 molecules/cm^3 and a 12-hour day. Due to the long atmospheric half-life, some bromomethane will gradually diffuse into the stratosphere above the ozone layer where it will slowly degrade due to direct photolysis from high-energy UV radiation and contribute to the catalytic removal of stratospheric ozone. The direct photolysis half-life in the stratosphere is estimated to be about 35 years (Butler and Rodriguez 1996). The total lifetime of atmospheric bromomethane is calculated by summing its reciprocal lifetime due to each major sink as shown in the equation below (Butler and Rodriguez 1996; WMO 2011; Yvon and Butler 1996):

$$\frac{1}{\tau_{total}} = \frac{1}{\tau_{p}} + \frac{1}{t_{o}} + \frac{1}{\tau_{s}}$$

where t_{total} is the total lifetime of atmospheric bromomethane, t_p is the lifetime in the troposphere and stratosphere, t_o is the lifetime due to ocean uptake, and t_s represents the lifetime due to terrestrial uptake. Using lifetimes of 1.7, 2.7, and 3.4 years for t_p, t_o, and t_s, the total atmospheric lifetime of bromomethane (t_{total}) was estimated as 0.8 years (Shorter et al. 1995; Yvon and Butler 1996). There is a great deal of uncertainty in this estimate, however, since all of the sources and sinks of bromomethane are not thoroughly understood; therefore, this lifetime can only be considered a best estimate for the global lifetime of atmospheric bromomethane.

Water. Bromomethane degrades in water through a combination of abiotic and biotic processes. Hydrolysis of bromomethane takes place by S_N2 nucleophilic substitution reaction, yielding methanol, the bromide anion, and the hydrogen ion as hydrolysis products. At neutral pH and a temperature of 25°C, the half-life of bromomethane in nonsterile purified deionized water was reported as 20 days (Papiernik et al. 2000). The hydrolysis half-life of bromomethane was studied in distilled water over a pH range of 3–8, and at temperatures of 18 and 30°C (Gentile et al. 1989). At 18°C, the hydrolysis half-lives of bromomethane were reported as 29, 19, 12, and 9 days at pH 3, 5, 7, and 8, respectively. When the temperature was increased to 30°C, the observed half-lives were 28, 18, 10, and 8 days at pH 3, 5, 7, and 8, respectively, in the distilled water. Slightly longer hydrolysis half-lives were observed in groundwater with a pH of 7.5–7.8. Half-lives ranging from 36 to 50 days were observed at 18°C, and half-lives ranging from 15 to 19 days were observed in the groundwater at 30°C (Gentile et al. 1989). A 6–7-fold increase in the rate of hydrolysis was observed when an aqueous solution of bromomethane maintained at neutral pH was irradiated with UV light at 254 nm (Castro and Belser 1981). The enhanced degradation was attributed to hydrolysis of an excited state of bromomethane, but since this compound has only weak absorption above 290 nm, it is uncertain whether this enhanced hydrolysis rate is important under environmental conditions.

Goodwin et al. (1998) studied the microbial oxidation of bromomethane in freshwater, estuary water, coastal seawater, and hypersaline-alkaline water by monitoring the production of $^{14}CO_2$ from samples of $^{14}CH_3Br$ incubated in the different water types. Calculated half-lives were approximately 5, 36, 82, and 298 days for the freshwater, estuary water, coastal seawater, and hypersaline-alkaline water samples,

respectively (Goodwin et al. 1998). No $^{14}CO_2$ production was observed for sterilized controls. These data suggest that biotic degradation processes will occur at a rate similar to the hydrolysis rate in freshwater, but microbial degradation appears to be slower in seawater given these results. Bromomethane was shown to be oxidized using water samples obtained at different depths from Mono Lake, California (Connell et al. 1997). Oxidation only occurred in nonsterilized lake water samples, suggesting microbial-induced degradation as opposed to abiotic degradation mechanisms.

Sediment and Soil. Bromomethane degrades in soil by three principle mechanisms: hydrolysis, methylation by organic matter, and biological oxidation by microorganisms in the soil. For soils rich in organic matter, degradation by reaction with nucleophilic sites in the organic matter is thought to be the primary mechanism responsible for the consumption of bromomethane, whereas hydrolysis and microbially mediated oxidation are the main degradation mechanisms for soils of low organic matter content.

Evidence suggests that bromomethane undergoes nucleophilic substitution with sites in soil organic matter, resulting in the methylation of the organic matter and the release of the bromide anion (Papiernik et al. 2000). To study its abiotic degradation mechanisms, bromomethane was incorporated in an Arlington sandy loam (74.6% sand, 18.0% silt, 7.4% clay, 9.2 g/kg organic carbon, pH 6.73) and a Linne clay loam (36.7% sand, 32.0% silt, 31.3% clay, 25.1 g/kg organic carbon, pH 6.80) under sterile and nonsterile conditions (Papiernik et al. 2000). The half-lives of bromomethane in the Arlington sandy loam were approximately 38.5 and 46.2 days in non-autoclaved and autoclaved samples, respectively. Shorter half-lives of approximately 3.6 and 4.2 days were observed in non-autoclaved and autoclaved Linne clay loam samples, respectively. Because the rates of degradation were similar in the autoclaved and the non-autoclaved soil experiments, the authors concluded that abiotic processes were largely responsible for the observed loss rather than microbial activity. The greater content of organic matter in the Linne clay loam also resulted in much greater degradation rates as compared to the lower organic containing Arlington sandy loam. This observation is consistent with the data of Gan and Yates (1996), which observed a similar correlation between the consumption of bromomethane and soil organic matter content. In four soils containing 0.92, 2.51, 2.99, and 9.60% organic matter, the half-lives of bromomethane were reported as 22, 6, 6, and 6 days, respectively, and there was no statistically significant difference in degradation rates in sterilized versus nonsterilized soils, which again suggests the importance of abiotic transformations rather than microbially mediated degradation (Gan and Yates 1996).

Gan et al. (1994) studied the degradation of bromomethane in four California surface soils: Greenfield sandy loam (9.5% clay, 0.921% organic matter, pH 7.39), Wasco sandy loam (4.3% clay, 0.646% organic matter, pH 6.98), Linne clay loam (25.1% clay, 2.989% organic matter, pH 7.23), and Carsetas loamy sand (0.1% clay, 0.222% organic matter, pH 8.02) under moist, air-dried, and oven-dried conditions (Gan et al. 1994). The authors determined that the degradation of bromomethane was highly correlated with the amount of organic matter and nitrogen content contained in moist and air-dried soils, but not oven-dried soils. Half-lives of approximately 11–33 and 6–39 days were calculated for the four soils under moist and air-dried conditions, respectively, while half-lives of roughly 27–59 days were estimated in the oven-dried soil experiments.

Accelerated rates of bromomethane degradation were observed in experiments conducted employing six soils used to grow strawberries in California (Trikey-Dotan and Ajwa 2014). A bromomethane (67%)/chloropicrin (33%) mixture was applied at a rate of 100 mg/kg to 100 g of soil from the six different plots in sealed glass vials. In order to test the dissipation rates after repeated applications, soils were chosen from three locations (Oxnard, Salinas, and Watsonville) that either had been previously fumigated with chloropicrin or had never been fumigated. Half-lives ranged from under an hour to approximately 15 hours in the six soils. The half-lives of bromomethane in the Salinas and Watsonville soils were significantly shorter in the nontreated soils as compared to the previously fumigated soils. In contrast, a slightly longer half-life (14.5 hours) was observed in the nontreated soil from Oxnard as compared to the previously treated soil (half-life 11.6 hours). Unlike other studies, the authors did not find any significant correlation between soil properties and the degradation rate of bromomethane in these soils and surmised that the accelerated degradation rates of bromomethane observed in these soils was the result of biotic processes.

The bacterial oxidation of bromomethane under aerobic conditions in methanotrophic soils (soils containing bacteria that readily oxidize methane) has been demonstrated (Ou 1998). Using an application rate of 1,000 mg/g, bromomethane was completely degraded within 40–90 hours under aerobic conditions in methanotrophic soils. At an application rate of 10 mg/g, bromomethane was completely degraded in 5 hours under aerobic conditions, but degraded very slowly under anaerobic conditions (Ou 1998). Formaldehyde and the free bromide anion were reported as the primary degradation products (Ou 1998). The authors remarked that the majority of agricultural soils in the United States are not methanotrophic and have low methane oxidizing capabilities, so this may not be a particularly important environmental fate process. Low levels of bromomethane were shown to be rapidly degraded by an agricultural (corn field) soil and highly organic forest soil obtained from southern New Hampshire under aerobic conditions

(Hines et al. 1998). Bromomethane applied to vials of soil at 10 ppb was completely consumed in the forest soil in a matter of minutes, and in the agricultural soil in a matter of hours. Almost no degradation occurred in autoclaved soils or soils that had previously been sterilized by the addition of antibiotics 12 hours earlier, confirming that the source of degradation was biological. Experiments conducted using high levels of bromomethane (10–10,000 ppm) resulted in toxicity to the microbes and much slower degradation rates. Experiments conducted under a nitrogen-rich environment also showed little degradation of bromomethane for any of the soils tested, suggesting that biodegradation is very slow under anaerobic conditions. Although biodegradation under anaerobic conditions is considered to occur slowly in the environment, Oremland et al. (1994) demonstrated that bromomethane may react with free sulfide commonly found in anaerobic sediments and salt marshes, resulting in the production of methylated sulfur reaction products, which in turn are degraded by sulfate-reducing bacteria.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-6 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7.

Table 5-6. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.2 ppb	LeFevre et al. 1989
Drinking water	0.01 µg/L	EPA 1988c
Surface water and groundwater	0.01 µg/L	EPA 1988c
Whole blood	3 ng/mL blood	Pellizzari et al. 1985

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-7. Summary of Environmental Levels of Bromomethane

Media	Low	High	For more information
Outdoor air (ppbv)[a]	Not reported	0.46[b]	Section 5.5.1
Outdoor (ppbv)[c]	0.04	8.7	Section 5.5.1
Surface water (ppb)	Not detected		Section 5.5.2
Ground water (ppb)	0.50	6.4	Section 5.5.2
Drinking water (ppb)	Detected but not quantified		Section 5.5.2
Food (ppb)	Not detected		Section 5.5.4
Soil	No data	No data	Section 5.5.3

[a]Ambient air, non-agricultural areas.
[b]Data collected 2015 (EPA 2019a); median: 0.007 ppbv.
[c]Agricultural areas near bromomethane use.

Detections of bromomethane in air, water, and soil at NPL sites are summarized in Table 5-8.

Table 5-8. Bromomethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	7.00	11.5	10.9	10	10
Soil (ppb)	10.9	11.8	2.68	4	4
Air (ppbv)	0.700	0.325	10.4	4	4

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

5.5.1 Air

The global annual mean mixing ratio of bromomethane in the troposphere for 2008 was reported to range from about 7.3 to 7.5 pptv (0.0073–0.0075 ppbv), which is a decrease of about 20% from the estimates from 1996 to 1998, prior to the large-scale phase-out of bromomethane's use as an agricultural fumigant (WMO 2011). Background atmospheric levels of bromomethane were estimated to be approximately 5.3 pptv (0.0053 ppbv) prior to the introduction of this substance as a fumigant in the 1940s (UNEP 2015).

Data from the EPA Air Quality System (AQS) database are consistent with current estimates for levels of bromomethane in the atmosphere provided by the WMO and UNEP. Table 5-9 shows the annual mean 24-hour percentile distributions of bromomethane from multiple monitoring locations across the nation for the years 2010–2018 (EPA 2019a).

Table 5-9. Percentile Distribution of Annual Mean Bromomethane Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States

Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2010	257	0.0046	0.0088	0.013	0.043	0.14
2011	231	0.0028	0.0068	0.011	0.039	0.21
2012	231	0.00	0.0081	0.011	0.027	0.14
2013	217	0.00	0.0040	0.0089	0.021	0.13
2014	197	0.00	0.0090	0.011	0.024	0.90
2015	175	0.00	0.0034	0.012	0.026	0.40
2016	159	0.00	0.005	0.018	0.049	0.26
2017	124	0.00	0.00	0.00	0.022	0.31
2018	105	0.00	0.00	0.00	0.017	0.14

Source: EPA Air Quality System (AQS) annual summaries (EPA 2019a)

The 2013 National Monitoring Program sponsored by the EPA compiled 24-hour air sample data from 66 monitoring sites located in 26 states across the United States (EPA 2015c). Samples from 34 sites were assessed for volatile organic compounds, including bromomethane. Bromomethane was detected above the detection limits in 1,404 out of 1,883 samples collected at a maximum concentration of 3.37 ppbv (EPA 2015c). The arithmetic mean was reported as 0.014 ppbv and the median value was 0.011 ppbv.

In agricultural areas where bromomethane is applied as a fumigant, ambient air levels are often higher than in non-agricultural areas. Average concentrations at five monitoring sites in Ventura County, California were 0.02–0.39 ppbv with a highest 1-day concentration of 3.90 ppbv at one location over the monitoring period August 22 to September 30, 2005, which coincided with high bromomethane usage for this county (Cal EPA 2008). Average concentrations of 0.22–0.88 ppbv with a highest 1-day concentration of 5.92 ppbv were reported for Ventura County for sampling period June 14 to August 6, 2006 (Cal EPA 2008). Bromomethane was detected in all 23 samples of air obtained from urban communities in California that had high use of 1,3-dichloropropene and secondary use of bromomethane

at a mean concentration of 0.69 µg/m^3 (0.17 ppbv) and in all 30 samples of air from urban communities that had high use of bromomethane and secondary use of 1,3-dichloropropene at a mean concentration of 5.2 µg/m^3 (1.3 ppbv) (Lee et al. 2002). In rural communities that had high use of 1,3-dichloropropene and secondary use of bromomethane, bromomethane was detected in 117 out of 118 air samples at a mean concentration of 2.5 µg/m^3 (0.63 ppbv) and in rural communities with high bromomethane usage and secondary usage of 1,3-dichloropropene, it was detected in 149 out of 149 air samples at a mean of 12 µg/m^3 (3.0 ppbv) (Lee et al. 2002). Table 5-10 shows some monitoring data for bromomethane at various communities in California where it was applied as a fumigant.

Table 5-10. Ambient Air Concentrations in Parts per Billion Near Areas of Bromomethane Use

Concentration (ppbv)	Location (California)	Date	Sampling details	Reference
0.2–8.7	Camarillo/Oxnard	2010–2014	Data represents the highest 1-day concentration for each of the years	Cal EPA 2015
0.1–1.8	Watsonville	2010–2014	Data represents the highest 1-day concentration for each of the years	Cal EPA 2015
0.6–3.8	Santa Maria	2010–2014	Data represents the highest 1-day concentration for each of the years	Cal EPA 2015
0.13	Watsonville	2012	1-Year overall average concentration	Cal EPA 2014
0.45	Watsonville	2013	1-Year overall average concentration	Cal EPA 2014
0.26	Salinas	2011	1-Year overall average concentration	Cal EPA 2014
0.09	Salinas	2012	1-Year overall average concentration	Cal EPA 2014
0.39	Salinas	2013	1-Year overall average concentration	Cal EPA 2014
0.20	Santa Maria	2011	1-Year overall average concentration	Cal EPA 2014
0.09	Santa Maria	2012	1-Year overall average concentration	Cal EPA 2014
0.15	Santa Maria	2013	1-Year overall average concentration	Cal EPA 2014
0.17	Ripon	2011	1-Year overall average concentration	Cal EPA 2014
0.08	Ripon	2012	1-Year overall average concentration	Cal EPA 2014
0.11	Ripon	2013	1-Year overall average concentration	Cal EPA 2014

Table 5-10. Ambient Air Concentrations in Parts per Billion Near Areas of Bromomethane Use

Concentration (ppbv)	Location (California)	Date	Sampling details	Reference
0.23	Camarillo/Oxnard	2011	1-Year overall average concentration	Cal EPA 2014
0.10	Camarillo/Oxnard	2012	1-Year overall average concentration	Cal EPA 2014
0.06	Camarillo/Oxnard	2013	1-Year overall average concentration	Cal EPA 2014
0.11	Shafter	2011	1-Year overall average concentration	Cal EPA 2014
0.06	Shafter	2012	1-Year overall average concentration	Cal EPA 2014
0.04	Shafter	2013	1-Year overall average concentration	Cal EPA 2014
0.631	Parlier	2006	Highest 1-day concentration	Wofford et al. 2014
1.02	Monterey	1986	Mean concentration	Baker et al. 1996
1.10	Monterey	1986	Maximum concentration	Baker et al. 1996

Highest air levels of bromomethane are usually observed locally at field sites shortly following its application or at facilities where it is used as a fumigant. These situations appear to be the greatest acute exposure scenarios for humans. Bromomethane peak concentrations of 12.4 and 13.4 mg/m^3 (3.14 and 3.39 ppmv) were observed 4 hours postapplication above a field located in Moreno Valley, California in which bromomethane was injected at a depth of 25 cm (Yates et al. 1997). At a deeper injection depth (68 cm), the maximum concentration measured at 0.5 m above the field was 0.625 mg/m^3 (0.158 ppmv) and occurred roughly 12 hours postapplication. Bromomethane levels as high as 20 ppmv were observed in sealed trailers used to transport grapes that had been fumigated with bromomethane and 7 ppmv inside the refrigerated area at a facility (O'Malley et al. 2011). Table 5-11 summarizes bromomethane levels under high exposure scenarios.

Table 5-11. Bromomethane Levels Following Fumigation

Concentration (ppmv)	Sampling details	Reference
10–20	Inside trailer transporting grapes fumigated with bromomethane with vent doors closed	O'Malley et al. 2011
2.0–4.0	Enclosed refrigerated building storing fumigated grapes	O'Malley et al. 2011

Table 5-11. Bromomethane Levels Following Fumigation

Concentration (ppmv)	Sampling details	Reference
3.14–3.39	Peak concentration above a treated field when bromomethane was injected at a shallow 25 cm depth	Yates et al. 1997
~45	Peak concentration inside of a greenhouse shortly after fumigation	De Vreede et al. 1998

5.5.2 Water

Bromomethane occurs in ocean waters at a concentration of about 1–2 ng/L (0.001–0.002 µg/L) (Lovelock 1975; Singh et al. 1983), but is not a common contaminant in fresh waters in the United States. It was not detected in storm water runoff from 15 U.S. cities (Cole et al. 1984) or in influents to sewage treatment plants in four cities (EPA 1979b), and was detected in only 1.4% of >900 surface water samples recorded in the STORET database (Staples et al. 1985). The median concentration in these positive samples was <10 µg/L. Bromomethane was not detected in 297 surface water samples for which it was analyzed for in 2015 in the STORET database (EPA 2016d). Bromomethane has been identified, but not quantified, in drinking water supplies of several U.S. cities (Coleman et al. 1976; EPA 1975; Kool et al. 1982; Kopfler et al. 1977; EPA 1976). Bromomethane in drinking water is presumably generated as an inadvertent byproduct following chlorination. Bromomethane was monitored as part of the Unregulated Contaminant Monitoring Rule (UCMR-3) program to collect data for contaminants suspected to be present in drinking water, but that do not have health-based standards set under the Safe Drinking Water Act (SDWA). Bromomethane was detected above its minimum reporting level (0.2 µg/L) but not above its reference concentration (140 µg/L) in 115 out of 36,848 samples of drinking water obtained from public water systems (PWSs) (EPA 2017). It was detected above its minimum reporting level but not above its reference concentration in 49 out of 4,916 PWSs that reported results.

Observation of bromomethane in groundwater is somewhat more likely than in surface water, since evaporation is restricted. Bromomethane was detected at a concentration of 0.50 µg/L in groundwater at 1 out of 1,831 sites sampled by the U.S. Geological Survey (USGS) in monitoring studies conducted from 1992 to 1996 (Kolpin et al. 2000). Bromomethane was not detected in any of the 40 principal aquifers in the United States that are used for drinking water during a USGS assessment from 1991 to 2010. However, it was detected in 1 of the 22 urban aquifers (0.09% of total) at 0.29 µg/L. The laboratory reporting levels ranged from 0.1 to 0.4 µg/L (USGS 2015). A review of the EPA Pesticides in Groundwater Database showed that bromomethane was detected in only 2 out of 20,429 groundwater

wells sampled from 1971 to 1991 (EPA 1992). Both detections occurred at sampling locations in California at levels of 1.5 and 6.4 µg/L. There were no detections of bromomethane in 15,119 wells sampled in Florida and no detections in 93 wells sampled in Hawaii over the 2-decade study period. Plumb (1992) analyzed the occurrence of bromomethane and other contaminants in wells at active and abandoned hazardous waste sites for different regions of the country. Bromomethane was not detected in any wells covering EPA Regions 1, 2, 4, 5, 6, 7, 8, and 10; however, it was detected in 3.2% of groundwater wells in EPA Region 3 (Pennsylvania, West Virginia, Maryland, District of Columbia, and Delaware) and 0.8% of the groundwater wells in EPA Region 9 (California, Nevada, Utah, Hawaii, Guam, Samoa, Northern Mariana Islands, and Trust Territories). Bromomethane was not detected in 1,174 community wells or 617 private wells located in Wisconsin (Krill and Sonzogni 1986).

5.5.3 Sediment and Soil

No data were found on bromomethane levels in soil. Bromomethane is not expected to be a stable constituent of soil, since it either evaporates or reacts with organic soil components releasing the bromide ion. The background bromide content of soils normally is about ≤10 mg/kg depending upon the soil type (WHO 1995). Bromide ion concentrations were measured in greenhouse soil before and after the application of bromomethane at a rate of 80 g/m^2. Prior to fumigation, bromide levels were about 5 mg/kg. Two months post treatment, bromide levels of >30 mg/kg were observed; however, these levels decreased to <10 mg/kg 3 months later. The total bromide ion concentrations in two soils containing 2.81 and 0.93% organic carbon were 9 and 5 mg/kg, respectively, before application of bromomethane (IARC 1986). Following the application of bromomethane at a rate of 500 mg/kg to both soils, the bromide ion concentration increased to 63 mg/kg for the soil containing 2.81% organic carbon and 25 mg/kg for the soil containing 0.93% organic carbon after 24 hours (IARC 1986).

5.5.4 Other Media

Although bromomethane was used extensively as a fumigant for grains and other food products, it is rarely detected unchanged as a residue in foods. Most of the fumigant is rapidly lost to the atmosphere, and the remaining portion reacts with the food components, producing residues of inorganic bromide (IARC 1986; NAS 1978). Daft (1987, 1988, 1989) reported that bromomethane was not detected in hundreds of tested food products. The tolerances for residues on agricultural commodities and processed foods that have been set by EPA and FDA are for bromide ion, not bromomethane (EPA 2014b). Bromide ion is a frequently detected component in food samples. For example, it was detected in 27.9%

of lettuce samples, 27% of tomato samples, and 37.3% of rye tested in a European Union report on pesticide residues in food (EFSA 2015); however, bromide ion is a naturally occurring component in plants and it is not a unique indicator for bromomethane usage.

5.6 GENERAL POPULATION EXPOSURE

Inhalation of bromomethane in ambient air is the predominant exposure route for most people in the United States. Singh et al. (1981) calculated that average daily doses of bromomethane from air in three U.S. cities ranged from 4.5 to 24.5 µg/day, based on total air intake of 23 m^3/day by an adult. These estimates were based on 1979 monitoring data in urban areas that had mean concentrations well above current levels. Using the same air intake rate and ambient air levels of 7.3–7.5 pptv from the WMO for 2008 (WMO 2011), current intake is roughly 0.66–0.68 µg/day. Based on the very low levels of bromomethane in water and the negligible levels in food, it appears that exposure of the general population to bromomethane from sources other than air is likely to be insignificant under normal circumstances.

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) for survey years 2005–2012 does not include data for bromomethane or the bromide ion (CDC 2018).

Exposure of workers to bromomethane is highly variable, depending on conditions. The highest exposures are most likely to occur during fumigation activities, especially when bromomethane is first released to the environment after fumigation ends. Exposure levels under these conditions could reach from 25 to 2,500 ppmv (IARC 1986; NIOSH 1984; Van Den Oever et al. 1982), which would correspond to a dose of 100–10,000 mg/hour for an exposed worker.

Occupational exposure to bromomethane was examined in a 17-year study of 124 employees at a chemical factory primarily manufacturing bromomethane (Yamano et al. 2011). Workers aged 18–64 years were grouped based upon their responsibilities: synthesis group, filling group, and other group. The geometric mean workplace levels in the synthesis and filling areas were 0.68 and 0.77 ppmv, respectively. The median urinary concentration of bromide ion for all employees over the 17-year period was 11 µg/mg CRE (creatinine corrected). The synthesis group had urinary concentrations of bromide ion ranging from 2.5 to 51.8 µg/mg, with a median of 13.0 µg/mg. The filling group and other group had

median values of 11.9 and 7.2 µg/mg, respectively. Levels were ≥30 µg/mg in 16.3% of the workers in the synthesis group, 6.9% of the workers in the filling group, and in none of the workers of the other group. Exposure to bromomethane may have occurred during work procedures, such as the exchange of reaction equipment for maintenance or cleaning, during operations to adjust weights after filling canisters, or during canister recycling.

Concentrations of bromide in blood samples from six storage room workers (four females, two males) ages 32–54 years were examined (Baur et al. 2015; Kloth et al. 2014). The workers were accidentally exposed to fumigant offgassing while unloading and unpacking at a European company importing goods from overseas. Exposure incidents were reported 3 times during a 2-year period (2010–2012). Bromomethane was found in ambient air of the storage room at concentrations ranging from 2.5 to 200 ppmv (mean 125 ppmv) measured after the occurrence of the first incident, and also detected in the air after the second incident (concentration not reported). Serum bromide levels in the analyzed samples were similar to background levels; however, low levels of bromomethane were detected in the serum of one worker (0.24 µg/L) 5 days following the second incident.

Data were not located on the exposure of children to bromomethane. Children are likely to be exposed to low levels of bromomethane from inhalation of ambient air. Children residing in agricultural areas where a critical use exemption for bromomethane has been granted may be exposed to slightly greater levels.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population are not likely to be exposed to high levels of bromomethane except in the immediate vicinity of industrial facilities that release the gas into air, or near locations where bromomethane is being used as a soil or a space fumigant. This includes individuals returning to work or living in locations that have recently been fumigated, especially if insufficient time has been allowed for the chemical to disperse. Individuals living near waste sites that contain bromomethane might also be exposed, although the level of exposure is not known. Individuals involved in the production of bromomethane and those licensed to use it as a fumigant may be exposed to high levels if proper safety precautions are not followed; these individuals should check the label of specific products and follow the guidelines and instructions provided on the product labels for the proper use, disposal, application, and storage of each specific product.

Although bromomethane has been banned for use in homes or residential settings, a pest control company fumigated a resort in the U.S. Virgin Islands in the spring of 2015 with bromomethane, resulting in severe illness for a family of four persons staying at the resort (Kulkarni et al. 2015). Sampling of the housing units detected bromomethane at levels of 0.59–1.12 ppmv several days after the initial fumigation. In addition to the four individuals of the family who became ill, 37 individuals were identified who had potentially been exposed to bromomethane after the fumigation in the spring of 2015 or from a previous fumigation in the fall of 2014.

Two produce inspectors became ill when they were intermittently exposed to high levels of bromomethane while performing routine inspections of fumigated grapes inside a cold storage unit at a produce facility located in California (O'Malley et al. 2011). The measured serum bromide level for one worker was 4.4 mg/dL 5 days after working in the cold storage unit. A peak serum bromide level of 58 mg/dL was estimated on his last day of potential exposure by assuming a 12-day half-life for inorganic bromide. A second inspector had measured bromide levels of 1.5 mg/dL more than a month after his last day of work at the facility, which corresponded to a peak estimated level of approximately 85 mg/dL 1 month prior. Air samples obtained at three locations that either stored or transported the grapes showed median levels of bromomethane ranging from <0.4 to 15 ppmv, with a maximum level of 20 ppmv in trailers responsible for transporting the grapes.

The exposure to workers using bromomethane for quarantine purposes was evaluated by measuring ambient air levels during the fumigation process and monitoring urinary bromine levels of 251 employees involved in the fumigation of logs and grain products (Tanaka et al. 1991). Workers fumigated logs both inside the sealed holds of a transport ship and in sealed polyvinyl sheets at the shipyard. Additionally, other workers fumigated grains in a closed warehouse and a silo. Exposure periods for both the dispersion and degassing processes were roughly 120 minutes/day over a 6-day work week. Ambient concentrations during the bromomethane dispersion process averaged 1.1–3.8 ppmv and ambient levels averaged 0.5–74.6 ppmv during the degassing process. Urinary bromine levels of workers engaged in the fumigation activities ranged from 7.8 to 9.0 mg/L (0.78–0.90 mg/dL) and a control group of 379 workers who were not involved in the use of bromomethane averaged 6.3 mg/L (0.63 mg/dL) (Tanaka et al. 1991). Even though workers used full facepiece gas masks with a respiratory canister to limit inhalation exposure during the fumigation process, bromomethane was detected in the exhaled breath of a sampling of workers who fumigated logs aboard the ship and in the shipyard and fumigated grains in the closed warehouse.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of bromomethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of bromomethane.

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

6.1 INFORMATION ON HEALTH EFFECTS

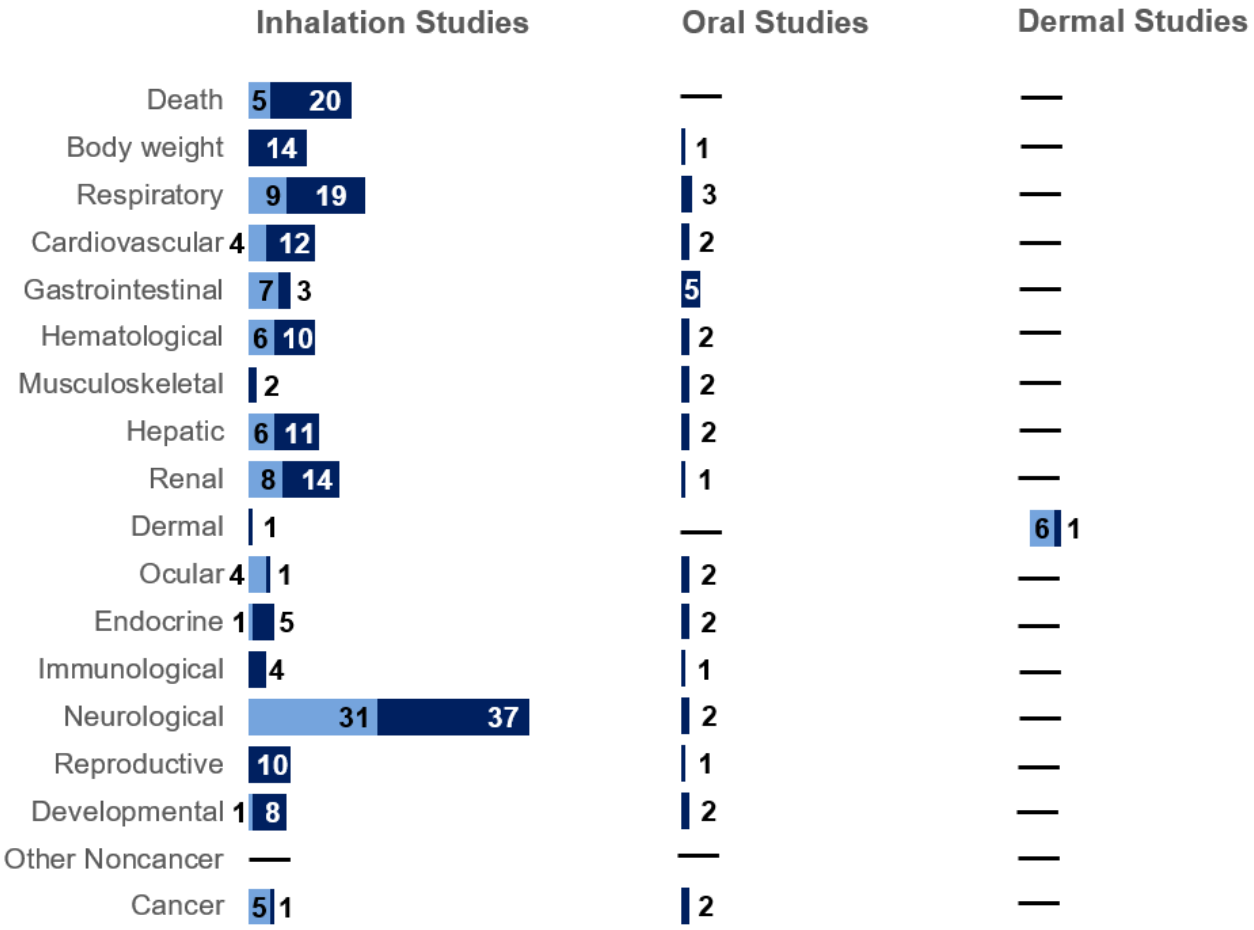
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to bromomethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of bromomethane. The number of human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

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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

Potential respiratory and neurological effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Studies may have examined multiple health effects. No dermal studies in humans or animals were located.

Acute-Duration MRLs. The acute-duration inhalation database was not considered suitable for derivation of an MRL for bromomethane. Acute inhalation studies identify the neurological and respiratory systems as the primary targets of acute inhalation of bromomethane in humans; however, information on these effects was obtained from case reports and, therefore, is not adequate for the basis of an acute MRL. Several targets for acute exposure to bromomethane have been identified in animal studies, including respiratory system, neurological system, liver, kidneys, heart, reproductive system, and the developing fetus. The most sensitive endpoint identified is a duration-adjusted LOAEL of 2.14 ppm; however, there is considerable uncertainty associated with classifying this concentration as a LOAEL. NTP (1992) reported that "neurological signs including trembling, jumpiness, and paralysis were observed in all groups but were most pronounced in the three highest dose groups (50, 100, 200 ppm)." However, the NTP report did not include incidence data for these effects and it is unclear whether any or all of the effects were observed at the lowest concentration tested (12 ppm). Additional acute-duration inhalation studies using low exposure levels (duration adjusted concentrations ≤5 ppm) are need to reliably define NOAEL and LOAEL values for neurological effects.

An acute-duration oral MRL was not derived. The only effect observed in acute-duration oral studies is damage to the glandular stomach (Kaneda et al. 1998). As noted earlier in Sections 1.2 and 2.1, there is some question as to whether the forestomach effects in rats are due to the bolus administration of a very reactive chemical and whether gavage administration is an appropriate model for human exposure to bromomethane. Longer duration exposure studies using dietary exposure did not observe damage to the gastrointestinal tract (Wilson et al. 2000). Additional acute-duration dietary oral exposures studies are important to determine if gastrointestinal tract damage is only observed when bromomethane is administered by gavage.

Intermediate-Duration MRLs. The database for intermediate-duration inhalation exposure to bromomethane was considered adequate for derivation of an MRL. The intermediate-duration oral database was not sufficient to derive an MRL. The most sensitive effect observed from oral gavage exposure was hyperplasia and focal hyperemia of the forestomach (Danse et al. 1984). As discussed above under Acute-Duration MRLs and in Sections 1.2 and 2.1, in this study, bromomethane was administered by gavage; therefore, there is uncertainty regarding the relevance of gastrointestinal damage to human health. Additional acute-duration dietary exposures studies are important to determine if gastrointestinal tract damage is only observed when bromomethane is administered by gavage.

Chronic-Duration MRLs. The database for chronic-duration inhalation exposure to bromomethane was considered adequate for derivation of an MRL. The chronic-duration oral database was not sufficient to derive an MRL. The two chronic-duration oral studies did not identify targets for bromomethane (EPA 1999; Wilson et al. 2000). Additional studies examining the effects of chronic-duration dietary bromomethane over a wide range of doses may provide information on potential targets of exposure.

Health Effects.

Neurotoxicity. There is clear evidence from studies in humans and animals that the nervous system is adversely affected by inhalation exposure to bromomethane. This includes evidence of clinical neurological signs and behavioral changes (Akca et al. 2009; Alexeeff et al. 1985; Anger et al. 1986; Balagopal et al. 2011; Behrens and Dukes 1986; Bishop 1992; Breslin et al. 1990; Clarke et al. 1945; Deschamps and Turpin 1996; Eustis et al. 1988; Greenberg 1971; Herzstein and Cullen 1990; Hine 1969; Hustinx et al. 1993; Irish et al. 1940; Kantarjian and Shaheen 1963; Longley and Jones 1965; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Prockop and Smith 1986; Rathus and Landy 1961; Viner 1945; Wyers 1945; Yamano and Nakadate 2006; Yamano et al. 2001), as well as biochemical changes and histological lesions in the brain (Alexeeff et al. 1985; Eustis et al. 1988; Honma 1987; Honma et al. 1982; Hurtt et al. 1987; Kato et al. 1986; NTP 1992). Although quantitative exposure information from humans is limited, the thresholds for acute, intermediate, and chronic inhalation exposures are known with reasonable precision. No information is available on humans exposed by the oral route, but two oral studies in rats (Boorman et al. 1986; Danse et al. 1984) did not produce any visible neurological signs. It is not known if this apparent route specificity is due simply to differences in dose, or to differences in absorption, distribution, or metabolism between routes. For this reason, additional oral dose-response studies in animals that focus specifically on histological, biochemical, or functional tests of nervous system injury would be valuable. If these tests indicate that the nervous system is not injured following oral exposure, additional toxicokinetic studies would be helpful in understanding the basis for the distinction between inhalation and oral effects.

Reproductive Toxicity. No information was located regarding reproductive effects in humans. Intermediate-duration inhalation studies in animals (Eustis et al. 1988; Kato et al. 1986) indicate that the testes may undergo degeneration and atrophy at high exposure levels, but the dose-response curve is not well defined. Further studies in animals to identify the threshold for this endpoint would be helpful. Two studies in female animals (Hardin et al. 1981; NIOSH 1980)

have not detected reproductive effects even at doses that produced maternal toxicity. Additional studies to confirm this in several different animal species would be helpful.

No information exists on reproductive effects in humans or animals after oral exposure. Based on the inhalation studies in animals that indicate that the testes are a target tissue, it would be valuable to include histological examination of the testes in any intermediate- or chronic-duration oral studies in animals. In addition, tests of male reproductive success would be valuable in assessing the functional significance of any testicular lesions.

Developmental Toxicity. There is no information on developmental effects in humans exposed to bromomethane. One study in rabbits found minor fetal malformations and variations at maternally toxic concentrations (Breslin et al. 1990). In contrast, no developmental effects were observed in a study in rats and rabbits (Hardin et al. 1981; NIOSH 1980). A summary of a neurodevelopmental study in rats reported neurological effects (decreased total and ambulatory activities) in high-dose male and mid-dose female offspring on postnatal day 21 (Beck 1994 [MRID46665001], as cited in EPA 2018a). Unfortunately, the study report is not available for review. Neurological effects have been well characterized in multiple species (rat, mouse, rabbit, and dog) and there is indication that protection factors for adults will be sufficient for infants and children. Therefore, it is considered that additional neurodevelopmental studies are not needed in determining the potential for adverse neurodevelopmental effects associated with gestational exposure to bromomethane. An oral exposure in rats and rabbits did not find developmental effects (Kaneda et al. 1998).

Gastrointestinal Toxicity. Gastrointestinal toxicity has not been reported in inhalation studies in animals. In oral toxicity studies, damage to the stomach has been observed in rats exposed for acute (Kaneda et al. 1998) and intermediate durations (Danse et al. 1984); however, in these studies, bromomethane was administered by gavage. In a chronic-duration oral study of dietary bromomethane, no gastrointestinal effects were observed (Wilson et al. 2000). Although oral exposure to bromomethane to humans is unlikely, if it occurs, exposure would be to small amounts in food or water. Therefore, there is uncertainty regarding the relevance of gastrointestinal damage of gavage administration to human health. Additional acute- and intermediate-duration dietary studies could provide information to determine if dietary exposure to bromomethane is relevant to human health.

Epidemiology and Human Dosimetry Studies. As noted previously, there are many reports on the adverse effects of bromomethane in humans. Most studies involve people with accidental acute high-level exposures in air, but there are also several studies of workers with repeated low-level exposures (Calvert et al. 1998a; Kishi et al. 1988; Verberk et al. 1979). These studies are sufficient to identify the main health effects of concern and to estimate the exposure levels that lead to effects. However, further studies of workers who are exposed to low levels during manufacture or use of bromomethane would be helpful, if reliable current and past exposure data are available. These additional quantitative human data would be valuable in increasing the confidence in the estimated safe exposure levels in the workplace and the environment. This would improve the ability to evaluate potential risk to humans exposed to low levels of bromomethane in air near waste sites.

Biomarkers of Exposure and Effect. The most common biomarker of exposure to bromomethane is serum bromide concentration. Studies in humans have established an association between bromide levels and severity of effect (Alexeeff and Kilgore 1983), although the quantitative relation between exposure level and bromide concentration has not been established. Since bromide is cleared from the blood with a half-life of 3–15 days, this test is best suited for detecting relatively recent exposures. Because bromide is a normal component of blood, and because bromide levels may be increased by other chemicals or drugs, increased serum bromide is not specific for bromomethane. Other possible biomarkers available include direct measurement of parent bromomethane or methanol in expired air or blood (Honma et al. 1985; Jaskot et al. 1988), and measurement of methylated adducts such as S-methylcysteine in hemoglobin (Iwasaki 1988a). Measurement of parent bromomethane or methanol is not likely to be helpful except in the interval immediately following an acute exposure, while measurement of stable methylated adducts, although not specific for bromomethane, could be useful for longer periods. Further studies in humans or animals would be helpful in determining the sensitivity of these biomarkers and evaluating their usefulness in monitoring people exposed to low levels of bromomethane near waste sites.

The most sensitive biomarkers of bromomethane effects appear to be changes in the nervous system. These can be detected in groups of exposed people by measuring the incidence of signs and symptoms such as weakness, nausea, ataxia, and vision problems. However, it is obvious that these are not specific for bromomethane-induced effects, and because of the large variation between people, these tests are not reliable for identifying preclinical effects in potentially exposed individuals. Studies to develop more specific and more objective biomarkers of bromomethane-induced effects would be useful in assessing the potential health significance of low-level bromomethane exposure near waste sites.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of bromomethane have not been thoroughly investigated in humans, but there is good information from studies in animals on uptake, distribution, and excretion following inhalation exposure (Bond et al. 1985; Gargas and Andersen 1982; Honma et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985), and there is one study on toxicokinetics following oral exposure (Medinsky et al. 1984). Available data indicate that the toxicokinetics of bromomethane absorption are mainly first-order except at very high doses. While the metabolism of related compounds such as chloromethane has been studied in detail (Kornbrust and Bus 1983), the metabolism of bromomethane has not been thoroughly investigated. Additional studies on the rate and extent of bromomethane hydrolysis and alkylation reactions *in vivo* would be valuable in understanding the basis of bromomethane toxicity, and in assessing the utility of various biomarkers of exposure (e.g., parent compound, bromide, methanol, adducts).

Comparative Toxicokinetics. Available studies indicate that bromomethane affects the same target tissues in humans and animals, although there are apparent differences in sensitivity between species, with rabbits being more sensitive than rats or mice (Irish et al. 1940). However, quantitative toxicokinetic data on absorption, distribution, and excretion are primarily available for rats (Bond et al. 1985; Gargas and Andersen 1982; Honma et al. 1985; Jaskot et al. 1988; Medinsky et al. 1984, 1985). Additional toxicokinetic studies would be helpful in understanding the basis of the differences in species sensitivity, and in determining which animal species is the most appropriate model for human exposure.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above. There are limited data on the toxicity of bromomethane in children; a report of an accidental exposure suggests that infants and adults would have similar toxic effects (Langard et al. 1996).

Physical and Chemical Properties. The physical and chemical properties of bromomethane are sufficiently well known to allow estimation of environmental fate. Although there is some disparity in reported values for the solubility in water and Henry's law constant for bromomethane (see Table 4-1), further studies to define these parameters more precisely are not essential, since volatilization from water is so rapid.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit

substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2014, became available in October of 2016. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The fate of bromomethane in the environment is dominated by rapid evaporation into air, where it is quite stable (EPA 1986b). The rates of volatilization from soil and water have been studied and are known with reasonable precision (although such rates are typically site-specific) (Anderson et al. 1996; Gan et al. 1996, 1997). The rates of breakdown by hydrolysis, reaction with hydroxyl radical, and direct photolysis in the stratosphere have also been estimated (Atkinson 1989; Castro and Belser 1981; Davis et al. 1976; Robbins 1976; WMO 2011; UNEP 2015). Further studies to improve the accuracy of available rate constants for these processes would be helpful, but are not essential to understanding the basic behavior of bromomethane in the environment.

Bioavailability from Environmental Media. Bromomethane is known to be well absorbed following inhalation and oral contact (Gargas and Andersen 1982; Medinsky et al. 1984). Small amounts may also be absorbed across the skin, but this has not been quantified. No information was located regarding the relative bioavailability of bromomethane from media such as food or soil. However, since bromomethane has a low K_{oc} value (EPA 1982), it is not likely that bioavailability would be much reduced by these media. Moreover, since bromomethane is rarely found in these media, research on this subject does not appear essential.

Food Chain Bioaccumulation. Although the bioconcentration, bioaccumulation, and biomagnification of bromomethane have not been formally investigated, it seems clear that these are not of significant concern. This is the result of several factors, including the high volatility and high water solubility of the compound, its low K_{ow}, and its relatively rapid metabolism by reaction with organic materials (EPA 1982; Medinsky et al. 1985). On this basis, it does not appear that research in this area is essential.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of bromomethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of bromomethane in the environment can be used in combination with the known body burden of bromomethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Bromomethane levels in ambient air are decreasing since the phase out of this substance in 2005 (EPA 2019a; WMO 2011; UNEP 2015). Detections of bromomethane in water are rare. Bromomethane has been analyzed for, but rarely detected, in foods (Daft 1987, 1988, 1989). The EPA RED (EPA 2008b) for bromomethane provides estimates of human exposure levels to handlers, workers, and bystanders associated with its use as a soil fumigant. An exposure assessment for the general population would be helpful.

Exposure Levels in Humans. Bromomethane is not normally measured in human tissues such as blood or urine, even in people exposed to high levels. This is because bromomethane is removed from the body very quickly after exposure ceases. Consequently, this is not likely to be a useful means of monitoring exposure of humans to low levels of bromomethane. Increased levels of bromide have been detected in blood of persons exposed to bromomethane in accidents or in the workplace, but no studies were located regarding bromide levels in persons potentially exposed to bromomethane near waste sites. Since bromide is a normal component of serum, and since the serum bromide level is quite variable, it does not seem that broad surveys of blood bromide levels in persons living near waste sites would be useful. However, site-specific studies at locations where bromomethane exposure is likely might prove helpful.

Exposures of Children. Data on the exposures of children to bromomethane were not located. Because humans are most likely to be exposed to bromomethane in air, studies that are tailored to assessing exposure of children to bromomethane in ambient air would be useful given the tendency for children to spend more time outdoors than many adults.

6.3 ONGOING STUDIES

No ongoing studies of bromomethane were identified by NIH RePORTER (2019).

CHAPTER 7. REGULATIONS AND GUIDELINES

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

Table 7-1. Regulations and Guidelines Applicable to Bromomethane

Agency	Description	Information	Reference
	Air		
EPA	RfC	$5x10^{-3}$ mg/m^3 [a]	IRIS 2002
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018b
	1-Day health advisory (10-kg child)	0.1 mg/L	
	10-Day health advisory (10-kg child)	0.1 mg/L	
	DWEL	0.05 mg/L	
	Lifetime health advisory	0.01 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	$1.4x10^{-3}$ mg/kg/day[b]	IRIS 2002
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances Added to Food	Not listed[c]	FDA 2018
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group D[d]	IRIS 2002
IARC	Carcinogenicity classification	Group 3[e]	IARC 1999
	Occupational		
OSHA	Ceiling[f] PEL for general industry, shipyards and construction	20 ppm[g]	OSHA 2018a, 2018b, 2018c
NIOSH	REL (up to 10-hour TWA)	None established[h]	NIOSH 2018
	IDLH	250 ppm	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016f
	AEGL-1[i]		
	10-minute	NR[j]	
	30-minute	NR[j]	
	60-minute	NR[j]	
	4-hour	NR[j]	
	8-hour	NR[j]	

Table 7-1. Regulations and Guidelines Applicable to Bromomethane

Agency	Description	Information	Reference
	AEGL-2[i]		
	10-minute	940 ppm	
	30-minute	380 ppm	
	60-minute	210 ppm	
	4-hour	67 ppm	
	8-hour	67 ppm	
	AEGL-3[i]		
	10-minute	3,300 ppm	
	30-minute	1,300 ppm	
	60-minute	740 ppm	
	4-hour	230 ppm	
	8-hour	130 ppm	
DOE	PACs-air		DOE 2018b
	PAC-1[k]	19 ppm	
	PAC-2[k]	210 ppm	
	PAC-3[k]	740 ppm	

[a]The RfC is based on a LOAEL(HEC) of 0.48 mg/m^3 for degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity in rats.
[b]The RfD is based on a NOAEL of 1.4 mg/kg/day for epithelial hyperplasia of the forestomach in rats.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Group D: not classifiable as to human carcinogenicity.
[e]Group 3: not classifiable as to its carcinogenicity to humans.
[f]An employee's exposure will at no time exceed the exposure limit given for that substance. If instantaneous monitoring is not feasible, then the ceiling will be assessed as a 15-minute TWA exposure, which will not be exceeded at any time over a working day.
[g]Skin designation.
[h]Potential occupational carcinogen.
[i]Definitions of AEGL terminology are available from EPA (2018c).
[j]NR: not recommended due to insufficient data.
[k]Definitions of PAC terminology are available from U.S. DOE (2018a).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HEC = human equivalent concentration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint Expert Committee on Food Additives; LOAEL = lowest-observed-adverse-effect level; NIOSH = National Institute for Occupational Safety and Health; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
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: Neurological and respiratory systems are the primary targets of acute inhalation of bromomethane in humans. Studies in laboratory animals identify several organ systems (respiratory tract, cardiovascular system, liver, kidneys, immunological system, reproductive system, neurological system, and the developing fetus) as targets of acute exposure to inhaled bromomethane, with neurotoxicity identified as the most sensitive effect. A 2-week study in mice identified neurological effects at an exposure level of 12 ppm (NTP 1992). However, there is considerable uncertainty associated with classifying this concentration as a LOAEL. NTP (1992) reported that "neurological signs including trembling, jumpiness, and paralysis were observed in all groups but were most pronounced in the three highest dose groups (50, 100, 200 ppm)." However, the NTP report did not include incidence data for these effects and it is unclear whether any or all of the effects were observed at the lowest concentration tested (12 ppm). At this time, the database is not considered suitable for identifying a point of departure (POD) for derivation of an acute-duration inhalation MRL because of the uncertainty in establishing the NOAEL and/or LOAEL values in the NTP (1992) study based on the information provided in the study report.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.02 ppm
Critical Effect: Decreased locomotor activity
Reference: NTP 1992
Point of Departure: $LOAEL_{[HEC]}$ of 1.8 ppm
Uncertainty Factor: 90
LSE Graph Key: 41
Species: Mouse

MRL Summary: The intermediate-duration inhalation MRL for bromomethane was derived based on neurobehavioral effects (temporary decreased locomotor activity in male mice) observed at the 6-month (but not at the 0-, 3-, 9-, 12-, 15-, 18-, 21-, or 24-month) evaluation period of a 2-year cancer bioassay (NTP 1992). In this study, various neurological effects were sporadically observed in male and female mice, but effects did not exhibit temporal- or exposure-related dependence. The MRL of 0.02 ppm was derived from a minimal LOAEL of 10 ppm, adjusted for intermittent exposure, converted to a human equivalent concentration [HEC] of 1.8 ppm, and divided by a total uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Principal Study: The NTP (1992) study in rats and mice was selected as the principal study for deriving the intermediate-duration inhalation MRL because this study identified the lowest LOAEL value for neurological effects. The study conducted extensive evaluations of neurobehavioral and neurological endpoints using functional observational battery (FOB) testing at numerous intermittent exposure durations and exposure levels. In addition, the study evaluated comprehensive toxicological endpoints.

Selection of the Critical Effect: The MRL was based on a minimal LOAEL of 10 ppm for decreased locomotor activity in male mice. The 10 ppm concentration was considered a minimal LOAEL because of the small magnitude of change (16%) in locomotor activity.

Alterations in performance on neurobehavioral tests were observed in rats and mice throughout the exposure period. However, statistically significant alterations in neurobehavioral effects were not observed at all time points (see Table A-1 for an overview of the statistically significant alterations). The earliest effect was an increased startle response latency in male rats exposed to 120 ppm for 3 weeks and the lowest LOAEL was 10 ppm for decreased locomotor activity in male mice and altered exploratory behavior (decreased novel side crossings and decreased novel side duration) in female mice exposed for 6 months. It is noted that the decreases in locomotor activity were not statistically significant at 9 months, but were significant at ≥10 ppm in female mice exposed for 12 months. There is extensive evidence in humans and laboratory animals that the nervous system in general and motor function specifically is a sensitive target of bromomethane toxicity. Ataxia has been reported in some severe cases of bromomethane poisoning in humans (Balagopal et al. 2011; Behrens and Dukes 1986). Ataxia, gait disturbances, paralysis, and limb crossing and twitching have been observed in laboratory animals exposed to lethal concentrations (Alexeeff et al. 1985; EPA 1988a; Eustis et al. 1988; Hurtt et al. 1987;

NTP 1992). Cerebellar and cerebral degeneration or necrosis have also been observed in rats and mice exposed to ≥100 ppm (Eustis et al. 1988; Kato et al. 1986; NTP 1992).

Although the alterations were not observed at all time points, the decrease in locomotor activity observed in male and female mice exposed for 6 months was selected as the critical effect for the MRL.

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
Startle response latency				
3 weeks	—	120 ppm ↑	No assessment	No assessment
6 weeks	—	—		
9 weeks	—	—	No assessment	No assessment
12 weeks		120 ppm ↑		
3 months	Not evaluated	Not evaluated	100 ppm ↓	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Startle response amplitude				
3 weeks	—	—	No assessment	No assessment
6 weeks	60 ppm ↓ 120 ppm ↓	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↑	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Activity latency				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	80 ppm ↑	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	80 ppm ↓
3 months	Not evaluated	Not evaluated	100 ppm ↑	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Novel side time				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	10 ppm ↓ 33 ppm ↓ 100 ppm ↑
9 months	Not evaluated	Not evaluated	—	—
Novel side crossings				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	120 ppm ↑		—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	
6 months	Not evaluated	Not evaluated	—	10 ppm ↓ 33 ppm ↓ 100 ppm ↑
9 months	Not evaluated	Not evaluated	—	—
Locomotor activity				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	—
6 months	Not evaluated	Not evaluated	10 ppm ↓ 33 ppm ↓	33 ppm ↓ 100 ppm ↓
9 months	Not evaluated	Not evaluated	—	—
Hindlimb foot splay				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	—	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
Hindlimb grip strength				
3 weeks	—	—	No assessment	No assessment
6 weeks	120 ppm ↓	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↑	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	33 ppm ↓	—
Forelimb grip strength				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	—	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Hot plate latency				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	80 ppm ↑	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	—	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—

— = no significant alterations; ↓ = decreased response; ↑ = increased response

[a]See Table A-2 for magnitude of the alteration.

Source: NTP 1992

Selection of the Principal Study: The NTP (1992) study was selected as the principal study for deriving an intermediate-duration inhalation MRL for bromomethane because it identified the lowest reliable LOAEL for acute effects.

Summary of the Principal Study:

NTP. 1992. Toxicology and carcinogenesis studies of methyl bromide (CAS No. 74-83-9) in B6C3F1 mice (inhalation studies). National Toxicology Program. Technical report series No. 385. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr385.pdf. May 27, 2015

NTP (1992) conducted the following series of studies: (1) groups of 10 male and 10 female B6C3F1 mice exposed to 0, 10, 20, 40, 80, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (2) groups of 10 male and 10 female F344/N rats exposed to 0, 30, 60, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (3) groups of 8 male and 8 female F344/N rats exposed to 0, 30, 60, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (4) groups of 8 male and 8 female B6C3F1 mice exposed to 0, 20, 40, or 80 ppm, 5 days/week for 13 weeks; (5) interim neurobehavioral and histopathological assessments (conducted at 3, 6, and 9 months) in groups of 6–13 male and 6–16 female B6C3F1 mice exposed to 0, 10, 33, and 100 ppm bromomethane for 6 hours/day, 5 days/week as part of a 2-year cancer bioassay, and (6) groups of 15 male and female B6C3F1 mice exposed to 0 or 160 ppm, 6 hours/day, 5 days/week for up to 6 weeks (the data for this study are reported in detail in Eustis et al. 1988). In the 13-week studies involving eight animals/sex/species, neurobehavioral assessment were conducted at weeks 3 (rats only), 6, 9, 12 (rats only), and 13 (mice only). Other evaluations at the end of the 13-week treatment period (10 animals/sex/species) included body weight, hematology, clinical chemistry, organ weights, and histopathology of comprehensive tissues. In the 6-week study, histopathology of selected tissues, including brain, was assessed at the end of the treatment period, which was the duration in which mortality was >50% (14 exposures for male rats, 30 exposures female rats, 8 exposures in male mice, and 14 exposures in female mice). In the 2-year cancer bioassay, neurobehavioral effects were evaluated at 3, 6, and 9 months, and histopathology of comprehensive tissues was conducted at 6 months.

Adverse neurological effects of inhaled bromomethane and LOAEL values, with associated NOAELs, for each exposure level and assessment time-point are summarized in Table A-2. Neurobehavioral effects were observed in mice throughout the 6-week to 6-month assessment period. The study authors classified the severity of neurobehavioral effects as mild. In rats, neurobehavioral effects were observed at 3, 6, and 12 weeks, but not at 9 weeks. The study authors classified the severity of neurobehavioral effects as minor. Microscopic evaluation of brain tissues showed neuronal necrosis of the cerebral cortex (mice and rats), cerebellum (mice), and thalamus (rats) following 6 weeks of exposure to 160 ppm. However, no histopathological changes to the brain were observed in mice and rats exposed to ≤120 ppm for 13 weeks. Comparison of LOAEL values for rats and mice in the 6-week exposure study with exposure concentrations up to 120 ppm suggests that mice are more sensitive than rats; the NOAEL and LOAEL values for neurological effects were 80 and 120 ppm in rats, respectively, and 40 and 60 ppm in mice, respectively.

In addition to neurological effects, decreased body weight and histopathological alterations in several tissue types were observed. In rats and mice exposed to 160 ppm for up to 6 weeks (exposures levels that produced substantial mortality), histopathological changes were observed in the nasal cavity, heart, spleen, liver, adrenal glands, and testes. Decreased body weight gain was observed in male and female mice and rats exposed to 160 ppm for up to 6 weeks and to 120 ppm for 13 weeks. In female rats exposed for 13 weeks, decreased erythrocyte count was observed at 60 and 120 ppm, and decreased hematocrit and hemoglobin were observed at 120 ppm (NTP 1992). Additional details on non-neurological adverse effects reported in NTP (1992) are provided in Table 2-1 in Chapter 2.

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
13-Week exposure study (6 hours/day, 5 days/week)		
3 Weeks 0, 30, 60, or 120 ppm	No death at any exposure 60 ppm: decreased startle response amplitude (males; 15%; p≤0.05) 120 ppm: decreased startle response amplitude (males; 28%; p≤0.01); increased startle response latency (females; 12%; p≤0.05) **NOAEL/LOAEL: 30 ppm/60 ppm**	No assessment in mice
6 Weeks Mice: 0, 20, 40, 80, or 120 ppm Rats: 0, 30, 60, or 120 ppm	No death at any exposure 120 ppm: decreased hindlimb strength (males: 32%; p≤0.05) **NOAEL/LOAEL: 80 ppm/120 ppm**	No death at any exposure 80 ppm: increased activity latency (males: 156%, p≤0.01); increased hot plate latency (males: 80%, p≤0.05) 120 ppm: severe curling and crossing of the hindlimbs and twitching of the forelimbs **NOAEL/LOAEL: 40 ppm/80 ppm**
9 Weeks 0, 30, 60, or 120 ppm	No death at any exposure No neurobehavioral effects observed (increased hot plate latency in females at 120 ppm was <0.5% and was not considered toxicologically relevant) **NOAEL/LOAEL: 120 ppm/X**	No assessment in mice
12 Weeks (rats), 13 weeks (mice) Mice: 0, 10, 20, 40, 80, or 120 ppm Rats: 0, 30, 60, or 120 ppm	No death at any exposure 120 ppm: increased novel side crossing frequency (males: 480%; p≤0.05); decreased hindlimb foot splay (females: 20%; p≤0.05); decreased forelimb grip strength (females: 25%; p≤0.05); increased startle response latency (females: 17%; p≤0.05); decreased startle response amplitude (females: 22%, p≤0.05) **NOAEL/LOAEL: 80 ppm/120 ppm**	No death at any exposure 80 ppm: decreased activity latency (females 76%, p<0.05) 120 ppm: severe curling and crossing of hindlimbs and twitching of forelimbs **NOAEL/LOAEL: 80 ppm/120 ppm**

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
6-Week exposure study (6 hours/day, 5 days/week) (detailed report of this study is presented in Eustis et al. 1988)		
Rats and mice: 0 or 160 ppm Male rats and male mice were sacrificed after 14 exposures due to high mortality; female mice were sacrificed after 8 exposures	Substantial mortality was observed in both sexes[a]. Lethargy and neurological signs (curling and crossing of the hindlimbs, forelimb twitching and tremors); the study authors noted that severity was less than in mice Neuronal necrosis of cerebral cortex (males and females) and thalamus (females) **NOAEL/LOAEL: not applicable (serious LOAEL at 160 ppm)**	Substantial mortality was observed in both sexes[a] Lethargy and neurological signs (curling and crossing of the hindlimbs, forelimb twitching and tremors) Neuronal necrosis of cerebral cortex (males) and cerebellum (males and females) **NOAEL/LOAEL: not applicable (serious LOAEL at 160 ppm)**
24-Month exposure study (6 hours/day, 5 days/week)		
3 Months 0, 10, 33, or 100 ppm	–	10 ppm: no mortality 33 ppm: no mortality 100 ppm: 10/86 deaths in males; 1/86 deaths in females; decreased startle response latency (males: 32%, p≤0.01; females; 38%, p≤0.01); increases startle response amplitude (males: 62%, p≤0.01; females: 66%, p≤0.01); increased activity latency (males: 370%; p≤0.01); decreased novel side time (males: 44%, p≤0.05); increased novel side time (females: 19%, p≤0.05), decreased novel side crossing (males: 67%, p≤0.01); decreased locomotor activity (males: 39%; p≤0.01); increased hind limb grip strength (males: 30%, p≤0.05; females: 32%, p≤0.01); increased hot plate latency (females: 39%; p≤0.01) **NOAEL/LOAEL: 33 ppm/100 ppm**
6 Months 0, 10, 33, or 100 ppm	–	10 ppm: 1/86 deaths in males; no deaths in females; decreased novel side crossings (females: 37%, p≤0.05); decreased locomotor activity (males: 16%, p≤0.01; females: 10%, p≤0.05) 33 ppm: no mortality; decreased novel side crossings (females: 28%, p≤0.05);

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
		deceased locomotor activity (males: 14%, p≤0.01; females: 11%, p≤0.05) 100 ppm: 45/86 deaths in males; 14/86 deaths in females; increased novel side crossings (females: 31%, p≤0.01), decreased novel side crossings (females: 55%, p≤0.01); deceased locomotor activity (females: 28%, p≤0.01) (no assessment in males due to excessive mortality) **NOAEL/LOAEL: X/10 ppm**
9 Months 0, 10, 33, or 100 ppm	–	Control: 18/86 deaths in males; 23/85 deaths in females 10 ppm: 22/85 deaths in males; 18/86 deaths in females 33 ppm: 18/85 deaths in males; 18/86 deaths in females decreased hindlimb grip strength (males: 21%, p≤0.01) 100 ppm: 55/86 deaths in males; 22/86 deaths in females; no assessment due to excessive mortality (males) **NOAEL/LOAEL: 10 ppm/33 ppm**

[a]Incidence data for mortality were not reported.

LOAEL = lowest observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; X = NOAEL or LOAEL value not identified

Source: NTP 1992

Selection of the Point of Departure for the MRL: In selecting the POD for derivation of the intermediate-duration inhalation MRL, an important consideration is that death was observed in rats continuously exposed to 10 ppm bromomethane for 3 weeks; no mortality was observed at 0, 1, or 5 ppm (Sato et al. 1985). Therefore, adverse effects associated with $LOAEL_{adj}$ values >5 ppm (adjusted for intermittent exposure) were not considered as the basis of the intermediate-duration inhalation MRL. The $LOAEL_{adj}$ value of 1.8 ppm for decreased locomotor activity in mice (a NOAEL value was not identified) is the only $LOAEL_{adj}$ value ≤5 ppm (NTP 1992); therefore, this was selected as the critical effect.

To determine the POD for derivation of the intermediate-duration inhalation MRL, data sets for decreased locomotor activity in male and female mice (summarized in Table A-3) were analyzed by continuous variable models in the EPA Benchmark Dose Software (BMDS, version 3.1.1). The benchmark response (BMR) for continuous models is defined as a change equal to 1 standard deviation (SD) from the control

mean. Adequate model fit is judged by three criteria: goodness-of-fit (p>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 BMCL (the lower limit of a one-sided 95% CI on the BMC) is selected as a reasonably conservative POD when differences between the BMCLs estimated from these models are >3-fold; otherwise, the BMCL from the model with the lowest Akaike's information criterion (AIC) is chosen.

For male and female mice, none of the BMC models provided adequate fit to the locomotor activity data. Therefore, the minimal LOAEL of 10 ppm in male mice was selected as the POD for derivation of the intermediate-duration inhalation MRL.

Table A-3. Decreased Locomotor Activity in Male and Female Mice Exposed to Inhaled Bromomethane for 6 Months

Exposure level (ppm)	Number	Mean activity (in instrument units)	SE	SD
Male mice				
0	13	184	4.3	15.5
10	16	155[a]	10.8	43.2
33	16	158[a]	4.2	16.8
100	X	X	X	X
Female mice				
0	12	187	3.5	12.1
10	15	168[b]	5.0	19.4
33	16	166[b]	8.5	34
100	10	135[a]	9.5	30

[a]p≤0.01.
[b]p≤0.05.

SD = standard deviation; SE = standard error; X = due to significant mortality in male mice, neurobehavioral assessments were not conducted

Source: NTP 1992

Calculations

Intermittent Exposure: The LOAEL of 10 ppm identified in male mice was adjusted for intermediate exposure:

$LOAEL_{adj}$ = [(LOAEL of 10 ppm) (6 hours/24 hours) (5 days/7 days) = 1.8 ppm

Human Equivalent Concentration: The HEC for mice for extrathoracic effects ($RGDR_{ET}$) was calculated by multiplying the $LOAEL_{adj}$ by the regional gas dose ratio (RGDR) for extrarespiratory effects. In the absence of available blood:gas partition coefficients for humans and mice, the default ratio for the $RGDR_{ET}$ of 1 was used:

$LOAEL_{adj}$ x RGDR = $LOAEL_{HEC}$
1.8 ppm x 1 = 1.8 ppm

Uncertainty Factor: The total uncertainty factor was 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability):

$LOAEL_{adjHEC}$/total uncertainty factor = intermediate-duration inhalation MRL
1.8 ppm/90 = 0.02 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Specific information regarding effects of intermediate-duration inhalation exposure of humans is limited to a case report of two workers; no exposure data were reported (O'Malley et al. 2011). Signs and symptoms of neurotoxicity (difficulty with concentration and memory, dizziness, visual disturbances, difficulty with speech, ataxia, and abnormal gait) were reported. Although available data on intermediate-duration exposure of humans is limited, it is well established that exposure to inhaled bromomethane is neurotoxic to humans (Bulathsinghala and Shaw 2014; de Souza et al. 2013).

Several animal studies have evaluated the effects of intermediate-duration inhalation exposure to bromomethane. Results show that bromomethane affects several organ systems, with adverse effects observed in the respiratory tract (Eustis et al. 1988; Irish et al. 1940; Kato et al. 1986; NTP 1992), heart (Eustis et al. 1988; Kato et al. 1986), liver (Eustis et al. 1988; Kato et al. 1986), immunological system (Eustis et al. 1988), nervous system (EPA 1988a; Eustis et al. 1988; Honma et al. 1982; Ikeda et al. 1980; Irish et al. 1940; Kato et al. 1986; NTP 1992), reproductive system (EPA 1988a; Eustis et al. 1988), and the developing fetus (Mayhew et al. 1986, as cited in EPA 1986a; Kato et al. 1986). The lowest effect levels adjusted for intermittent exposure ($LOAEL_{adj}$) identified for each outcome were 10 ppm for pulmonary hemorrhage (Sato et al. 1985), 17.9 ppm for focal fibrosis of the heart (Kato et al. 1986), 28.6 ppm for thymus inflammation and atrophy (Eustis et al. 1988), 1.79 ppm for decreased locomotor activity (NTP 1992), 21.4 ppm for decreased sperm density (EPA 1984), and 5.36 ppm for decreased pup weight (Mayhew et al. 1986, as cited in EPA 1986a).

Numerous studies in laboratory animals support identifying the nervous system as a critical target of toxicity. Overt signs of neurological effects have been observed in animals, including paralysis, tremors, and curling and crossing of limb in monkeys exposed to ≥66 ppm (Irish et al. 1940), rats exposed to 300 ppm (Kato et al. 1986), mice exposed to ≥80 ppm (EPA 1988a), and rabbits exposed to ≥33 ppm (Irish et al. 1940). A dog study reported that during a neurological examination, one dog appeared depressed and one dog was unresponsive and motionless (EPA 2001b). Both dogs were exposed to 5.3 ppm 7 hours/day, 5 days/week for 7 weeks; these symptoms were not observed in the remaining six dogs in this group. The investigators considered the significance of this finding as unclear. However, in a subsequent study, no overt signs of neurotoxicity were observed in eight dogs exposed to 5.3 ppm (EPA 2002); alterations in proprioceptive placing were sporadically observed in dogs exposed to 10 or 20 ppm.

Although there is some uncertainty regarding the toxicological significance of the findings in the two dogs exposed to 5.3 ppm for 7 weeks (EPA 2001b), the findings were not confirmed in a subsequent 6-week dog study (EPA 2002) and the MRL is 250 times lower than this exposure concentration and is likely to be protective of the effect.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL: 0.001 ppm
Critical Effect: Respiratory effects (basal cell hyperplasia of the olfactory epithelium)
Reference: Reuzel et al. 1991
Point of Departure: $LOAEL_{(HEC)}$ of 0.110 ppm
Uncertainty Factor: 90
LSE Graph Key: 50
Species: Rat

MRL Summary: The chronic-duration inhalation MRL for bromomethane was derived from a minimal LOAEL value of 3.1 ppm (adjusted for intermittent exposure and converted to a $LOAEL_{(HEC)}$ of 0.108 ppm) for basal cell hyperplasia of the olfactory epithelium. A total uncertainty factor of 90 was applied (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Critical Effect: The most sensitive effects of chronic exposure of animals to inhaled bromomethane are lesions of the respiratory epithelium in male and female rats (Reuzel et al. 1987, 1991) and mild neurotoxicity in female mice (NTP 1992). Basal cell hyperplasia of the olfactory epithelium was selected as the critical effect because the $LOAEL_{adj}$ of 0.55 ppm (a NOAEL was not identified) for respiratory lesions is lower than the $LOAEL_{adj}$ of 1.79 ppm (a NOAEL was not identified) for neurotoxicity reported by NTP (1992).

Selection of the Principal Study: The Reuzel et al. (1991) study was selected as the principal study because it reported the lowest $LOAEL_{adj}$ value of 0.55 ppm (a NOAEL was not identified) for lesions of the olfactory epithelium in male and female rats. In addition, the study demonstrated exposure-related increases of hyperplasia of the olfactory epithelium in both male and female rats after 128 weeks of exposure. Severity of nasal lesions increased with exposure concentration and duration.

Summary of the Principal Study:

Reuzel PG, Dreef-van der Meulen HC, Hollanders VM, et al. 1991. Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. Food Chem Toxicol 29(1):31-39. (Data also reported in Reuzel PG, Kuper CF, Dreef-Van Der Meulen HC, et al. 1987. Initial submission: Chronic (29-month) inhalation toxicity and carcinogenicity study of methyl bromide in rats with cover letter dated 081092. DuPont Chem Co. Submitted to the U.S. EPA under TSCA Section 8ECP. EPA Document No. 88-920008788.OTS0546338.)

Groups of 60 male and female Wistar rats were exposed to target concentrations of 0, 3, 60, or 90 ppm (actual concentrations were 3.1, 29.6, and 89.1 ppm) bromomethane for 6 hours/day, 5 days/week for 128 weeks (males) and 129 weeks (females). Animals were examined daily for clinical signs and mortality, and rats were weighed weekly for the first 12 weeks of the study, then monthly for the remainder of the study. Assessments for hematology, clinical chemistry, and urinalysis were conducted at weeks 12–14 and 52–53. Gross pathological examination was performed on all animals at the end of

treatment or upon early death. At the end of the treatment period, organ weights were recorded for selected tissues and histopathological examination was conducted on comprehensive tissues.

Cumulative mortality was significantly increased in the 89.1 ppm group at exposure week 114 in male rats (36/60; $p<0.05$) and at exposure week 121 in female rats (38/50; $p<0.05$); significant increases were not observed at other time points. Body weights were also decreased throughout the study in males and females exposed to 89.1 ppm. No treatment-related effects were observed for hematology, clinical chemistry, or urinalysis. Significant, exposure-related histopathological changes were observed in the nasal cavity (basal cell hyperplasia of the olfactory epithelium) at all bromomethane concentrations tested, with changes classified as very slight or slight at 3.1 ppm, slight at 29.6 ppm, and slight to moderate at 89.1 ppm. Hyperkeratosis of the esophagus was observed in male rats in the 89.1 ppm group. Microscopic examination of the heart showed cartilaginous metaplasia in males, thrombi in males and females, and moderate to severe myocardial degeneration in females exposed to 89.1 ppm. The incidences of neoplastic lesions in treatment groups were similar to controls.

Selection of the Point of Departure for the MRL: The most sensitive effect identified in the Reuzel et al. (1991) study is nasal lesions (basal cell hyperplasia of the olfactory epithelium) in male and female rats, with a LOAEL of 3.1 ppm at the lowest concentration tested; data are summarized in Table A-4. To determine the POD to derive the chronic-duration inhalation MRL, incidence data were fit to all available dichotomous models in EPA's BMDS (version 3.1.1) using the extra risk option. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), 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 BMCL (the lower limit of a one-sided 95% CI on the BMC) is selected as a reasonably conservative POD when differences between the BMCLs estimated from these models are >3-fold; otherwise, the BMCL from the model with the lowest AIC is chosen (EPA 2012).

Table A-4. Incidence and Severity Data for Basal Cell Hyperplasia of the Olfactory Epithelium in Male and Female Rats Exposed to Inhaled Bromomethane for 29 Months

Exposure level (ppm)	Number of rats affected/number of rats examined	Severity (number of rats)
Male rats		
0	4/46	Very slight: 2 Slight: 2 Moderate: 0
3.1	13/48[a]	Very slight: 9 Slight: 3 Moderate: 1
29.6	23/48[b]	Very slight: 7 Slight: 12 Moderate: 4
89.1	31/48[b]	Very slight: 8 Slight:14 Moderate: 9

Table A-4. Incidence and Severity Data for Basal Cell Hyperplasia of the Olfactory Epithelium in Male and Female Rats Exposed to Inhaled Bromomethane for 29 Months

Exposure level (ppm)	Number of rats affected/number of rats examined	Severity (number of rats)
Female rats		
0	9/58	Very slight: 7 Slight: 2 Moderate: 0
3.1	19/58[a]	Very slight: 17 Slight: 2 Moderate: 0
29.6	25/59[a]	Very slight: 13 Slight: 9 Moderate: 3
89.1	42/59[b]	Very slight: 10 Slight: 23 Moderate: 9

[a]p≤0.05
[b]p≤0.01

Source: Reuzel et al. 1987, 1991

Only the LogLogistic model provided adequate fit to the incidence data for basal cell hyperplasia of the olfactory epithelium in male rats (BMC_{10} 5.81 ppm; $BMCL_{10}$ 3.65 ppm) (Table A-5). The goodness of fit (p-value) was <0.1 for all other models. The selected model fit is shown in Figure A-1. For basal cell hyperplasia of the olfactory epithelium in female rats, dichotomous models provided adequate fit to the incidence data, except for the Hill and probit models (Table A-6). Using the criteria for model selection, the LogLogistic model (BMC_{10} 6.41 ppm; $BMCL_{10}$ 4.13 ppm) was selected as the best fit model. The selected model fit is shown in Figure A-2. None of the models provided adequate fit for the combined male and female data sets.

Table A-5. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
All doses									
Gamma[c]	2	5.47	0.06	1.25	1.03	-1.50	221.83	ND-0.10	ND-0.10
Hill	1	0.11	0.74	-0.02	-0.12	0.17	218.22	ND-10	ND-10
Logistic	2	8.65	0.01	0.73	1.71	-2.11	225.61	ND-0.10	ND-0.10
LogLogistic[d,e]	***2***	**3.56**	**0.17**	**1.35**	**0.29**	**1.35**	**219.68**	**5.67**	**3.56**
LogProbit[d]	1	0.14	0.71	-0.02	0.12	-0.29	218.25	ND-10	ND-10

Table A-5. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]			AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Multistage (1-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Multistage (2-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Multistage (3-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Probit	2	8.48	0.01	1.78	-2.08	-2.08	225.31	ND-0.10	ND-0.10
Weibull[c]	2	5.47	0.06	1.25	1.03	-1.50	221.83	ND-0.10	ND-0.10

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The only model that provided adequate fit to the data was the Log-Logistic.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND-0.10 = not determined, goodness-of-fit criteria, p<0.10; ND-10 = not determined, BMDL is 10-fold lower than the lowest non-zero dose; Hill model $BMCL_{10}$ = 0.028; LobProbit model $BMCL_{10}$ = 0.043

Figure A-1. Selected Model (LogLogistic) for Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

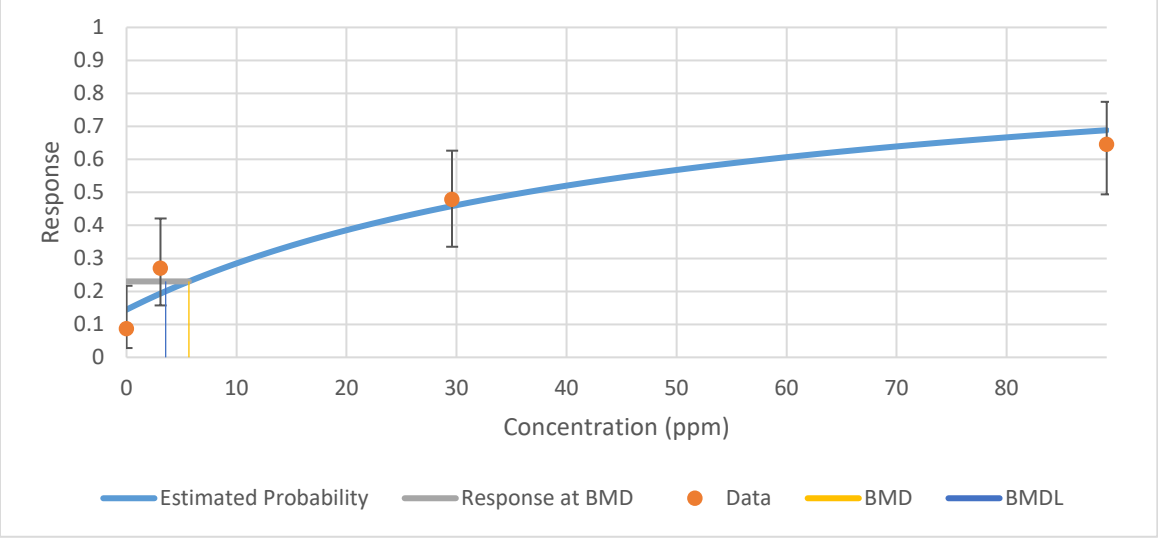


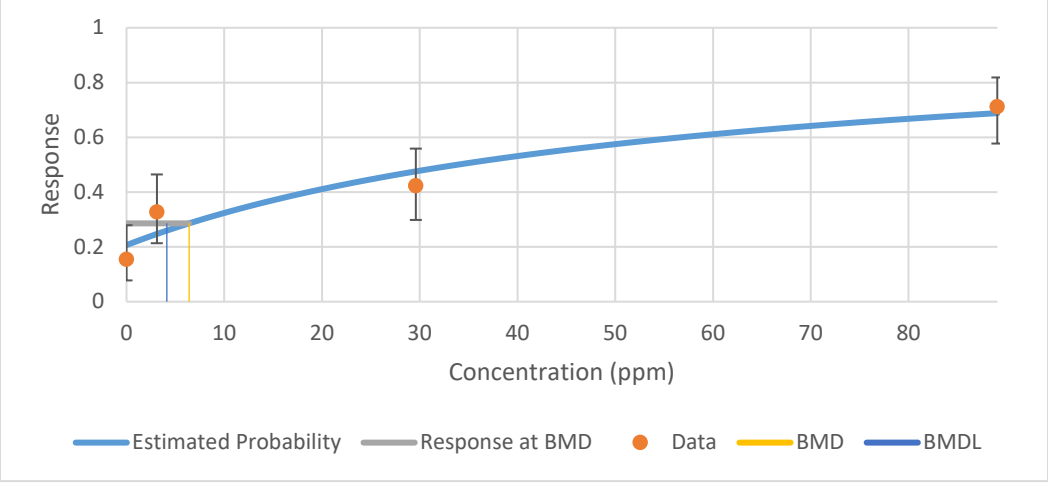
Table A-6. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Female Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Scaled residuals[b] Dose above BMC	Scaled residuals[b] Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Hill	1	3.16	0.07	0.83	-1.31	0.83	283.86	ND-0.10	ND-0.10
Logistic	2	4.24	0.12	1.22	0.48	-1.57	283.12	15.94	13.01
LogLogistic[d,e]	***2***	**3.75**	**0.15**	**1.42**	**-0.80**	**1.42**	**282.39**	**6.41**	**4.13**
LogProbit[d]	1	3.40	0.06	1.48	0.20	-1.56	284.11	ND-0.10	ND-0.10
Multistage (1-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Multistage (2-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Multistage (3-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Probit	2	4.19	0.12	1.24	0.47	-1.55	283.06	15.56	12.83
Weibull[c]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >2–3-fold). Therefore, the model with lowest BMCL was selected (Log-Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND-0.10 = not determined, goodness-of-fit criteria, p<0.10

Figure A-2. Selected Model (LogLogistic) for Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Female Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)



The $BMCL_{10}$ values of 3.56 and 4.13 ppm for olfactory epithelial basal cell hyperplasia in male and female rats, respectively, which are theoretical no-effect levels, are higher than the empirical LOAEL of 3.1 ppm, suggesting that the BMD models are not predictive of low-concentration effects. Therefore, to determine the POD for derivation of the chronic inhalation MRL, $LOAEL_{adj}$ value for olfactory epithelial hyperplasia was converted to a HEC ($LOAEL_{HEC}$) by multiplying the $LOAEL_{adj}$ by the RGDR values for extrathoracic effects, as shown in Table A-7.

Table A-7. Possible PODs for the Chronic-Duration Inhalation MRL

Species	Exposure	Effect	LOAEL (ppm)	$LOAEL_{adj}$ (ppm)[a]	RGDR	$LOAEL_{HEC}$ (ppm)[b]	Reference
Male rats	29 Months, 6 hours/day, 5 days/week	Basal cell hyperplasia of the olfactory epithelium	3.1	0.55	0.280[c]	0.154	Reuzel et al. 1991
Female rats	29 Months, 6 hours/day, 5 days/week	Basal cell hyperplasia of the olfactory epithelium	3.1	0.55	0.200[c]	0.110	Reuzel et al. 1991

[a]Adjusted for intermittent exposure. See details below under *Calculations*.
[b]HEC: $LOAEL_{adj\text{-}HEC}$ = ($LOAEL_{adj}$)(RGDR). See details below under *Calculations*.
[c]RGDR for rats for extrathoracic respiratory effects ($RGDR_{ET}$). See details below under *Calculations*.

HEC = human equivalent concentration; LOAEL = lowest observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RGDR = regional gas dose ratio

Calculations

Intermittent Exposure: The LOAEL of 3.1 ppm in female rats was adjusted for intermittent exposure (6 hours/day, 5 days/week):

$LOAEL_{adj}$ = [(LOAEL of 3.1 ppm) (6 hours/24 hours) (5 days/7 days) = 0.55 ppm

Human Equivalent Concentration: The RGDR for rats for extrathoracic respiratory effects ($RGDR_{ET}$) was calculated using the following equation (EPA 1994b):

$$RGDR_{ET} = \frac{\left(V_E / SA_{ET}\right)_{Rat}}{\left(V_E / SA_{ET}\right)_{Human}}$$

where V_E is the ventilation rate (m^3/day; humans: 20; male Wistar rats: 0.42; female Wistar rats: 0.30; EPA 1988b), and SA_{ET} is surface are of the extrathoracic region of the respiratory tract (cm^2; humans: 200; male and female rats: 15) (EPA 1994b).

$LOAEL_{adj}$ x RGDR = $LOAEL_{HEC}$
0.55 ppm x 0.20 = 0.110 ppm

Uncertainty Factor: The total uncertainty factor was 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability):

$LOAEL_{adjHEC}$/total uncertainty factor = Chronic-duration inhalation MRL
0.11 ppm/90 = 0.001 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Information regarding effects of chronic-duration inhalation exposure of humans is limited to occupational survey studies (Akca et al. 2009; Anger et al. 1986) and case reports (Geyer et al. 2005; Greenberg 1971; Hine 1969) in bromomethane workers. Results show that chronic inhalation exposure to bromomethane produces signs and symptoms of neurotoxicity (headache, dizziness, decreased upper extremity sensation, decreased recall, uncoordinated movements, ataxia, seizures, confusion), respiratory effects (nasal irritation, dyspnea, cough, increased phlegm), nausea, and vomiting. The Anger et al. (1986) survey study conducted in 32 bromomethane workers employed as fumigators showed increased muscle ache and fatigue and mild neurotoxic effects (headache, dizziness, decreased upper extremity sensation, and decreased recall). However, exposure levels were not determined for these workers. The reported mean exposure level of 2.3 ppm was determined from personal monitoring data collected in different populations of fumigators. However, since exposures of workers in the survey study are unknown, the outcomes observed cannot quantitatively be related to exposure levels.

Results of animal studies show that chronic exposure to bromomethane produces toxicity to the respiratory tract in rats (Gotoh et al. 1994; Reuzel et al. 1987, 1991) and mice (NTP 1992;), heart in rats (Reuzel et al. 1987, 1991) and mice (NTP 1992), gastrointestinal tract in rats (Reuzel et al. 1987, 1991), skeleton in mice (NTP 1992), and neurological system in mice (NTP 1992). In addition, decreased body weight gain was observed in rats (Reuzel et al. 1987, 1991) and mice (NTP 1992). The lowest effect levels adjusted for continuous exposure ($LOAEL_{adj}$) were 1.79 ppm for decreased locomotor activity (NTP 1992), 17.9 ppm for dysplasia of the sternum (NTP 1992), 0.54 ppm for basal cell hyperplasia of the olfactory epithelium (Reuzel et al. 1987, 1991), 16.1 ppm for myocardial degeneration (Reuzel et al. 1987, 1991), and 16.1 ppm for hyperkeratosis of the esophagus (Reuzel et al. 1987, 1991).

Identification of the respiratory tract as one of the most sensitive targets of toxicity is supported by findings of nasal irritation and cough noted in cases reports and a rat study by Gotoh et al. (1994). Non-neoplastic lesions of the nasal cavity were observed in a 2-year study in male and female F344 rats exposed to 0, 4, 20, or 100 ppm bromomethane 6 hours/day, 5 days/week (Gotoh et al. 1994). Inflammation of the nasal cavity was observed in males exposed to 4, 20, and 100 ppm and in females exposed to 100 ppm, and necrosis of the olfactory epithelium was observed in males exposed to 100 ppm.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. One acute-duration oral study was identified (Kaneda et al. 1998). This study exposed pregnant rats to 0, 3, 10, or 30 mg/kg/day and pregnant rabbits to 0, 1, 3, or 10 mg/kg/day bromomethane in corn oil by gavage on gestation days 6–15. In rats, erosion and thickening of the wall of the non-glandular stomach or adhesion of the stomach to the spleen, liver, or diaphragm was seen in all rats in the 30 mg/kg/day dose group. No clinical signs of toxicity, effects on reproductive function, or developmental effects in fetuses were observed. The only effects observed in rabbits were significant decreases in body weight and decreased food consumption in the 10 mg/kg/day group. Effects on body weight gain in rats and rabbits were considered to be secondary to the decreased food consumption.

It is unclear if effects observed in the glandular stomach are due to the bolus administration of a very reactive chemical, and if gavage administration would be an appropriate model for human exposure to bromomethane. In chronic-duration dietary studies, no gastrointestinal lesions were observed in rats (EPA 1999) or dogs (Wilson et al. 2000). The general population is not likely to be exposed to bromomethane via the oral route; however, exposure to a small amount of bromomethane could occur via contaminated water or food and, therefore, would not mimic the gavage exposure in animal studies. Given the uncertainty of whether the observed forestomach lesions are unique to gavage administration of bromomethane, an acute-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. Two intermediate-duration gavage studies conducted male rats were identified (Boorman et al. 1986; Danse et al. 1984). These studies administer bromomethane by gavage at doses of 0, 0.4, 2, 10, or 50 mg/kg/day (Boorman et al. 1986) for 13 weeks and 0 or 50 mg/kg/day for 13–25 weeks (Danse et al. 1984). Mild focal hyperemia in the forestomach was observed at 2 mg/kg/day (Danse et al. 1984) and forestomach ulceration was observed at 50 mg/kg/day (Boorman et al. 1986; Danse et al. 1984). A 4-week feeding study in rats did not identify any adverse effects of dietary exposure to microencapsulated bromomethane at doses up to 7.98 mg/kg/day (EPA 1996). Although mean body weight gain was decreased by 14% in males during the first week of exposure and by 33% in females during weeks 1–2, but not during other weeks (EPA 1996). These changes were accompanied by decreased food intake and, therefore, are not considered adverse.

It is unclear if effects observed in the forestomach of rats are due to the bolus administration of a very reactive chemical, and if gavage administration would be an appropriate model for human exposure to bromomethane. The general population is not likely to be exposed to bromomethane via the oral route; however, exposure to a small amount of bromomethane could occur via contaminated water or food and, therefore, would not mimic the gavage exposure in animal studies. Given the uncertainty of whether the observed forestomach lesions are unique to gavage administration of bromomethane, an acute-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. Two chronic-duration oral studies were identified: one study exposing dogs to dietary bromomethane at doses up to in 0.28 mg/kg/day in males and 0.27 mg/kg/day in females for 1 year (Wilson et al. 2000) and one study exposing rats to microencapsulated bromomethane at doses up to 11.10 and 15.12 mg/kg/day in males and females, respectively, for 12–24 months (EPA 1999). No adverse effects were observed in the study in dogs (Wilson et al. 2000). In rats, decreases in body weight gain were observed in the first 12–18 months at the highest dose levels. However, decreased food consumption were also observed at these doses during the same time period; therefore, decreased body weight gain is not considered adverse (EPA 1999). No other compound-related effects were observed.

This database was not considered adequate for derivation of a chronic-duration oral MRL because the targets of toxicity have not been established.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BROMOMETHANE

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 bromomethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were 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 bromomethane. 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 bromomethane 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 bromomethane 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
Developmental effects

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

	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 bromomethane 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 bromomethane. 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 bromomethane 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	(74-83-9[rn] OR "methyl bromide"[nm] OR "Bercema"[tw] OR "Brom-O-Gas"[tw] OR "Brom-O-Sol"[tw] OR "BROMO METHANE"[tw] OR "Bromomethane"[tw] OR "Celfume"[tw] OR "Curafume"[tw] OR "Dawson 100"[tw] OR "Detia gas EX-M"[tw] OR "Dowfume MC-2"[tw] OR "Dowfume MC-2R"[tw] OR "Dowfume MC-33"[tw] OR "Drexel Plant Bed Gas"[tw] OR "Edco"[tw] OR "Embafume"[tw] OR "F 40B1"[tw] OR "Halon 1001"[tw] OR "Haltox"[tw] OR "Iscobrome"[tw] OR "Kayafume"[tw] OR "M-B-C Fumigant"[tw] OR "M-B-R 98"[tw] OR "MBC Soil Fumigant"[tw] OR "Mbc-33 Soil Fumigant"[tw] OR "MBX"[tw] OR "Metafume"[tw] OR "Meth-O-Gas"[tw] OR "Methane, bromo"[tw] OR "Methogas"[tw] OR "Methybrom"[tw] OR "Methyl bromide"[tw] OR "Methyl fume"[tw] OR "Methylbromide"[tw] OR "Monobromomethane"[tw] OR "Pestmaster"[tw] OR "Profume"[tw] OR "R 40B1"[tw] OR "Terabol"[tw] OR "Terr-O-Cide II"[tw] OR "Terr-O-Gas"[tw] OR "Tri-Brom"[tw] OR "Zytox"[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	(74-83-9[rn] OR "Bercema" OR "Brom-O-Gas" OR "Brom-O-Sol" OR "BROMO METHANE" OR "Bromomethane" OR "Celfume" OR "Curafume" OR "Dawson 100" OR "Detia gas EX-M" OR "Dowfume MC-2" OR "Dowfume MC-2R" OR "Dowfume MC-33" OR "Drexel Plant Bed Gas" OR "Edco" OR "Embafume" OR "F 40B1" OR "Halon 1001" OR "Haltox" OR "Iscobrome" OR "Kayafume" OR "M-B-C Fumigant" OR "M-B-R 98" OR "MBC Soil Fumigant" OR "Mbc-33 Soil Fumigant" OR "MBX" OR "Metafume" OR "Meth-O-Gas" OR "Methane, bromo" OR "Methogas" OR "Methybrom" OR "Methyl bromide" OR "Methyl fume" OR "Methylbromide" OR "Monobromomethane" OR "Pestmaster" OR "Profume" OR "R 40B1" OR "Terabol" OR "Terr-O-Cide II" OR "Terr-O-Gas" OR "Tri-Brom" OR "Zytox") 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 14:16:04 ON 01 MAY 2019 CHARGED TO COST=EH011.10.LB.01.05 L1 5026 SEA FILE=TOXCENTER 74-83-9 L2 4155 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 4039 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 243 SEA FILE=TOXCENTER L3 AND ED>=20150101 ACT TOXQUERY/Q ---

Table B-2. Database Query Strings

Database search date	Query string
	L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29

Table B-2. Database Query Strings

Database search date	Query string
	L31 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?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 --------- L36 146 SEA FILE=TOXCENTER L4 AND L35 L37 133 DUP REM L36 (13 DUPLICATES REMOVED) ANSWERS '1-133' FROM FILE TOXCENTER L*** DEL 146 S L4 AND L35 L*** DEL 146 S L4 AND L35 L38 133 SEA FILE=TOXCENTER L37 L39 17 SEA FILE=TOXCENTER L38 AND MEDLINE/FS D SCAN L37

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
05/2019	Compounds searched: 74-83-9
NTP	
05/2019	"74-83-9" "Methyl bromide" "Methylbromide" "Bromomethane" "Monobromomethane" "BROMO METHANE" "Bercema" "Methane, bromo" "Edco" "MBX" "Terabol" "Halon 1001" "Brom-O-Gas" "Brom-O-Sol" "Celfume" "Curafume" "Dawson 100" "Detia gas EX-M" "Dowfume MC-2" "Dowfume MC-2R" "Dowfume MC-33" "Drexel Plant Bed Gas" "Embafume" "F 40B1" "Haltox" "Iscobrome" "Kayafume" "M-B-C Fumigant" "M-B-R 98" "MBC Soil Fumigant" "Mbc-33 Soil Fumigant" "Metafume" "Meth-O-Gas" "Methogas" "Methybrom" "Methyl fume" "Pestmaster" "Profume" "R 40B1" "Terr-O-Cide II" "Terr-O-Gas" "Tri-Brom" "Zytox"
Regulations.gov	
05/2019	74-83-9 "Methyl bromide" "Methylbromide" "Bromomethane" "Monobromomethane"
NIH RePORTER	
05/2019	Text Search: "Bercema" OR "Brom-O-Gas" OR "Brom-O-Sol" OR "BROMO METHANE" OR "Bromomethane" OR "Celfume" OR "Curafume" OR "Dawson 100" OR "Detia gas EX-M" OR "Dowfume MC-2" OR "Dowfume MC-2R" OR "Dowfume MC-33" OR "Drexel Plant Bed Gas" OR "Edco" OR "Embafume" OR "F 40B1" OR "Halon 1001" OR "Haltox" OR "Iscobrome" OR "Kayafume" OR "M-B-C Fumigant" OR "M-B-R 98" OR "MBC Soil Fumigant" OR "Mbc-33 Soil Fumigant" OR "MBX" OR "Metafume"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	OR "Meth-O-Gas" OR "Methane, bromo" OR "Methogas" OR "Methybrom" OR "Methyl bromide" OR "Methyl fume" OR "Methylbromide" OR "Monobromomethane" OR "Pestmaster" OR "Profume" OR "R 40B1" OR "Terabol" OR "Terr-O-Cide II" OR "Terr-O-Gas" OR "Tri-Brom" OR "Zytox" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 335
- Number of records identified from other strategies: 47
- Total number of records to undergo literature screening: 382

B.1.2 Literature Screening

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

- 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.

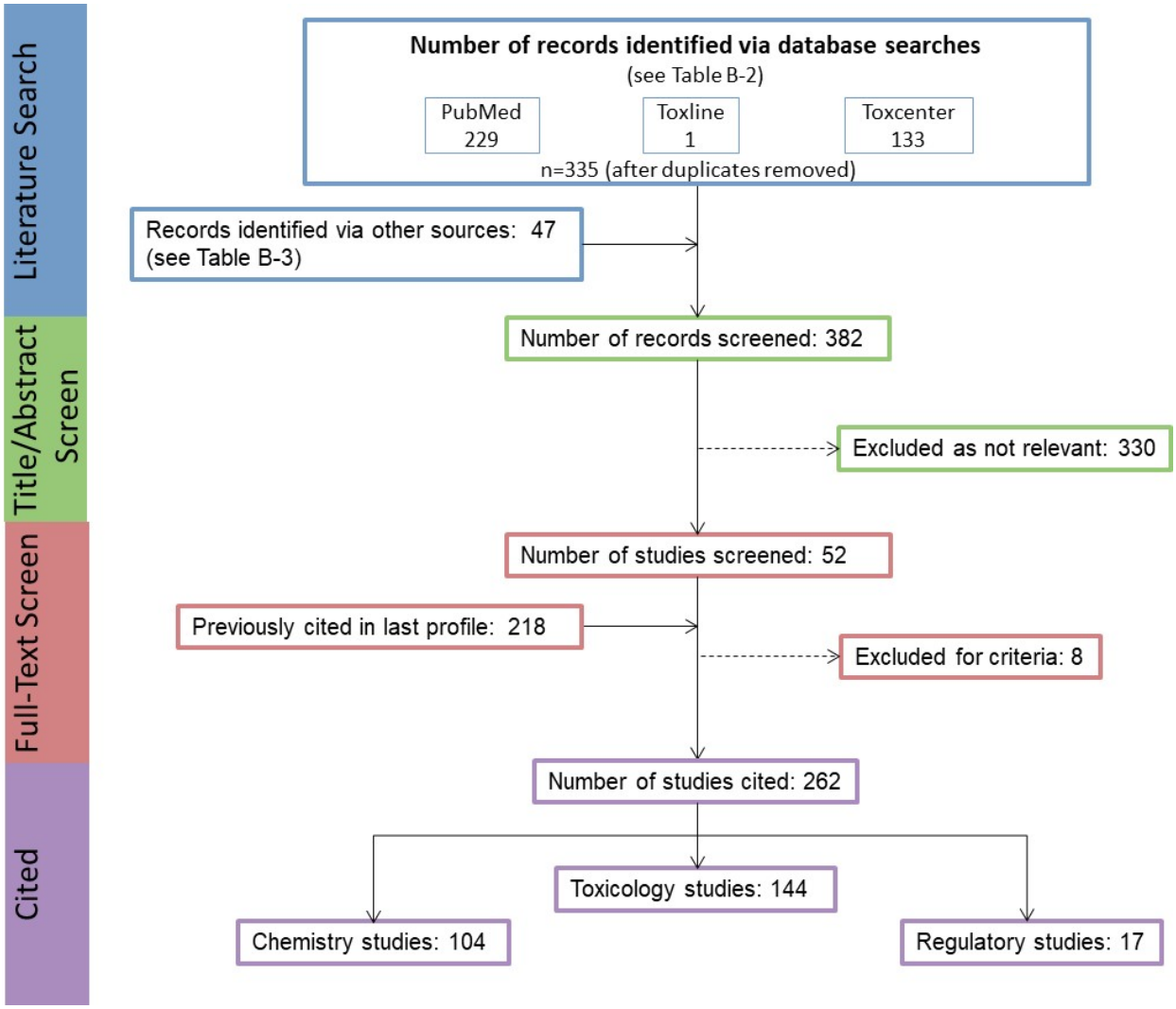
- Number of titles and abstracts screened: 382
- Number of studies considered relevant and moved to the next step: 52

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: 52
- Number of studies cited in the pre-public draft of the toxicological profile: 218
- Total number of studies cited in the profile: 262

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

Figure B-1. April 2018 Literature Search Results and Screen for Bromomethane



APPENDIX C. 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 C-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 C-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 C

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

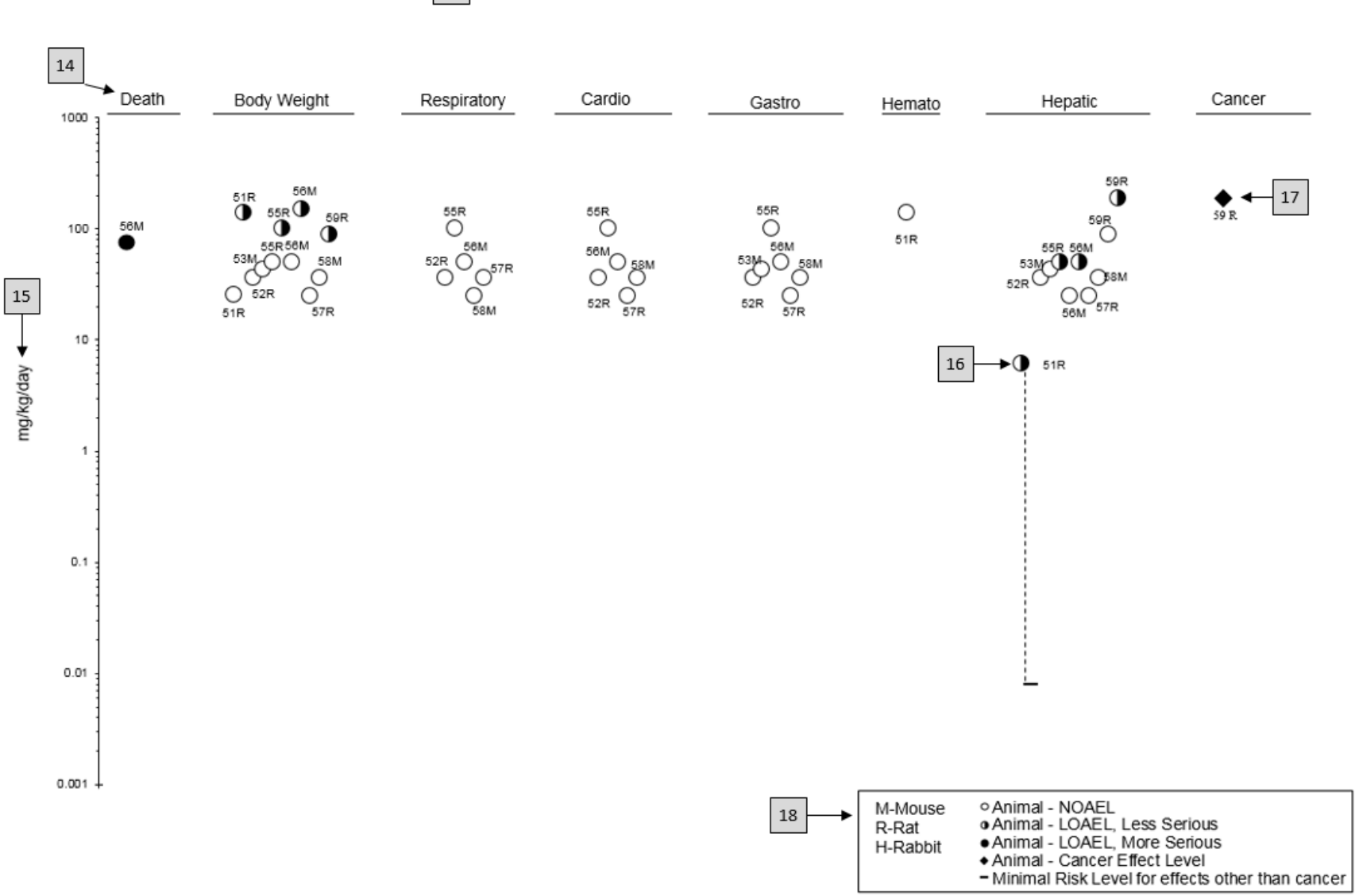
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
(2) **CHRONIC EXPOSURE**									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	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
(10) **Aida et al. 1992**									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	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).

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



APPENDIX D. 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 E. 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 F. 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
QPS	quarantine and preshipment
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