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.

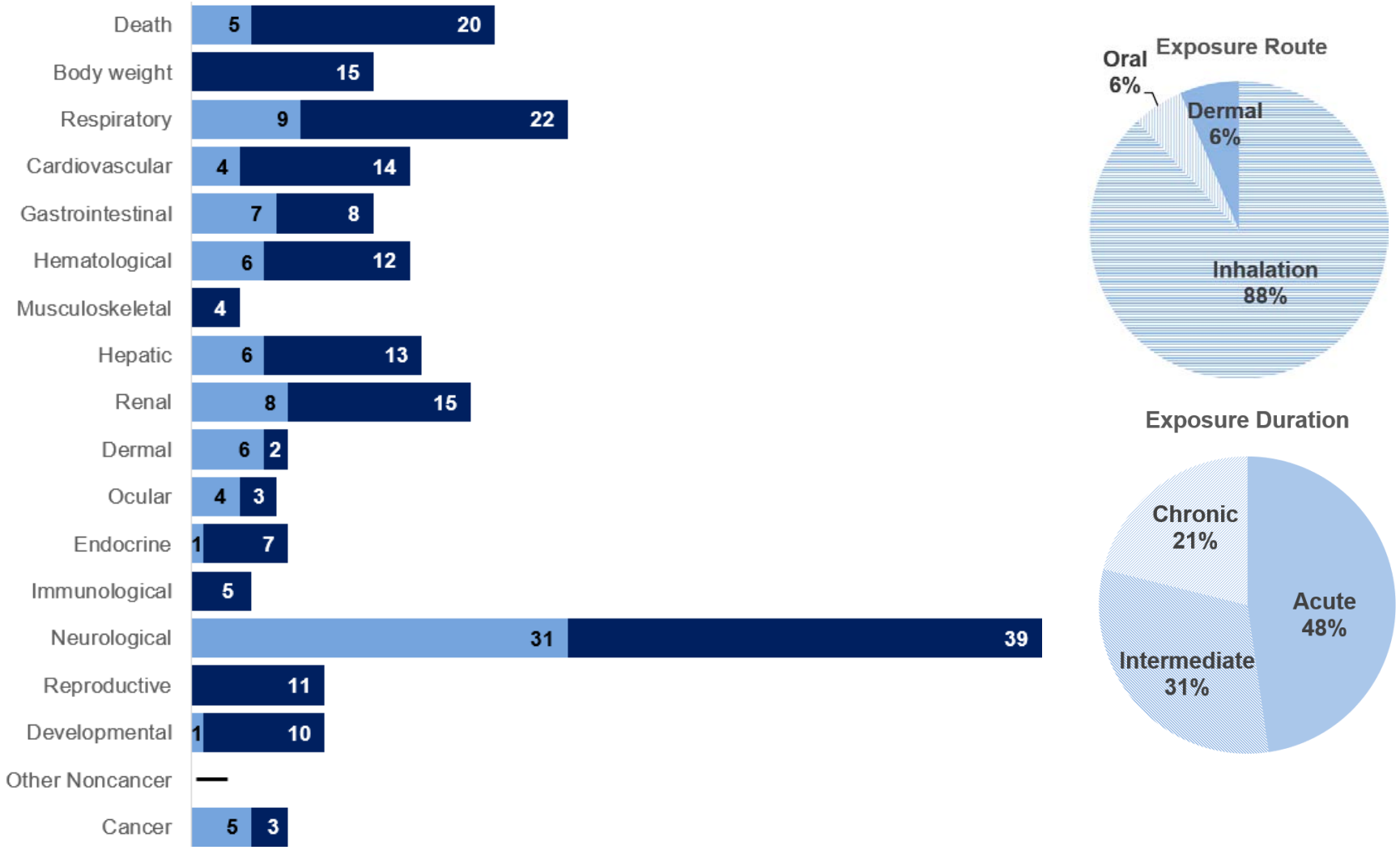
- **Developmental Endpoints:** In animal studies, increased incidences of gallbladder agenesis and fused sternebrae, and decreased fetal weight have been observed in the offspring of rabbits exposed to inhaled bromomethane. However, these effects have not been observed in inhalation studies in other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

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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

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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									

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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									

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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									

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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									

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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			

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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			

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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									

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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			

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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)

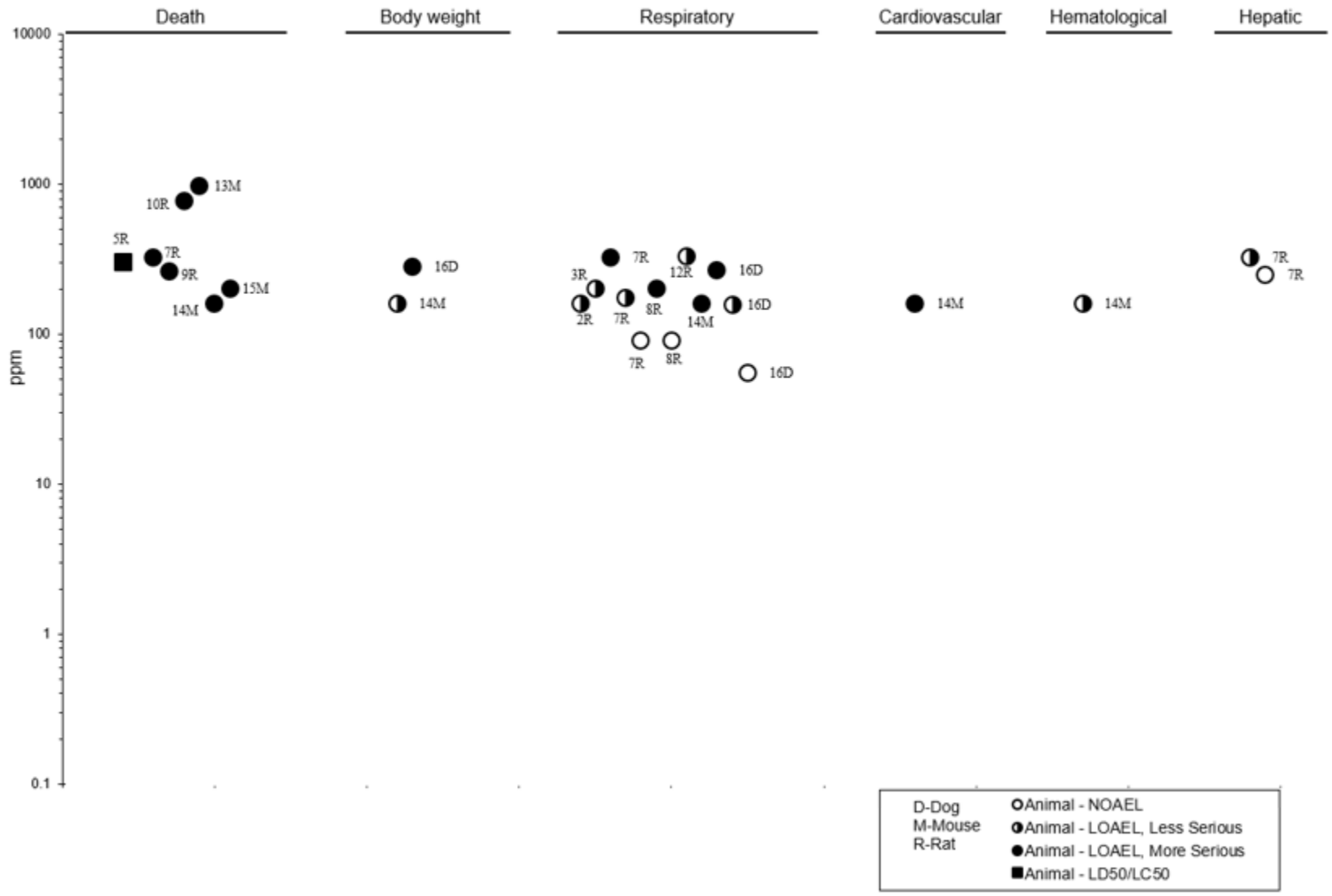


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation

Acute (≤14 days)

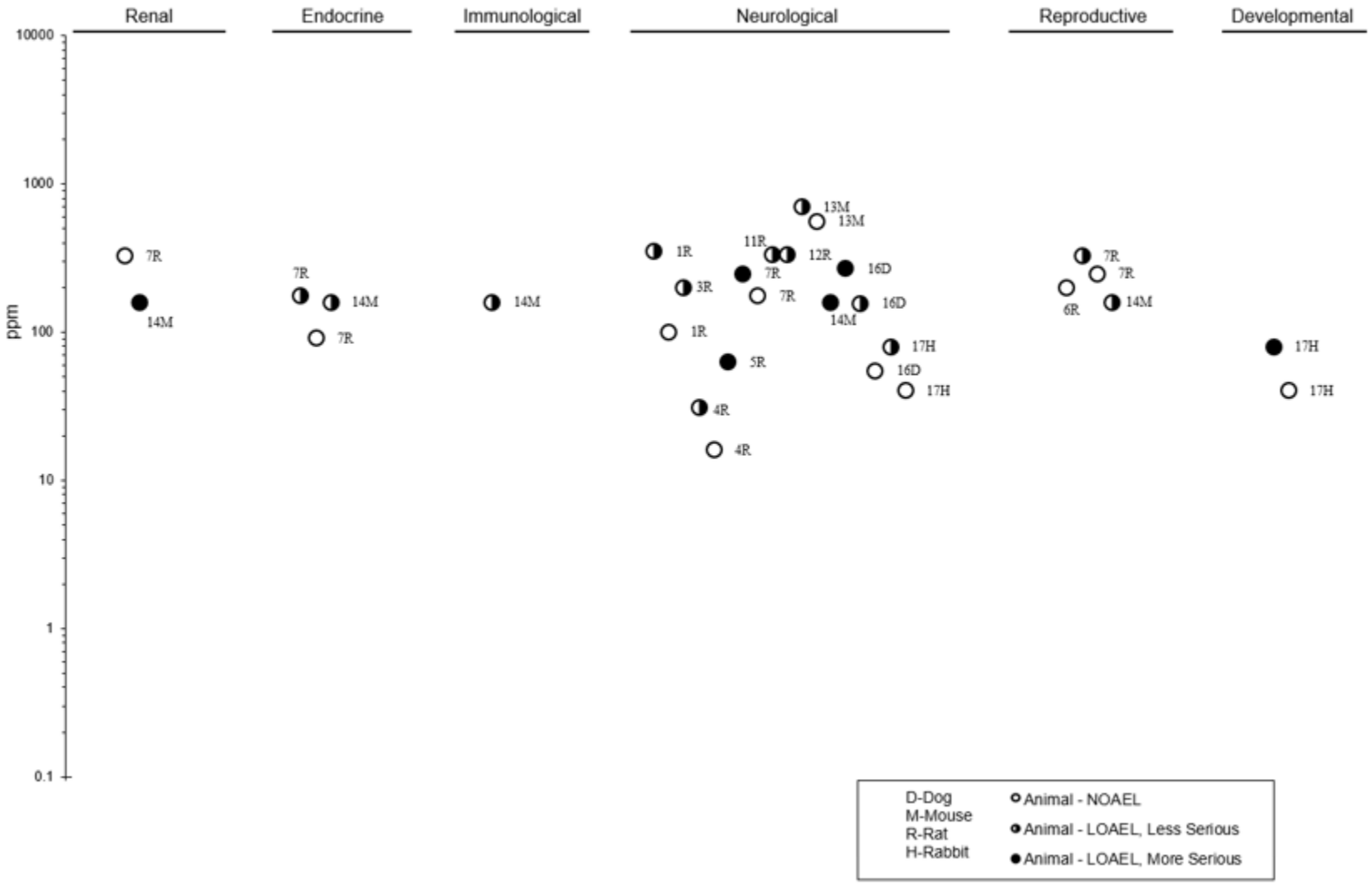


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

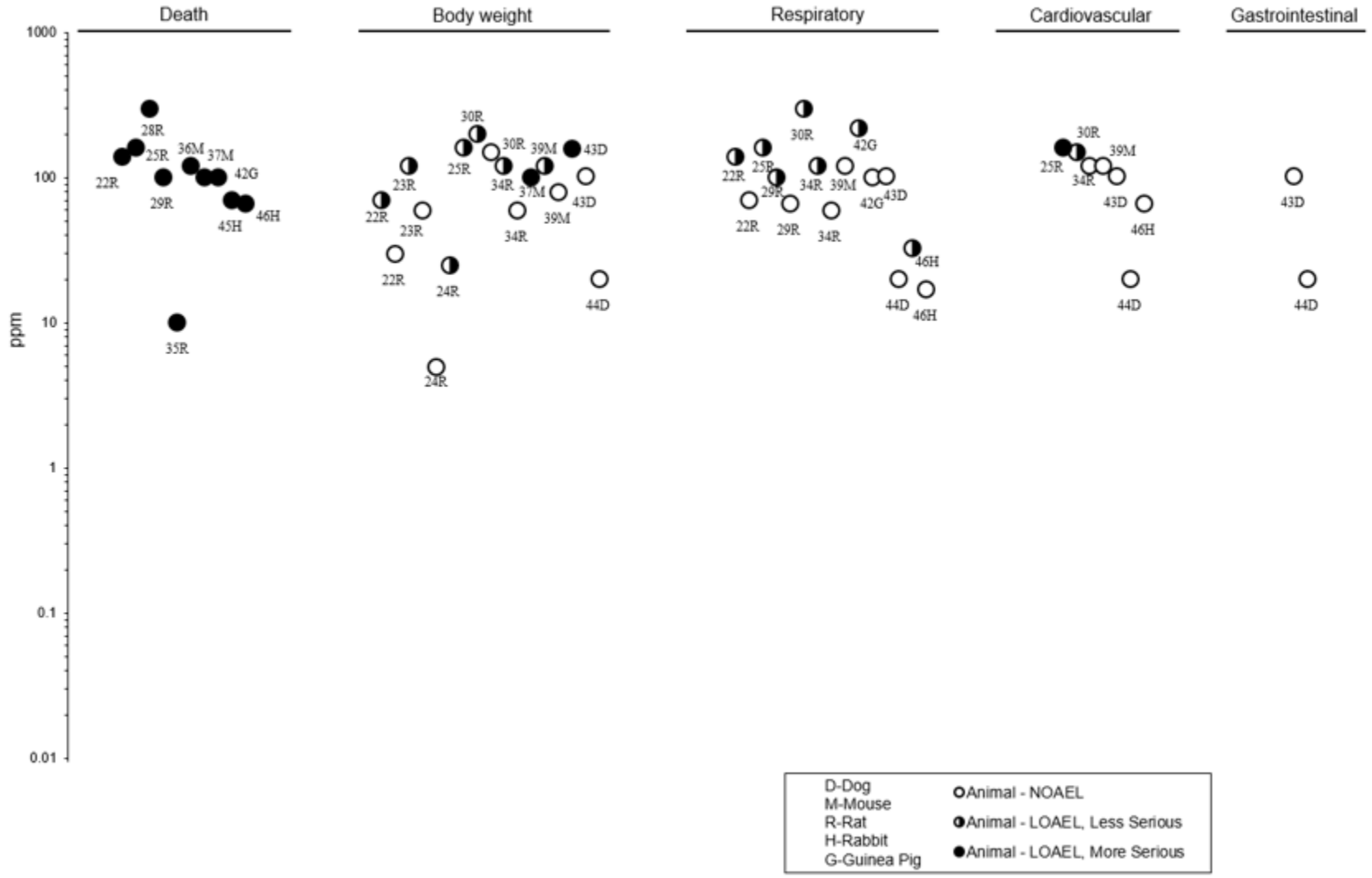


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

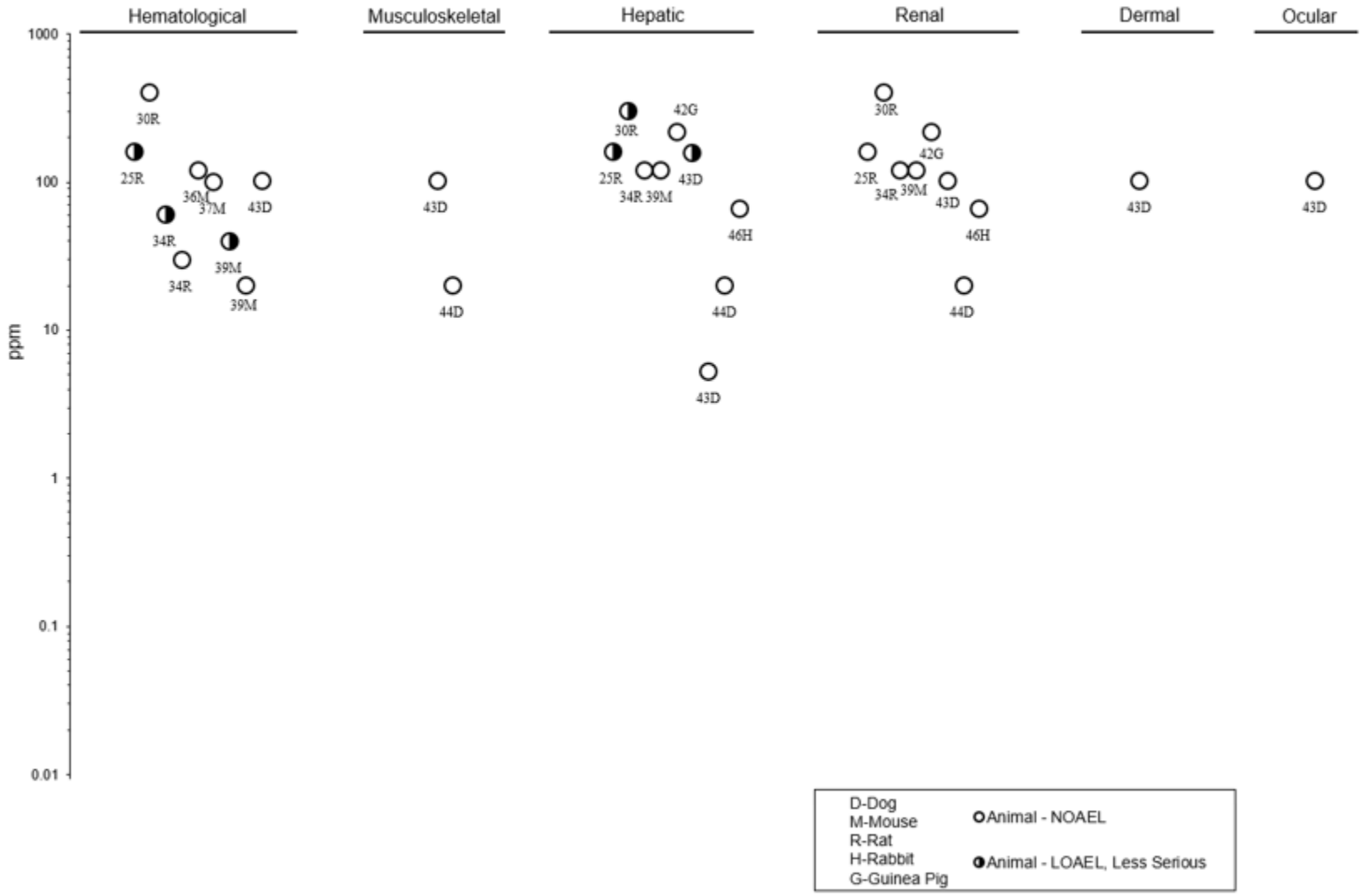


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Intermediate (15-364 days)

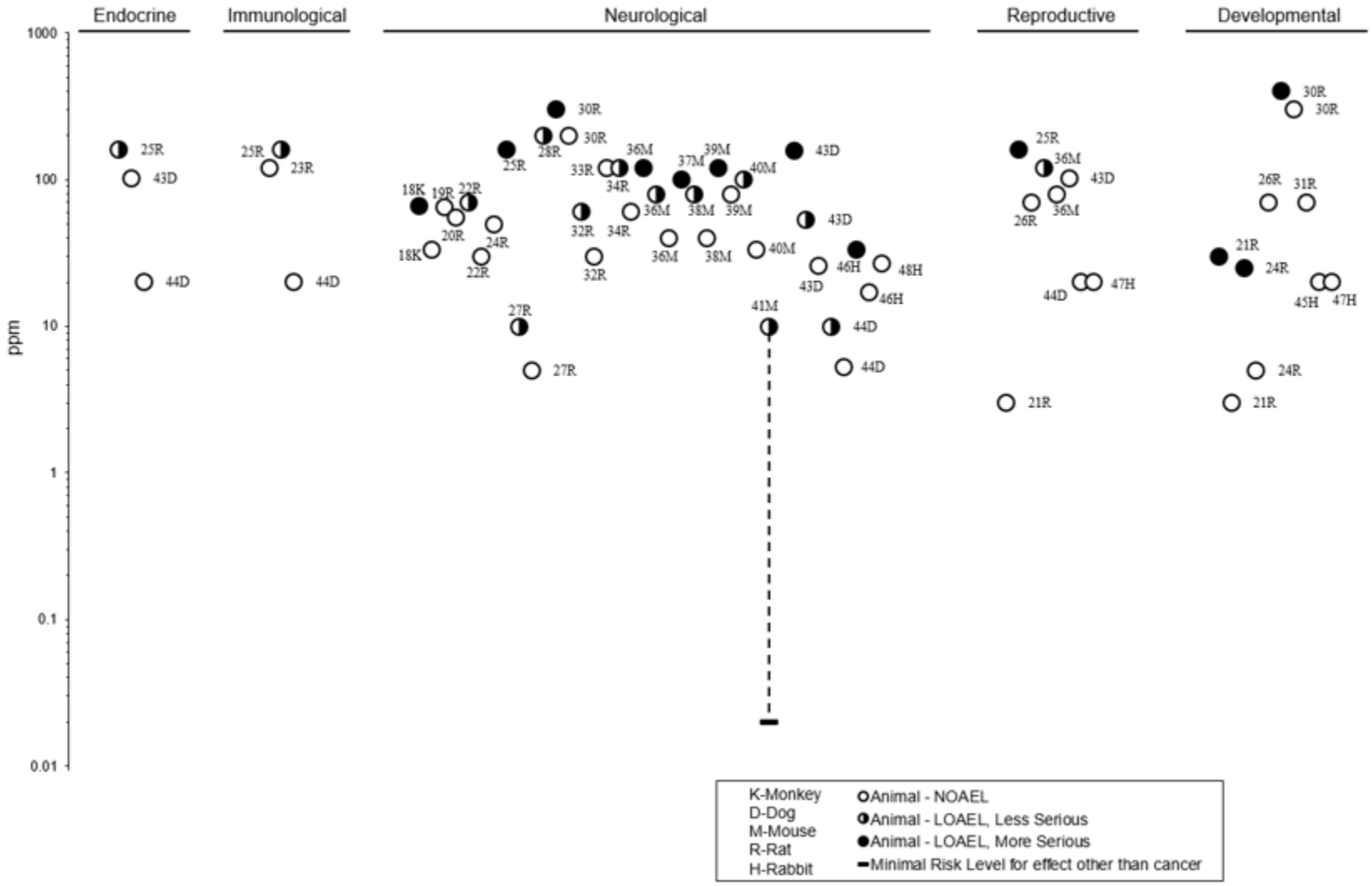


Figure 2-2. Levels of Significant Exposure to Bromomethane – Inhalation
Chronic (≥365 days)

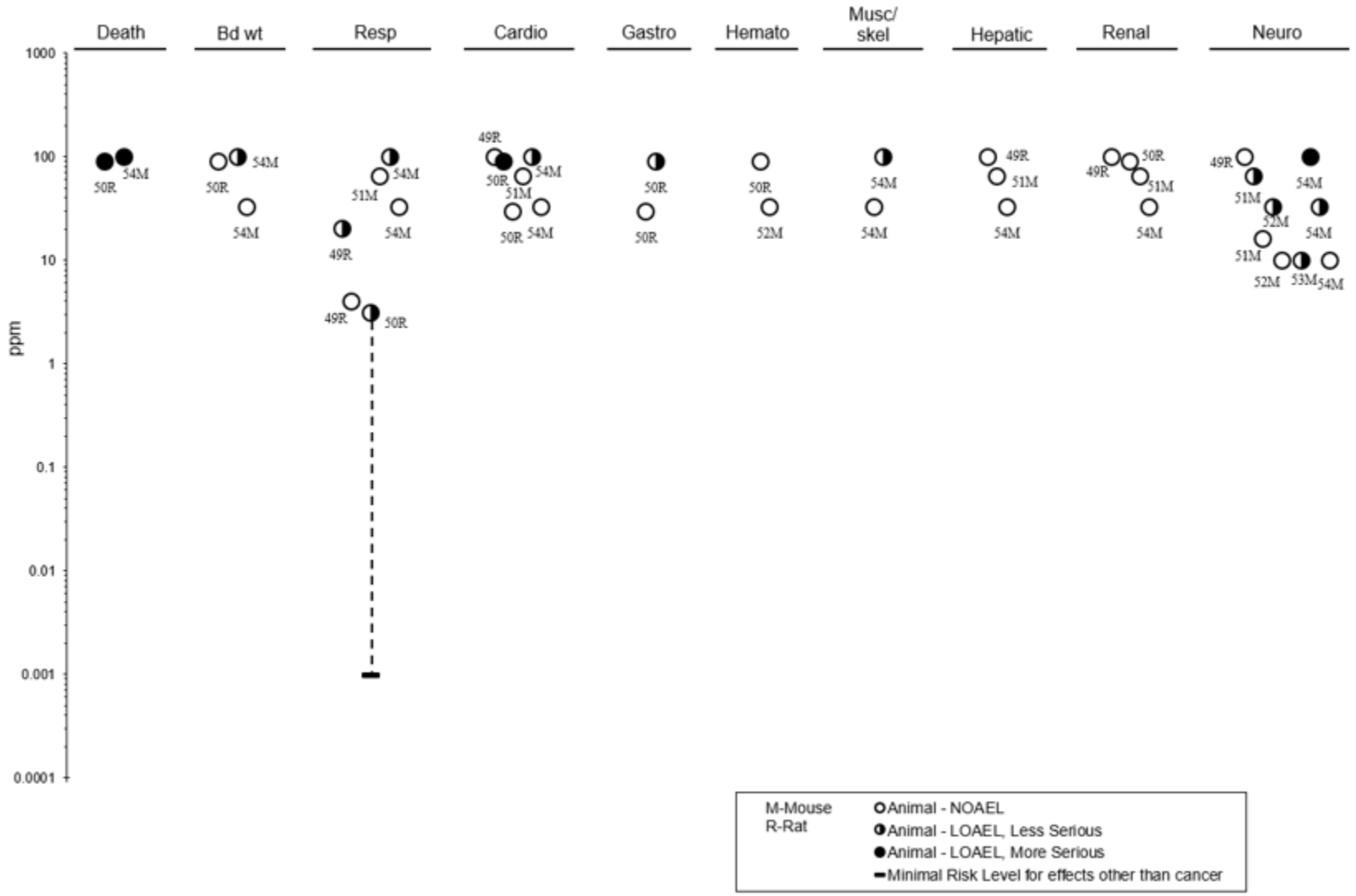


Table 2-2. Levels of Significant Exposure to Bromomethane – Oral

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)

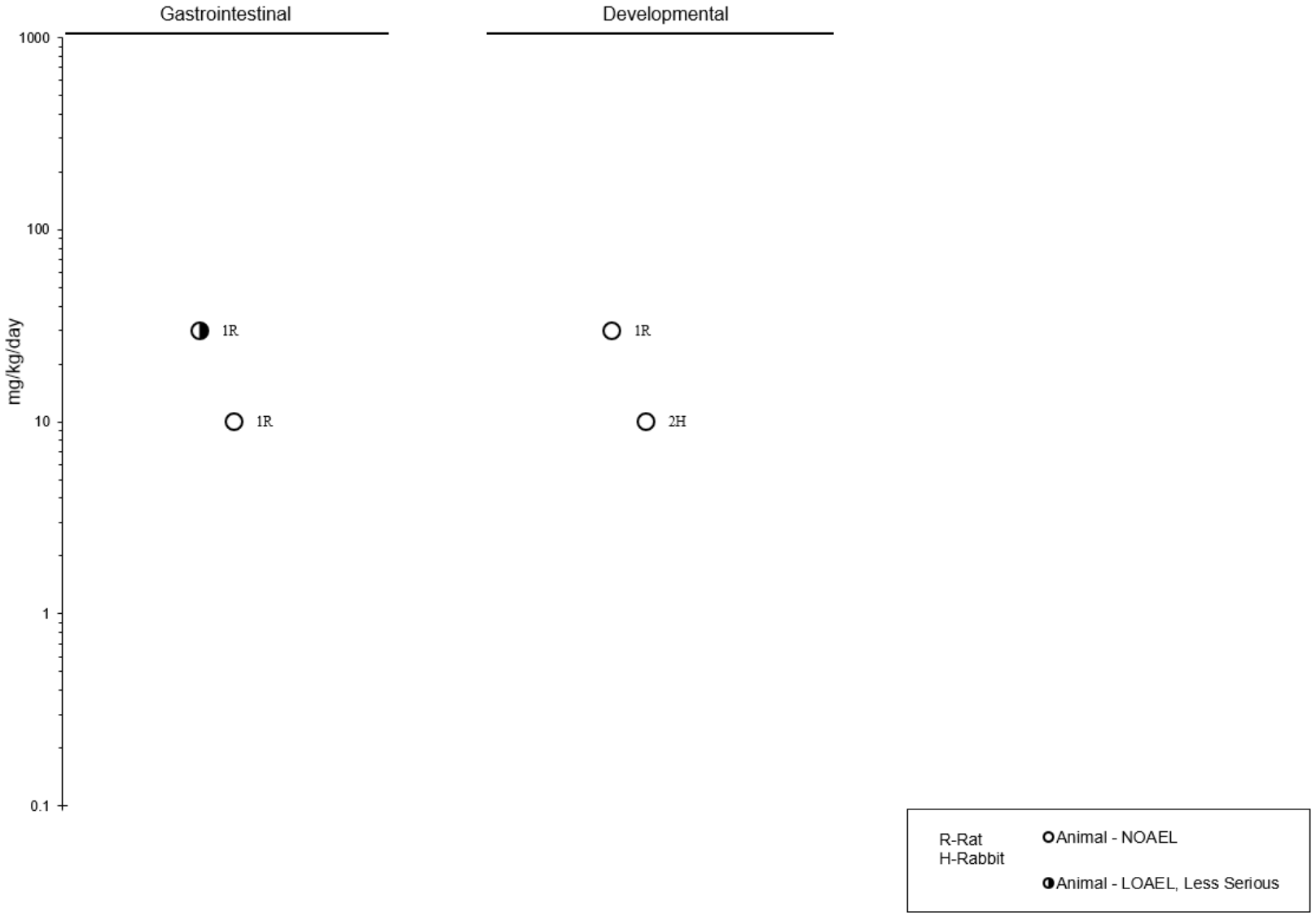


Figure 2-3. Levels of Significant Exposure to Bromomethane – Oral

Intermediate (15-364 days)

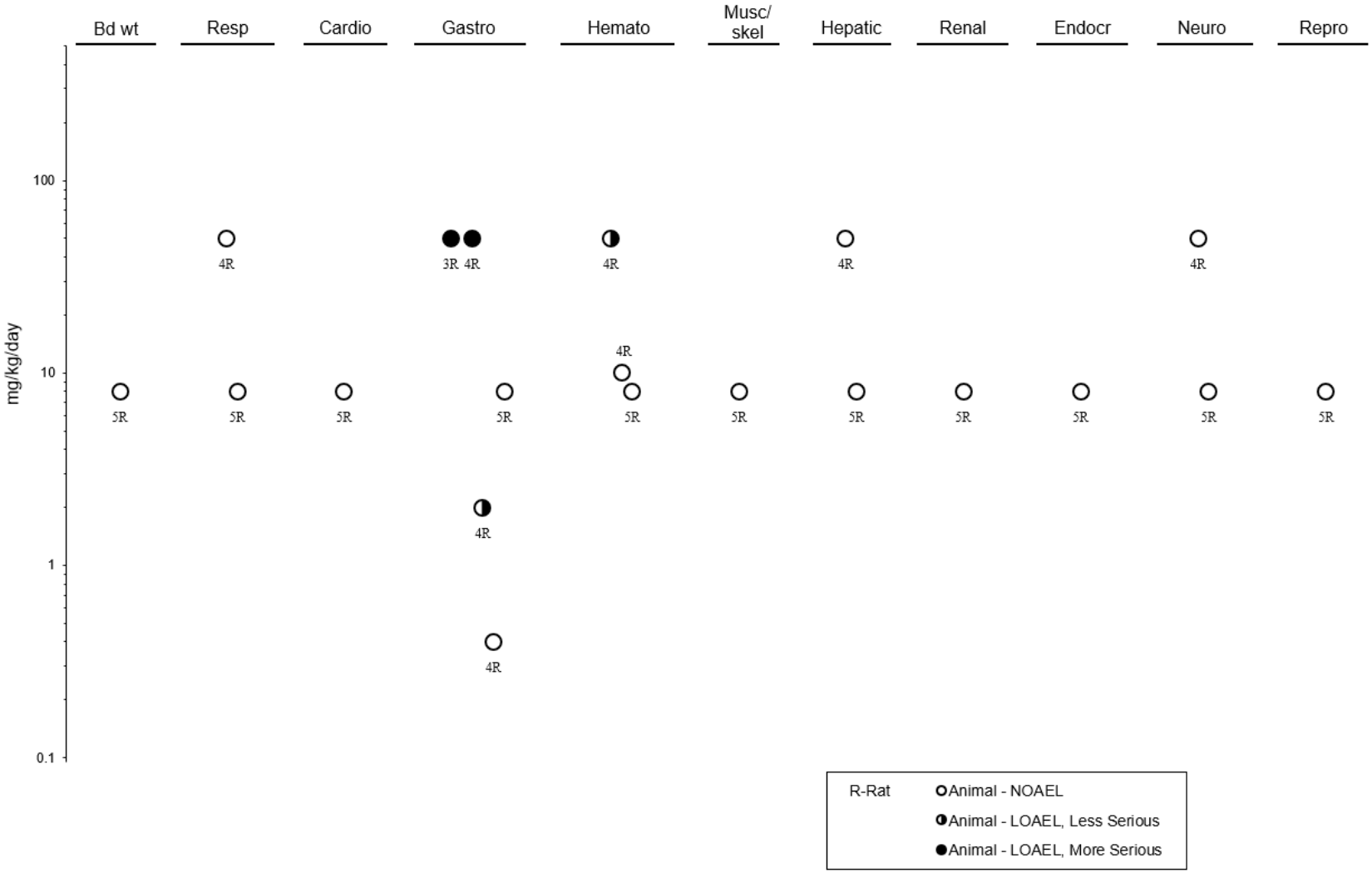
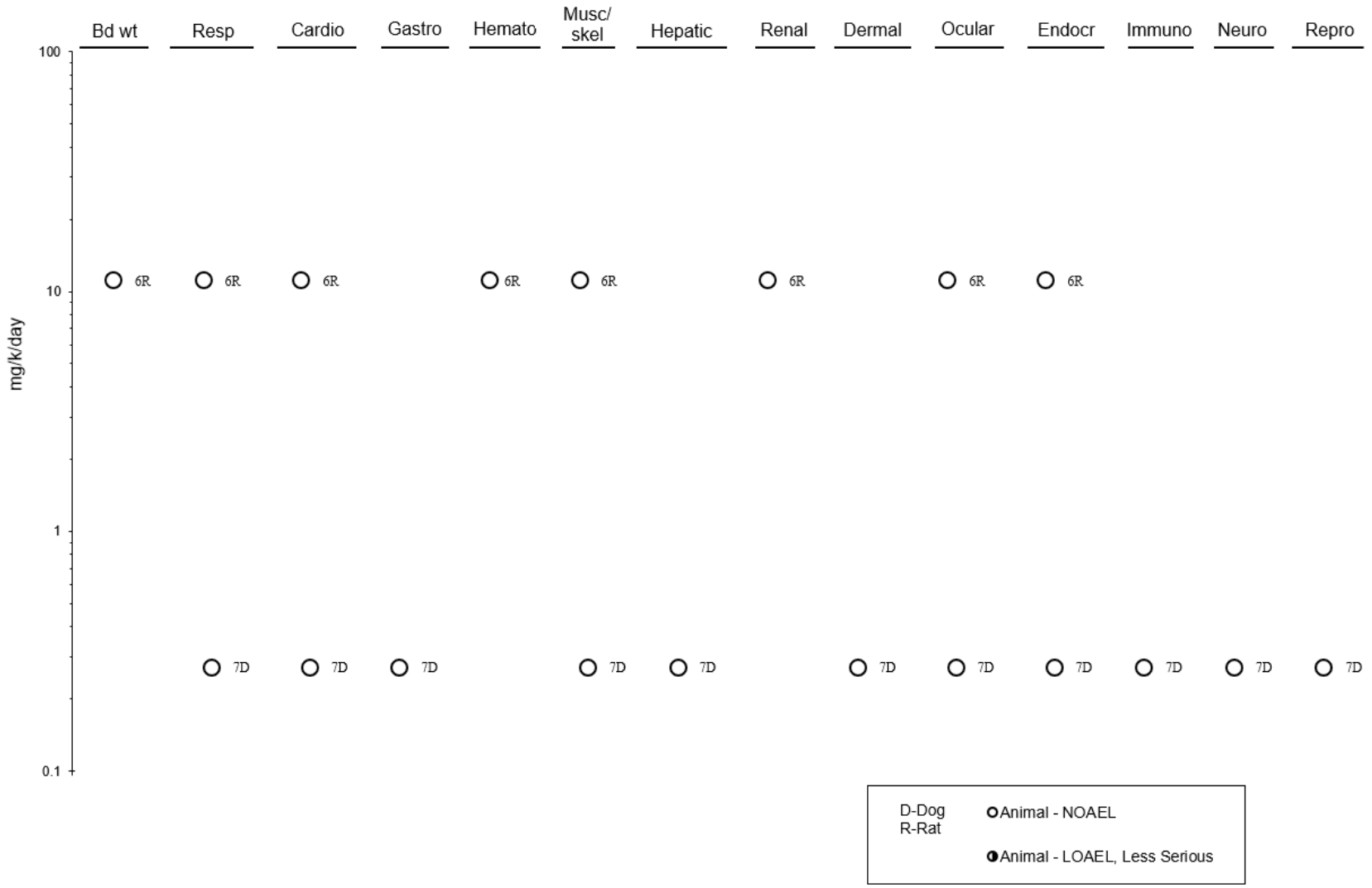


Figure 2-3. Levels of Significant Exposure to Bromomethane – Oral

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).