3. HEALTH EFFECTS

3.1 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 1-bromopropane. 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.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure 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 end point 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 end points. 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.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1-bromopropane are indicated in Table 3-1 and Figure 3-1.

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

Unless otherwise stated, all animal studies mentioned in Section 3.2 tested commercial-grade 1-bromopropane (purity ≥99%).

3.2.1 Inhalation Exposure

In occupational studies and case reports described below, exposure to 1-bromopropane occurred primarily via the inhalation route, but dermal exposure may have also occurred. Since (in most cases) it is not known whether the workers were using protective clothing and/or respirators, the specific contribution of each route of exposure is not possible to determine. Therefore, the reader should keep in mind that both inhalation and dermal routes combined may have contributed to the effects described.

3.2.1.1 Death

No reports of deaths in humans following inhalation exposure to 1-bromopropane were located in the available literature.

Lethal exposure concentrations have been identified in rats in acute-duration studies and in mice in intermediate-duration studies. In male and female rats exposed for 4 hours to concentrations of 1-bromopropane vapors ranging from 11,000 to 17,000 ppm, the combined LC_{50} was 14,374 ppm (95%

confidence interval [CI], 13,624–15,596) (Kim et al. 1999). No rats died in the 11,000-ppm exposure group, and all rats exposed to 17,000 ppm 1-bromopropane died during the 14-day observation period. Necropsy did not reveal gross alterations. Light microscopy showed that some exposed rats had cytoplasmic vacuolization of hepatocytes. In another study of male and female rats exposed for 4 hours to concentrations of 1-bromopropane vapors ranging from 6,040 to 8,500 ppm, the combined LC_{50} was 7,000 ppm (Elf AtoChem S.A. 1997). At necropsy, pulmonary lesions consisting of edema and "emphysema" were observed.

In intermediate-duration studies, exposure to 500 ppm 1-bromopropane vapors 6 hours/day, 5 days/week resulted in significant lethality in male and mice during the first 2 weeks of exposure (Anderson et al. 2010; NTP 2011). No deaths occurred in mice exposed to 250 ppm 1-bromopropane. The cause of death was not specified in these studies, but NTP stated that in the 14-week study, lethargy and abnormal breathing were observed in moribund mice on week 1. Since the 16-day and 14-week NTP studies also tested rats exposed up to 2,000 and 1,000 ppm 1-bromopropane, respectively, and there were no compound-related deaths, mice appear to be considerably more sensitive than rats to the acute toxicity of 1-bromopropane.

The LC_{50} from Kim et al. (1999) and the lethal doses from Anderson et al. (2010) and NTP (2011) are listed in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. One preliminary health survey and several case reports of workers experiencing frank neurotoxicity following exposure to 1-bromopropane indicate that occupational exposure to 1-bromopropane can cause mild respiratory irritation. In a preliminary health survey, 10/24 female and 6/13 male workers from a Chinese 1-bromopropane factory reported nose and/or throat irritation; workers were exposed to 1–171 ppm 1-bromopropane for 1–115 months (Ichihara et al. 2004a). In three female workers from a cushion company who were hospitalized for neurological symptoms following exposure to 1-bromopropane for 8–9 hours/day for ≥3 months, two of the women complained of sore throat, hoarseness, and/or sinus irritation (Ichihara et al. 2002). The mean daily time-weighted exposure level was 133±67 ppm (range 60–261 ppm). Raymond and Ford (2007) reported sinusitis in a woman who

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	4 hr				7000 (4-hour LC50)	Elf AtoChem S.A. 1997 1-Bromopropane	
2	Rat (Sprague-Dawley)	4 hr				14374 (4-hour LC50)	Kim et al. 1999 1-Bromopropane	
3	Mouse (B6C3F1)	4-10 wk 5 d/wk 6 hr/d				500 F (3/8 died in the first week)	Anderson et al. 2010 1-Bromopropane	
4	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d				500 M (4/5 deaths during first week)	NTP 2011 1-Bromopropane	
5	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d				500 (4/10 males and 5/10 females died in the first 2 weeks)	NTP 2011 1-Bromopropane	
Systemic								
6	Rat (Sprague-Dawley)	14 d Gd 6-19 6 hr/d	Bd Wt	100 F	498 F (14.3% reduction in net body weight change on Gd 6-20)	996 F (24.6% reduction in net body weight change on Gd 6-20)	BSOC 2001b 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
7	Rat (Wistar)	4 hr	Resp	6040		6920 (pulmonary edema and emphysema)	Elf AtoChem S.A. 1997 1-Bromopropane	
			Hemato	7280 M				
			Bd Wt	7280 M				
				7020 F				
8	Rat (Wistar)	7 d 8 hr/d	Bd Wt	800 M			Wang et al. 2002 1-Bromopropane	
9	Rat (Wistar)	7 d 8 hr/d	Endocr	1000 M			Zhang et al. 2013 1-Bromopropane	Endocrine NOAEL is for adrenal gland weight and plasma corticosterone.
			Bd Wt	800 M	1000 M (11% reduction in final body weight)			
Neurological								
10	Human	< 2 wks (Occup)			107 F (subjective complaints of headache, dizziness, numbness, weakness)		Raymond and Ford 2007 1-Bromopropane	Case reports (n=2)
11	Rat (Fischer- 344)	14 d 8 hr/d		200[b] M	1000 M (reduced forelimb grip strength)		Honma et al. 2003 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	4 hr			11000 (decreased activity, ataxia)		Kim et al. 1999 1-Bromopropane	
13	Rat (Sprague-Dawley)	1 hr		300	1800 (decreased activity; mild ataxia)		Kim et al. 1999 1-Bromopropane	
14	Rat (Wistar)	7 d 8 hr/d		1000 M			Zhang et al. 2013 1-Bromopropane	NOAEL is for neurogenesis in the hippocampus.
Reproductive								
15	Rat (Sprague-Dawley)	14 d Gd 6-19 6 hr/d		996 F			BSOC 2001b 1-Bromopropane	
16	Rat (Wistar)	4 hr		8500 M			Elf AtoChem S.A. 1997 1-Bromopropane	NOAEL is for histopathology of the testes.
17	Mouse (C57BL/6N)	6 hr			800 M (37% reduced sperm motility)		Garner et al. 2007 1-Bromopropane	CYP2E1-null mice showed only a 12% reduction in sperm motility.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Developmental								
18	Rat (Sprague-Dawley)	14 d Gd 6-19 6 hr/d		498	996 (7.4% reduced fetal weight)		BSOC 2001b 1-Bromopropane	
INTERMEDIATE EXPOSURE								
Systemic								
19	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	600			Albemarle Corporation 1997 1-Bromopropane	NOAELs are for clinical chemistry, urinalysis, and organ weight/ histology
			Cardio	600				
			Gastro	600				
			Hemato	600				
			Musc/skel	600				
			Hepatic	400 M	600 M (vacuolation of centrolobular hepatocytes and increased liver weight)			
			Renal	600				
			Endocr	600				
			Dermal	600				
			Ocular	600				
			Bd Wt	600				
			Metab	600				

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
20	Rat (Wistar)	6 wk 7 d/wk 8 hr/d	Cardio	400 M	1000 M (15-20% increase in systolic blood pressure)		Banu et al. 2007 1-Bromopropane	
			Bd Wt	400 M		1000 M (Body weight reduced 30% at exposure cessation)		
21	Rat (Sprague-Dawley)	2-gen 70 d 6 hr/d	Resp	750			BSOC 2001a 1-Bromopropane	
			Hepatic	100 M	250 M (hepatocellular vacuolization in F0 and F1 males)			
			Renal	250 F	500 F (transitional renal epithelial hyperplasia and pelvic mineralization in F0 females)			
			Endocr	500 M	750 M (20% decrease absolute weight of F1 male adrenals and pituitary)			
			Bd Wt	250 F	500 F (12-14% reduced body weight F0 and F1 dams on Gd 20)			
22	Rat (Wistar)	42 d 8 hr/d	Bd Wt	400 F	800 F (11% reduced maternal body weight on postnatal day 21)		Furuhashi et al. 2006 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
23	Rat (Fischer- 344)	3 wk 7 d/wk 8 hr/d	Bd Wt	200 M	1000 M (12% weight loss during exposure period)		Honma et al. 2003 1-Bromopropane	
24	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Cardio		1000 M (approximately 15% increase in systolic blood pressure)		Huang et al. 2016 1-Bromopropane	
			Hepatic		1000 M (21.8% increase in absolute liver weight)			
			Bd Wt		1000 M (12.2% reduction in body weight)			
25	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Resp	800 M			Ichihara et al. 2000a 1-Bromopropane	NOAELs are for organ weight and histopathology.
			Cardio	800 M				
			Hemato	800 M				
			Musc/skel	800 M				
			Hepatic	800 M				
			Renal	800 M				
			Endocr	800 M				
			Bd Wt	400 M	800 M (final body weight reduced 12%)			

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
26	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Musc/skel	400 M		800 M (alteration in myofilaments in soleus muscle)	Ichihara et al. 2000b 1-Bromopropane	
			Bd Wt	400 M	800 M (12% reduction in terminal body weight)			
27	Rat (Wistar)	4-12 wk 5 d/wk 6 hr/day	Hepatic		700 M (47-49% decrease plasma ALT activity)		Ishidao et al. 2002 1-Bromopropane	No microscopic examination of the liver was conducted.
28	Rat (Sprague-Dawley)	8 wk 5 d/wk 6 hr/day	Resp	1800			Kim et al. 1999 1-Bromopropane	
			Cardio	1800				
			Hemato	1800 M				
			Hepatic		50 (hepatocyte vacuolization)			
			Renal	300 F	1800 F (tubular casts in the kidneys)			
			Endocr	1800				
			Bd Wt	1800				

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
29	Rat (Fischer- 344)	16 d 5 d/wk 6 hr/d	Hepatic		125 F (increased relative and absolute liver weight)		NTP 2011 1-Bromopropane	
			Renal		125 F (increased relative kidney weight)			
			Bd Wt	1000 M		2000 M (final body weight reduced 27%)		

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
30	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d	Resp	1000			NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology and organ weight. Vacuolization in hepatocytes at >=250 ppm.
			Cardio	1000				
			Gastro	1000				
			Hemato	1000				
			Musc/skel	1000				
			Hepatic	62.5 F	125 F (significant increase in absolute and relative liver weight)			
			Renal	500 F	1000 F (increased absolute and relative kidney weight)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 M	1000 M (12% reduction in final body weight)			
31	Rat (Fischer- 344)	20 d 8 hr/d	Bd Wt	1000 F			Sekiguchi et al. 2002 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
32	Rat (Sprague-Dawley)	13 wk 5 d/wk 6/hr/d	Bd Wt	1250			Sohn et al. 2002 1-Bromopropane	
33	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Bd Wt	800 M	1000 M (15% reduction in terminal body weight)		Subramanian et al. 2012 1-Bromopropane	
34	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Bd Wt	400 M	800 M (12% reduction in terminal body weight)		Wang et al. 2003 1-Bromopropane	
35	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Hepatic		200 F (significant increase in absolute and relative liver weight)		Yamada et al. 2003 1-Bromopropane	
			Renal		200 F (significant increase in absolute and relative kidney weight)			
			Endocr	800 F				
			Bd Wt	400 F		800 F (final body weight reduced 30%)		

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
36	Rat (Wistar)	7 wk 7 d/wk 8 hr/d	Hemato	1000 M			Yu et al. 1998 1-Bromopropane	Hepatic and renal NOAELs are for organ histopathology.
			Hepatic	1000 M				
			Renal	1000 M				
			Bd Wt		1000 M (19% reduced body weight)			
37	Rat (Wistar)	7 wk 7 d/wk 8 hr/d	Hemato	1000 M			Yu et al. 2001 1-Bromopropane	NOAELs are for tissue histopathology
			Hepatic	1000 M				
			Renal	1000 M				
			Bd Wt		1000 M (19% reduced terminal body weight)			
38	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Endocr	1000 M			Zhang et al. 2013 1-Bromopropane	Endocrine NOAEL is for adrenal gland weight and serum corticosterone.
			Bd Wt	800 M	1000 M (10% reducton in final body weight)			

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
39	Mouse (BALB/cA)	4 wk 7 d/wk 8 h/d	Hepatic		50 M (hepatocellular degeneration and focal necrosis)		Liu et al. 2009 1-Bromopropane	
			Bd Wt	250 M				
40	Mouse (C57BL/6J)	4 wk 7 d/wk 8 hr/d	Hepatic		100 M (liver necrosis)		Liu et al. 2010 1-Bromopropane	Nfr2-null mice were more susceptible than the wild type to 1-BP-induced liver toxicity.
41	Mouse (B6C3F1)	17 d 5 d/wk 6 hr/d	Resp		125 (minimal grade necrosis and regeneration in bronchioles)		NTP 2011 1-Bromopropane	Nasal lesions observed in olfactory and respiratory epithelium at 500 ppm and higher.
			Cardio	500 M	1000 M (decreased absolute and relative heart weight)			
			Hepatic	250 M		500 M (moderate to marked centrilobular necrosis)		
			Renal	500 F	1000 F (increased absolute and relative kidney weight)			
			Bd Wt	2000				

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d	Resp	250	500 (cytoplasmic vacuolization in nasal respiratory epithelium, trachea, and bronchioles)		NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology and organ weight
			Cardio	500				
			Gastro	500				
			Hemato	500				
			Musc/skel	500				
			Hepatic	250		500 (necrosis and hepatocyte degeneration)		
			Renal	250	500 (increased absolute and relative kidney weight)			
			Endocr	250 F		500 F (moderate to marked necrosis of adrenal cortex)		
			Dermal	500				
			Ocular	500				
			Bd Wt	500				
43	Mouse C57BL/6J	4 wk 8 hr/d	Hepatic		50 M (mild centrilobular hepatocyte degeneration)	250 M (severe liver necrosis, hemorrhage, and hepatocyte degeneration).	Zong et al. 2016 1-Bromopropane	
			Bd Wt	250 M				

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
44	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for organ weight/histology
45	Rat (Fischer- 344)	4-10 wk 5 d/wk 6 hr/d		250 F	500 F (decreased CD4+/CD8- cells in spleen at 10 weeks)		Anderson et al. 2010 1-Bromopropane	Suppression of IgM response to SRBC at 1,000 ppm (10 wks)
46	Rat (Sprague-Dawley)	2-gen 70 d 6 hr/d		750			BSOC 2001a 1-Bromopropane	Increased brown pigment in the spleen considered not toxicologically significant.
47	Rat (Wistar)	12 wk 7 d/wk 8 hr/d		800 M			Ichihara et al. 2000a 1-Bromopropane	NOAEL is for organ weight and histopathology of the spleen and thymus.
48	Rat (Sprague-Dawley)	8 wk 5 d/wk 6 hr/day		1800			Kim et al. 1999 1-Bromopropane	NOAEL is for histopathology of thymus and spleen.
49	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		1000			NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
50	Rat (Wistar)	12 wk 7 d/wk 8 hr/d		800 M			Yamada et al. 2003 1-Bromopropane	NOAEL is for weight and histopathology of spleen and thymus.
51	Mouse (B6C3F1)	4-10 wk 5 d/wk 6 hr/d			125 F (suppression of IgM response to SRBC at 10 weeks)		Anderson et al. 2010 1-Bromopropane	
52	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		500			NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.
Neurological								
53	Human	2-12 mo				133 F (ataxia, numbness, weakness, autonomic dysfunction, mood changes)	Ichihara et al. 2002 1-Bromopropane	Case reports (n=3)
54	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for FOB, motor activity, and organ weight/histology
55	Rat (Wistar)	6 wk 7 d/wk 8 hr/d		400 M	1000 M (decreased hindlimb muscle strength)		Banu et al. 2007 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
56	Rat (Sprague-Dawley)	2-gen 70 d 6 hr/d		750			BSOC 2001a 1-Bromopropane	NOAEL is for histopathology of the brain of the F0 generation.
57	Rat (Wistar)	4 wk 5 d/wk 6 h/d				1500 M (ataxic gate, convulsions)	Fueta et al. 2002 1-Bromopropane	
58	Rat (Wistar)	8 wk 5 d/wk 6 hr/d			700 M (increased excitability in hippocampal neurons)		Fueta et al. 2004 1-Bromopropane	Experiments were conducted ex vivo in hippocampal slices.
59	Rat (Wistar)	12 wk 5 d/wk 6 hr/d		200 M	400 M (increased excitability in hippocampal neurons)		Fueta et al. 2007 1-Bromopropane	Experiments were conducted ex vivo in hippocampal slices.
60	Rat (Fischer- 344)	3 wk 8 hr/d		10[c] M	50 M (increased spontaneous locomotor activity)		Honma et al. 2003 1-Bromopropane	
61	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 M (significantly reduced hindlimb grip strength)		Ichihara et al. 2000b 1-Bromopropane	Morphological and physiological changes in peripheral nerve occurred at 800 ppm.
62	Rat (Sprague-Dawley)	8 wk 5 d/wk 6 hr/day		1800			Kim et al. 1999 1-Bromopropane	NOAEL is histopathology of the brain.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
63	Rat (Fischer- 344)	4 wk 7 d/wk 8 hr/d		400 M	800 M (decrease density of noradrenergic axons in brain areas)		Mohideen et al. 2011 1-Bromopropane	
64	Rat (Fischer- 344)	4 wk 7 d/wk 8 hr/d			400 M (morphological alterations in astrocytes in cerebellum)		Mohideen et al. 2013 1-Bromopropane	
65	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		1000			NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
66	Rat (Sprague-Dawley)	13 wk 5 d/wk 6/hr/d		1250			Sohn et al. 2002 1-Bromopropane	NOAEL is for histopathology of central and peripheral nervous tissues.
67	Rat (Wistar)	4 wk 7 d/wk 8 hr/d		800 M	1000 M (morphological alterations in cerebellar microglia)		Subramanian et al. 2012 1-Bromopropane	
68	Rat (Wistar)	12 wk 5 d/wk 6 hr/d			400 M (increased excitability in hippocampal neurons)		Ueno et al. 2007 1-Bromopropane	Excitability was tested in hippocampal slices.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
69	Rat (Wistar)	7 wk 7 d/wk 8 hr/d				1000 M (hindlimb paralysis)	Yu et al. 1998 1-Bromopropane	Motor nerve conduction velocity was decreased 18%.
70	Rat (Wistar)	7 wk 7 d/wk 8 hr/d				1000 M (peripheral nerve degeneration)	Yu et al. 2001 1-Bromopropane	
71	Rat (Wistar)	4 wk 7 d/wk 8 hr/d		600 M		900 M (reduced neurogenesis in hippocampus)	Zhang et al. 2013 1-Bromopropane	NOAEL and LOAEL are TWA exposure concentrations over study duration.
72	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		500			NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
Reproductive								
73	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for organ weight/histology
74	Rat (Wistar)	6 wk 7 d/wk 8 hr/d			400 M (23% reduced epididymal sperm count)	1000 M (>30% reduced absolute reproductive organs weight)	Banu et al. 2007 1-Bromopropane	

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
75	Rat (Sprague-Dawley)	2-gen 70 d 6 hr/d		100	250 M (reduced absolute prostate weight in F0 males) 250 F (increased estrous cycle length in F1 females)	750 (100% infertility)	BSOC 2001a 1-Bromopropane	
76	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 M (26-27% reduced absolute and relative seminal vesicles weight)		Ichihara et al. 2000a 1-Bromopropane	
77	Rat (Sprague-Dawley)	8 wk 5 d/wk 6hr/d		300 F	1800 F (27-30% increased relative ovaries weight)		Kim et al. 1999 1-Bromopropane	No effects were reported in the testes.
78	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		500 M 125 F	1000 M (reduced sperm count and motility) 250 F (alterations in estrus cycles length)		NTP 2011 1-Bromopropane	
79	Rat (Fischer- 344)	20 d 8 hr/d		1000 F			Sekiguchi et al. 2002 1-Bromopropane	NOAEL is for effects on estrous cycles and spontaneous ovulation.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
80	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 F (decreased ovarian antral follicle counts)		Yamada et al. 2003 1-Bromopropane	
81	Rat (Wistar)	7 wk 7 d/wk 8 hr/d		1000 M			Yu et al. 1998 1-Bromopropane	NOAEL is for testes histopathology.
82	Rat (Wistar)	7 wk 7 d/wk 8 hr/d		1000 M			Yu et al. 2001 1-Bromopropane	NOAEL is for histopathology of the testes.
83	Mouse (BALB/cA)	4 wk 7 d/wk 8 h/d			50 M (decreased sperm count and motility; increased abnormal sperm)		Liu et al. 2009 1-Bromopropane	
84	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		250	500 (decreased sperm per gram cauda; estrus cycles alterations)		NTP 2011 1-Bromopropane	
Developmental								
85	Rat (Sprague-Dawley)	2-gen 70 d 6 hr/d		250	500 (decreased F1 and F2 pups born and litter size; reduced [14-18%] F2 pup weight on Pnd 14 and 21)		BSOC 2001a 1-Bromopropane	Male F1 pup weight reduced 13.7% on Pnd 28 at 500 ppm.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
86	Rat (Wistar)	20 d GD 1-20 6 hr/d			700 (7.5 to 9.5% reduced pup weights on Pnd 14).		Fueta et al. 2015 1-Bromopropane	1-BP suppressed wet dog shakes induced by kainate.
87	Rat (Wistar)	42 d Gd 0-21 Ld 1-21 8 hr/d		100		800 (significantly decreased survival during lactation)	Furuhashi et al. 2006 1-Bromopropane	
CHRONIC EXPOSURE								
Systemic								
88	Human	~40 mo (Occup)	Hemato	22.58			Li et al. 2010	Values listed are median exposure levels. Hepatic and renal NOAELs are for serum chemistry.
			Hepatic	22.58				
			Renal	22.58				
			Endocr	1.28 F	6.6 F (83% increase in serum TSH)			
89	Human	4-9 yr (Occup)	Hemato	197			NIOSH 2002 1-Bromopropane	The NOAEL listed is the geometric mean.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
90	Human	~ 29 mo (Occup)	Hemato	45.7			NIOSH 2003a 1-Bromopropane	The NOAELs listed are the geometric means. The kidney NOAEL is for serum chemistry.
			Renal	45.7				
91	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d	Resp		125 (glandular hyperplasia in the nose [both sexes], chronic active nasal inflammation [females])		Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAELs are for tissues histopathology. Various respiratory tract lesions in the nose, larynx, trachea, and lungs were observed at 250 ppm and higher.
			Cardio	500				
			Gastro	500				
			Musc/skel	500				
			Hepatic	500				
			Renal	500				
			Endocr	500				
			Dermal	500				
			Ocular	500				
			Bd Wt	500				

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
92	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d	Resp		62.5 (various histological alterations in the nasal respiratory epithelium, larynx, trachea, and bronchioles)		Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology. Lesions of the olfactory epithelium were observed in females at 125 ppm and higher.
			Cardio	250				
			Gastro	250				
			Musc/skel	250				
			Hepatic	250				
			Renal	250				
			Endocr	250				
			Dermal	250				
			Ocular	250				
			Bd Wt	250				
Immuno/ Lymphoret								
93	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.
94	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
95	Human	~40 mo (Occup)			1.28[d] F (increased vibration sense threshold)		Li et al. 2010	LOAEL value listed is the median exposure level.
96	Human	> 3 yr (Occup)				108 (inability to walk, spastic paraparesis, sensory loss, hyperreflexia)	Majersik et al. 2007 1-Bromopropane	Case reports (n=5)
97	Human	4-9 yr (Occup)			117.1 (subjective complaints of neurotoxicity)		NIOSH 2002 1-Bromopropane	No referent group was included; LOAEL value listed is the geometric mean.
98	Human	~ 29 mo (Occup)			45.7 (Subjective complaints of anxiety, nervousness)		NIOSH 2003a 1-Bromopropane	The LOAEL listed is for the geometric mean.
99	Human	18 mo 5-6 d/wk 8.5-9.5 hr/d (Occup)				533 M (severe ataxia, motor and sensory impairments, axonal damage)	Samukawa et al. 2012 1-Bromopropane	Case report
100	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
101	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
Reproductive								
102	Human	4-9 yr (Occup)		168.9			NIOSH 2002 1-Bromopropane	The NOAEL (geometric mean) is for lack of self-reported reproductive issues.
103	Human	~ 29 mo (Occup)		45.7 F			NIOSH 2003a 1-Bromopropane	The NOAEL (geometric mean) is based on a lack of self-reported reproductive issues.
104	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of reproductive organs.
105	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the reproductive organs.
Cancer								
106	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d				125 M (CEL: skin keratoacanthoma; basal cell adenoma or carcinoma)	Morgan et al. 2011; NTP 2011 1-Bromopropane	125 ppm also CEL for pancreatic islet adenoma in males.

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
107	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d				62.5 F (CEL: combined alveolar/bronchiolar adenoma or carcinoma)	Morgan et al. 2011; NTP 2011 1-Bromopropane	

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 1 ppm for 1-BP based on a BMCL1SD of 97.40 ppm. The BMCL1SD was adjusted for intermittent exposure and multiplied by the ratio of the animal-to-human blood: gas partition coefficients to calculate a human equivalent concentration (HEC). The BMCL[HEC] was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

c Used to derive an intermediate-duration inhalation MRL of 0.1 ppm for 1-BP based on a NOAEL of 10 ppm. The NOAEL was adjusted for intermittent exposure and multiplied by the ratio of the animal-to-human blood: gas partition coefficients to calculate a human equivalent concentration (HEC). The NOAEL[HEC] was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

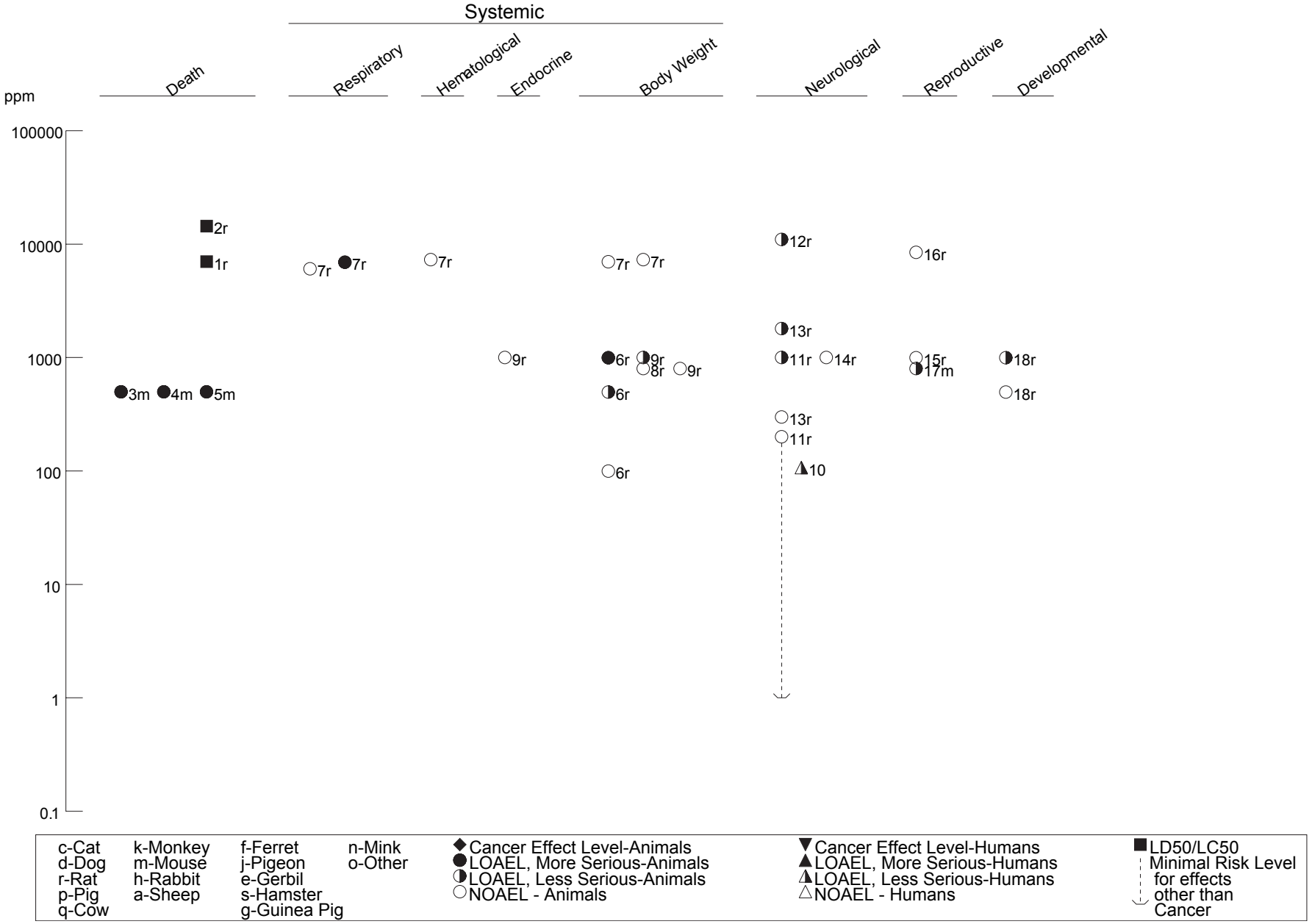
d Used to derive a chronic-duration (365 days or more) inhalation MRL of 0.02 ppm for 1-BP. The minimal LOAEL of 1.28 ppm was adjusted for continuous exposure (1.28 ppm × 5 days/7 days × 12 hours/24 hours = 0.46 ppm) and was divided by an uncertainty factor of 30 (3 for use of minimal LOAEL and 10 for human variability) to derive the MRL of 0.02 ppm.

ALT = alanine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; FOB = functional observation battery; Gastro = gastrointestinal; Gd = gestational day; gen = generation; Hemato = hematological; hr = hour(s); IgM = immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Occup = occupational; Resp = respiratory; SRBC = sheep red blood cell; TWA = time-weighted average; wk = week(s)

3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

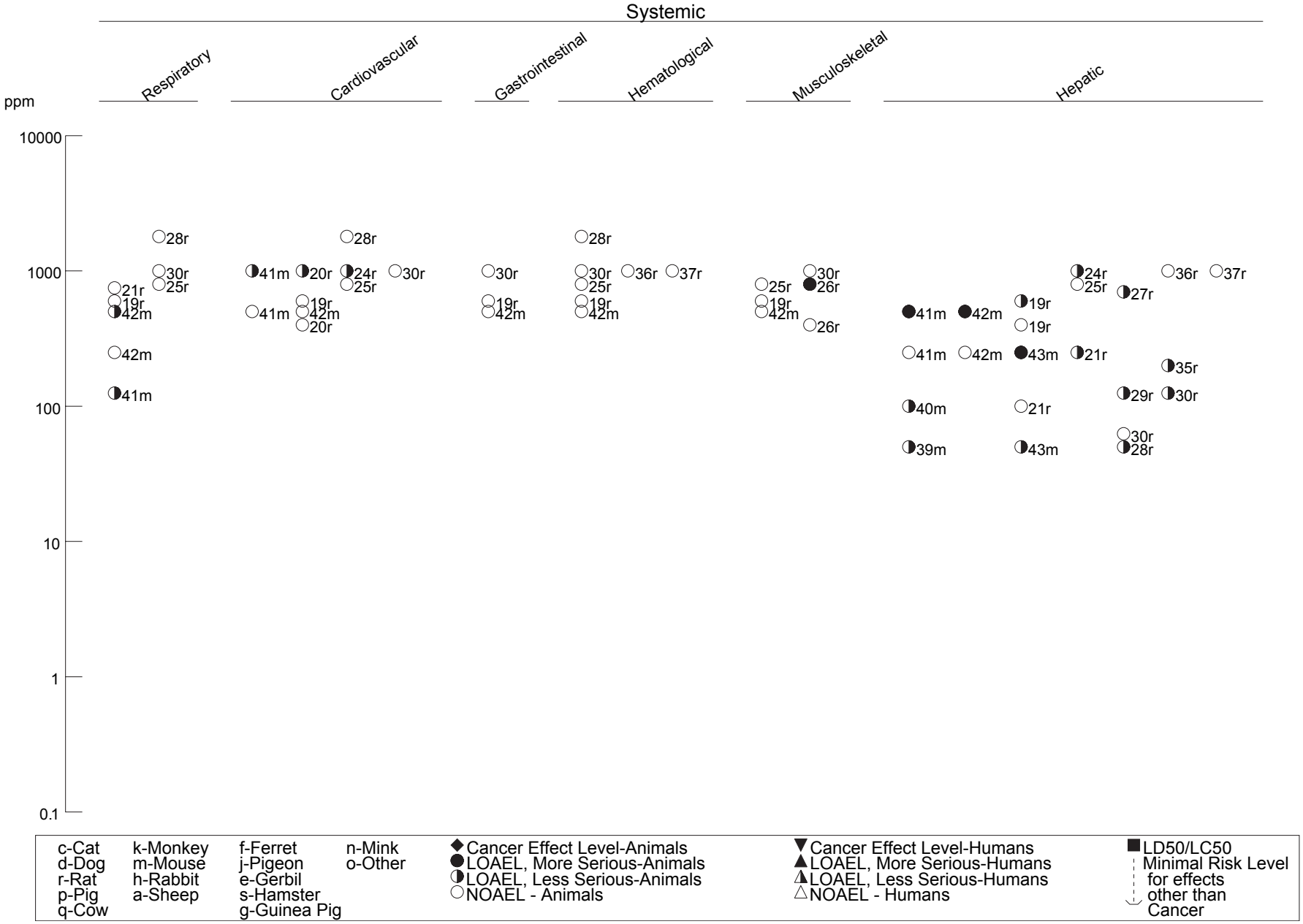
Acute (≤14 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation *(Continued)*

Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation *(Continued)*

Intermediate (15-364 days)

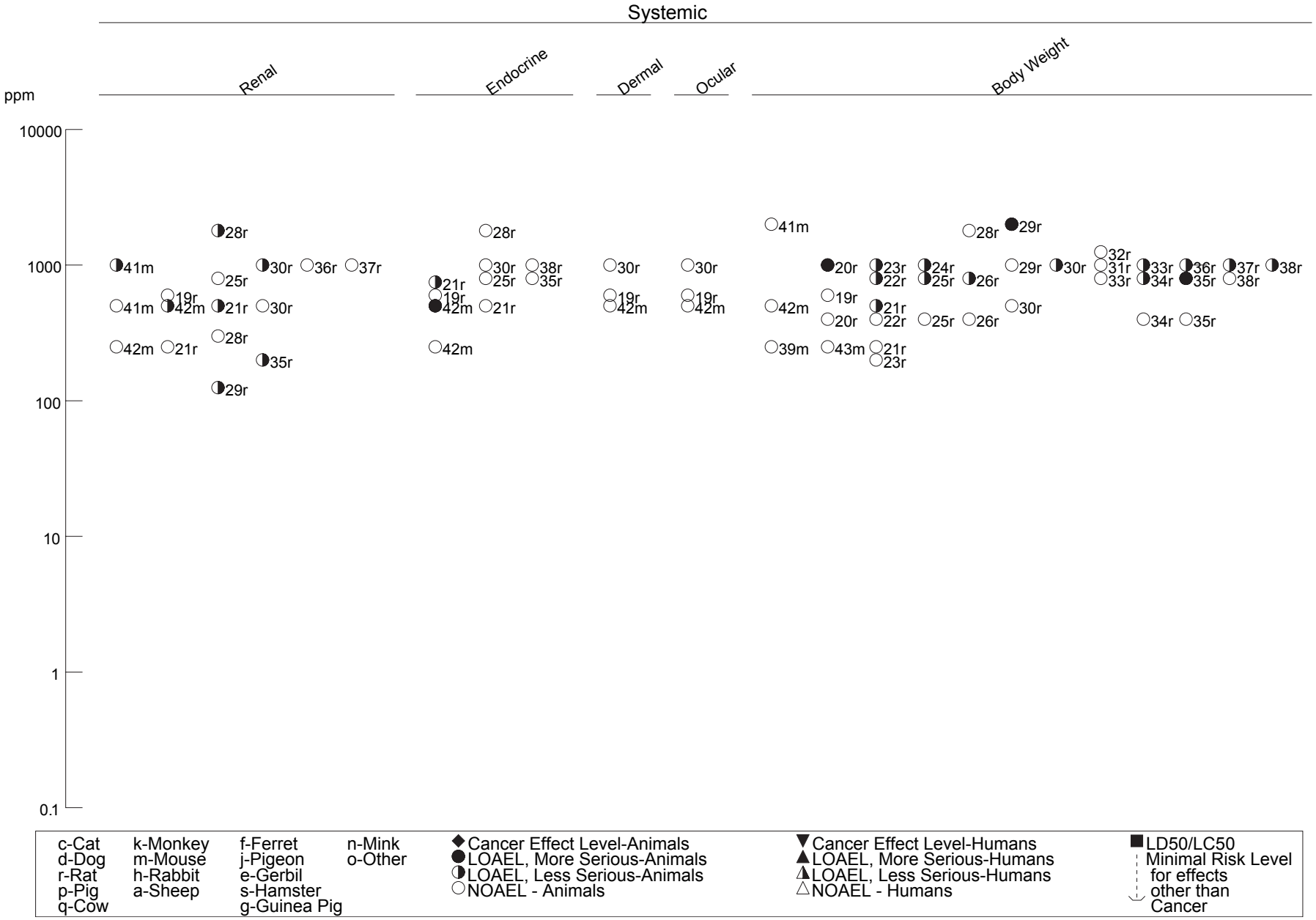
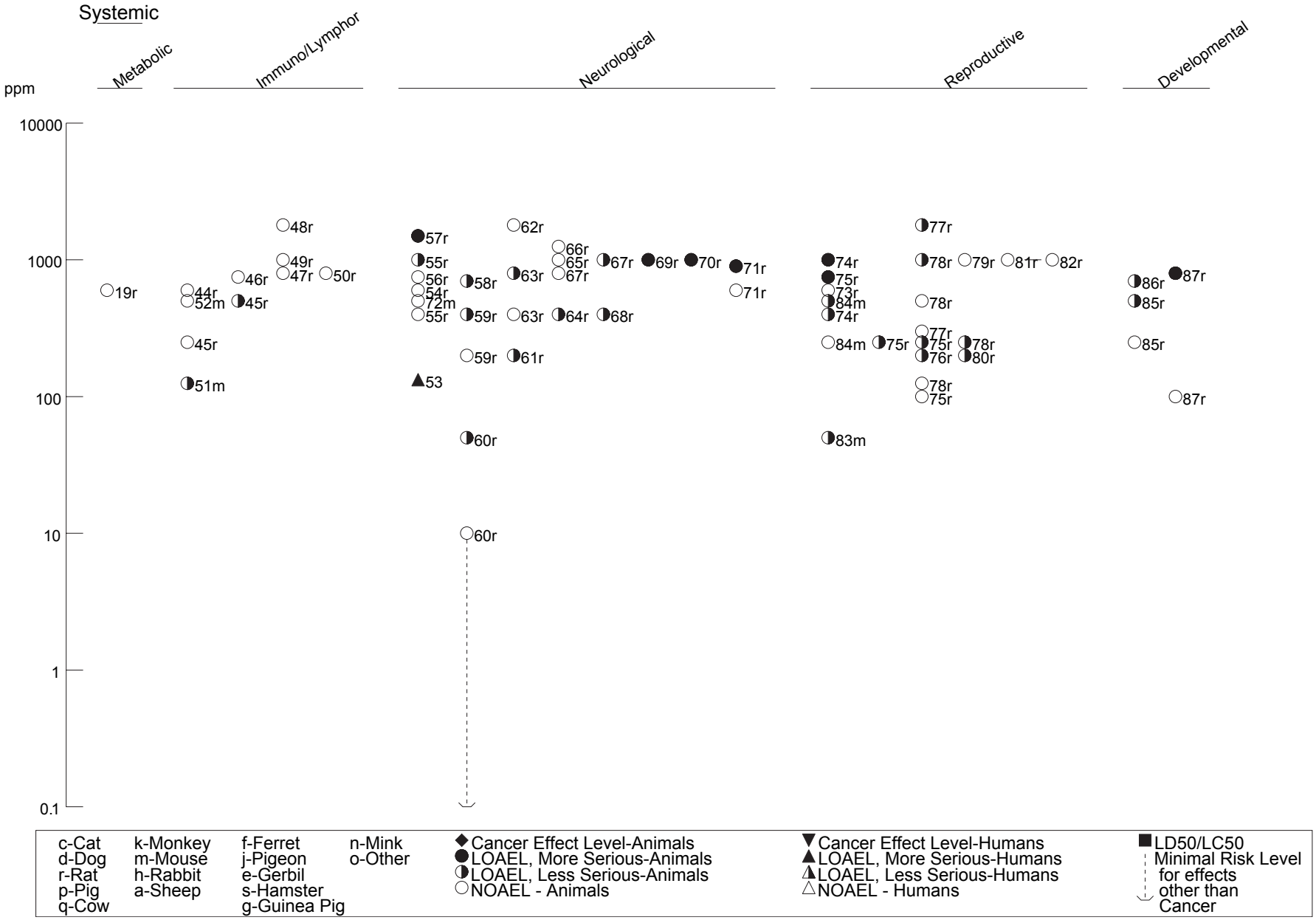


Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation *(Continued)*

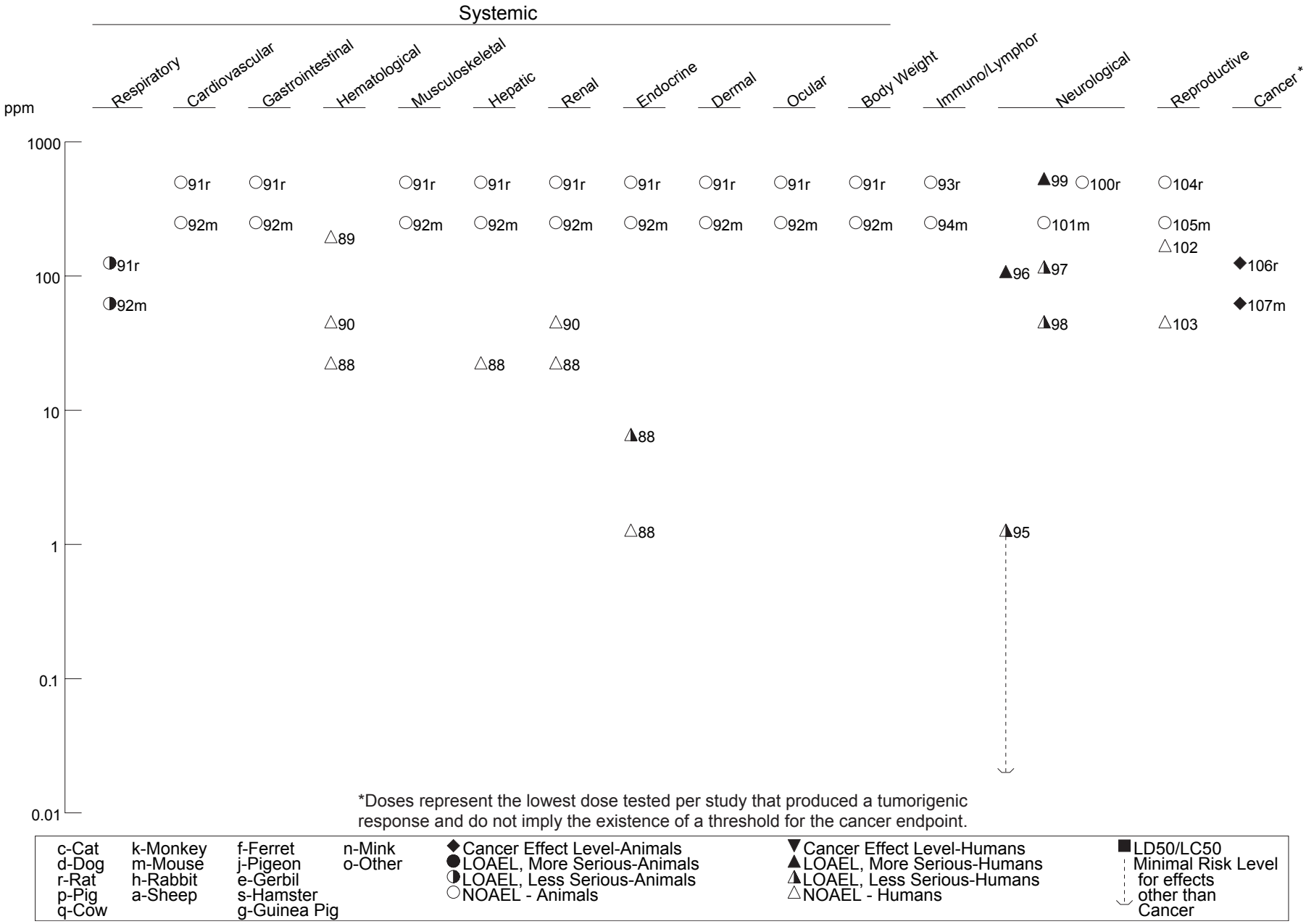
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation *(Continued)*

Chronic (≥365 days)



developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace. The geometric mean air concentration of 1-bromopropane was 107 ppm for glue sprayers (range 58–254 ppm). It should be mentioned that the woman had been a furniture gluer for 18 months prior to the introduction of 1-bromopropane into the workplace and had been in good health prior to the introduction of 1-bromopropane into the workplace.

In general, except for a chronic study, studies in rats and mice have used exposure concentrations higher than those associated with respiratory irritation in workers and have reported mainly histological alterations in the respiratory tract, with some inconsistencies between studies. Some studies provided data on lung weight. It also appears that mice are more susceptible than rats. Pulmonary lesions consisting of edema and "emphysema" were reported in rats exposed to ≥6,920 ppm, a lethal concentration, for 4 hours (Elf AtoChem S.A. 1997). Nasal lesions, including minimal necrosis of the respiratory epithelium and suppurative inflammation were observed in 1–2/5 male rats exposed to ≥500 ppm 1-bromopropane for 16 days, but no such lesions were observed in females exposed to doses up to 2,000 ppm for 16 days or males or females exposed to concentrations up to 1,000 ppm for 14 weeks (NTP 2011). No changes were observed in lung weights in the NTP studies in rats. In other intermediate-duration rat studies, no exposure-related changes in lung weight or histology were observed in rats intermittently exposed to concentrations up to 1,800 ppm 1-bromopropane (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999).

In intermediate-duration mouse studies, histopathological changes were observed in various levels of the respiratory tract of mice following intermittent exposure to 500 ppm 1-bromopropane for 14 weeks, including cytoplasmic vacuolization of the nasal respiratory epithelium and cytoplasmic vacuolization in the trachea and lung bronchioles (4/10 males, 5/10 females); incidences in the control group were 0/10 (NTP 2011). Absolute and relative lung weights were also increased in females exposed to 500 ppm 1-bromopropane. Exposure-related effects were not observed at ≤250 ppm. In the accompanying 17-day study, histopathological changes in the lungs were observed in all mice exposed to ≥125 ppm 1-bromo-propane (lowest concentration tested), including bronchiole necrosis, regeneration, and vacuolization and perivascular inflammation (NTP 2011). Histopathological changes in the nose were observed at ≥500 ppm, including olfactory epithelium atrophy, necrosis, and regeneration and respiratory epithelial necrosis and cytoplasmic vacuolization (NTP 2011).

In a chronic-duration study, respiratory tract lesions were observed in rats exposed to ≥125 ppm and mice exposed to ≥62.5 ppm 1-bromopropane for 105 weeks (lowest concentrations tested) (Morgan et al. 2011;

NTP 2011). Observed lesions in rats included glandular hyperplasia and chronic suppurative inflammation of the nose; chronic active inflammation of the nose, larynx, and trachea; chronic suppurative inflammation of the lungs; metaplasia of the olfactory epithelium; squamous metaplasia of the larynx; and epithelial hyperplasia of the trachea. In mice, observed lesions included regeneration of bronchioles; cytoplasmic vacuolization in the nasal respiratory epithelium, bronchioles, larynx, and trachea; hyperplasia in nasal respiratory epithelium; and metaplasia and atrophy in nasal olfactory epithelium.

Limited human data suggest that exposure to 1-bromopropane can cause respiratory tract irritation at exposure levels that might be found in occupational settings; however, definite levels at which respiratory lesions might occur in humans are unknown. Studies in animals suggest that mice can develop respiratory tract lesions at exposure levels reported in some occupational studies and may be a better animal model than rats for this end point.

Cardiovascular Effects. Only one report was located that provided some information regarding cardiovascular assessment in humans following likely exposure to 1-bromopropane at work. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had a normal electrocardiogram. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm). It should be mentioned that the woman had been a furniture gluer for 18 months prior to the introduction of 1-bromopropane into the workplace.

No generalizations can be made from the single case report mentioned above, and the available studies in animals have examined mostly histology of the heart, but not cardiovascular function. The animal studies indicate that morphological alterations of the heart are unlikely to occur following exposure to 1-bromopropane. Changes in heart weight were reported in one animal study. A significant decrease in absolute and relative heart weight was observed in male mice intermittently exposed to ≥1,000 ppm 1-bromopropane for 17 days; no exposure-related changes were observed in heart weight in males at ≤500 ppm or in females at ≤2,000 ppm (NTP 2011). No exposure-related changes in heart histology were observed in mice at concentrations up to 2,000 ppm 1-bromopropane for 17 days or 500 ppm for 14 weeks (NTP 2011). In rats, no exposure-related changes in heart weight or histology were observed in three strains intermittently exposed to concentrations up to 1,800 ppm 1-bromopropane for 8–14 weeks (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011).

A significant increase (15–20%) in systolic blood pressure (measured with a tail cuff) was reported in conscious male Wistar rats exposed to 1,000 ppm 1-bromopropane intermittently for 4–6 weeks (Banu et al. 2007; Huang et al. 2016). The blood pressure was still elevated 5 weeks after exposure ceased, but returned to control values by 8 weeks after exposure terminated. No significant effects were reported in rats exposed to 400 ppm 1-bromopropane. Biochemical assays in homogenates of left ventricle and aortic tissues showed that markers of oxidative stress were significantly elevated in exposed rats, which led Huang et al. (2016) to suggest that oxidative stress, through activation of NADPH oxidase pathways, might be a mechanism for 1-bromopropane-induced increased blood pressure.

In the only available chronic-duration study, no exposure-related changes in heart histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm 1-bromopropane, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data are insufficient to determine if 1-bromopropane exposure causes cardiovascular effects. While animal studies showed that morphological alterations of the heart did not occur following exposure to 1-bromopropane, no conclusions can be drawn regarding cardiovascular function that would support or refute the findings of the case report.

Gastrointestinal Effects. Several single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane reported gastrointestinal effects, including diarrhea and nausea/vomiting, at mean air concentrations of 107–133 ppm (Ichihara et al. 2002; Raymond and Ford 2007). These effects are considered secondary to neurological effects (see Section 3.2.1.4, Neurological Effects for more details).

No exposure-related histopathological lesions were observed in the gastrointestinal tract in intermediate-duration studies in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm 1-bromopropane, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; Morgan et al. 2011; NTP 2011). The limited information from animal studies suggests that the gastrointestinal tract is not a sensitive target for airborne 1-bromopropane.

Hematological Effects. The available human occupational studies show mixed results regarding hematological effects in 1-bromopropane workers. For example, a study was conducted of 60 female and 26 male Chinese individuals who had been exposed to the chemical in three 1-bromopropane production

factories for 3–4 years (Li et al. 2010). Based on assessments of individual exposures, median exposure concentrations for low-, mid-, and high-dose females were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for the low- and high-dose males were 1.05 and 12.5 ppm, respectively. The results of hematological tests showed small (8–20%) but significant decreases between exposed female groups and matched controls for white blood cell count, red blood cell count, hemoglobin, and hematocrit. However, no clear dose-response relationships were apparent and the effects were not significant in male workers. Regression analysis adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls showed significant negative trends for red blood cell count, hematocrit, and platelets in females; no significant trends were reported in males. The same regression analysis on the product of exposure levels and duration of exposure (cumulative exposure) showed significant increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) and significant decreases in red blood cell count and hematocrit in female workers. In a review of the Li et al. (2010) study, Smith et al. (2011) noted that since hematological parameters experience temporal fluctuations related to menstrual cycle, lack of control for the latter could have led to misleading results. Additionally, reported hematological values in female workers were within reported reference ranges for hematological parameters (CDC 2005); values for other parameters were not reported by study authors.

The findings of Li et al. (2010) are not supported by findings from two earlier surveys of workers in the United States exposed to 1-bromopropane during the spray application of solvent-based adhesives (NIOSH 2002, 2003a). Neither survey found exposure-related hematological effects in the workers who were exposed to concentrations of 1-bromopropane ranging from 7 to 381 ppm. Although exposure levels were monitored using full-shift personal breathing zone samples in both studies, these studies are limited due to relatively small sample sizes (69 subjects in one study and 13 the other) and lack of control for potential confounding factors (e.g., age).

Single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane suggest that hematological parameters are not particularly sensitive to 1-bromopropane exposure. For example, Samukawa et al. (2012) stated that routine blood tests (assuming that included standard hematological parameters) of a worker that may have been exposed to up to 553 ppm 1-bromopropane for 18 months were within normal limits. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had normal complete blood count. The geometric mean concentration of 1-bromopropane for glue sprayers was 107 ppm (range, 58–254 ppm). One of the cases described by Majersik et al. (2007) was that of a woman who worked as a foam cushion gluer for 4 years prior to

showing neurotoxic signs and symptoms. The investigators stated that a complete blood count showed "variant lymphocytes." However, no further details were provided. The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range 91–176 ppm) and a TWA of 108 ppm (range 92–127 ppm).

Studies in rats and mice exposed to 1-bromopropane have described alterations in hematological parameters of questionable biological significance and at exposure levels considerably higher than those measured in the human studies mentioned above. For example, nose-only exposure of male Wistar rats to 7,280 ppm 1-bromopropane for 4 hours resulted in a significant increase in polymorphonuclear neutrophils 24 hours after exposure ceased, but not 14 days after exposure (Elf AtoChem S.A. 1997). Other hematological parameters were not significantly altered by exposure to 1-bromopropane in this study.

Significant hematological alterations observed in male rats exposed intermittently to 1,800 ppm 1-bromopropane for 8 weeks included a 28% decrease in white blood cell count, 8% decrease in red blood cell count, 12% decrease in hematocrit, 3% decrease in MCV, 8% increase in MCH, and 11% increase in mean corpuscular hemoglobin concentration (MCHC) (Kim et al. 1999). Some of these parameters were also altered at 50 ppm, but none were altered at 300 ppm. The study authors did not consider these changes to be biologically relevant, as they were mostly within the normal range for rats. Similarly, no biologically relevant changes were observed in hematological parameters in females exposed to concentrations up to 1,800 ppm (Kim et al. 1999). Similarly, significant, but minor changes in hematology observed in male rats intermittently exposed to concentrations ≥400 ppm for 12 weeks, including a 3% increase in MCV and a 2.4–3.5% decrease in MCHC, were not considered biologically relevant (Ichihara et al. 2000a). No exposure-related hematological changes were reported in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively, for 7–14 weeks (Albemarle Corporation 1997; NTP 2011; Yu et al. 1998, 2001).

Available human and animal data are limited, but suggest that clinically relevant hematological changes are not likely to occur in humans following exposure to 1-bromopropane. Hematological parameters were not assessed in the chronic-duration study; therefore, it is unknown whether the findings of Li et al. (2010) in 1-bromopropane workers would also occur in animals following prolonged exposure to low levels of 1-bromopropane (Morgan et al. 2011).

Musculoskeletal Effects. No information was located regarding musculoskeletal effects in humans exposed to 1-bromopropane.

Animal studies provide limited relevant data. Irregular banding of the striated muscle fibers of the soleus muscle was observed in male rats intermittently exposed to 800 ppm for 12 weeks, and electron microscopy revealed loss of regular linearity in the Z line and zigzag arrangement of the myofilaments; no changes were observed at ≤400 ppm (Ichihara et al. 2000b). In other intermediate-duration studies, no exposure-related musculoskeletal effects were observed in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively (Albemarle Corporation 1997; Ichihara et al. 2000a; NTP 2011).

In the only available chronic-duration study, no exposure-related musculoskeletal effects were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

From these limited data, it would appear that neither skeletal muscle nor bone are sensitive targets for 1-bromopropane toxicity.

Hepatic Effects. Limited information is available regarding hepatic effects in humans exposed to 1-bromopropane. No evidence of adverse liver effects was observed in the Chinese cohort of workers exposed to 1-bromopropane studied by Li et al. (2010) as described above. In that study, liver function was assessed by clinical chemistry tests. The median exposure level in 60 female workers was 6.6 ppm with a range of 0.07–106.4 ppm. The corresponding values for 26 exposed male workers were 4.6 and 0.06–114.8 ppm. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into the workplace had hepatic clinical chemistry parameters within normal ranges. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm).

Unlike the limited human data, findings from animal studies indicate that the liver might be a target of 1-bromopropane at much higher exposure levels. A study aimed at determining an LC_{50} for 1-bromopropane in rats reported cytoplasmic vacuolization of hepatocytes in some exposed rats exposed to 11,000–17,000 ppm for 4 hours; however, there was no dose-response relationship (Kim et al. 1999).

Intermediate-duration studies in rats and mice have reported histological alterations consisting mostly of hepatocyte vacuolization and occasionally hepatocyte degeneration and necrosis at the higher exposure concentrations. Studies in rats identified LOAELs of 250 ppm (NTP 2011), 800 ppm (Yamada et al. 2003), and 600 ppm (Albemarle Corporation 1997); corresponding NOAELs were 125, 400, and 400 ppm 1-bromopropane. In general, male rats appeared to be affected at lower exposure concentrations than females. In these studies, exposure durations were ≥12 weeks. In an 8-week study, hepatocyte vacuolization was observed in rats exposed intermittently to 50–1,800 ppm 1-bromopropane; however, the study authors stated that findings were not dose-related, but incidence data were not provided (Kim et al. 1999). However, hepatocyte vacuolization was observed in parental male rats exposed to 250 ppm 1-bromopropane in a 2-generation reproductive study (BSOC 2001a). In shorter-duration studies (2–7 weeks), no exposure-related changes in liver histology were observed in rats exposed to concentrations up to 2,000 ppm (NTP 2011; Yu et al. 1998, 2001). LOAELs reported in mice include 50 ppm (lowest exposure concentration tested) for mild hepatocyte changes (Zong et al. 2016), 100 ppm (lowest exposure concentration tested) for hepatic necrosis (Liu et al. 2010), and 500 ppm for hepatocyte degeneration (NTP 2011). A NOAEL of 250 ppm 1-bromopropane was identified in NTP (2011).

Significant increases in liver weight (7–48%) have been reported in rats exposed intermittently for 2–14 weeks to ≥125 ppm 1-bromopropane but not at ≤62.5 ppm (Albemarle Corporation 1997; Huang et al. 2016; Kim et al. 1999; NTP 2011; Yamada et al. 2003). However, a study reported no exposure-related changes in liver weight in male rats following intermittent exposure to concentrations up to 800 ppm for 12 weeks (Ichihara et al. 2000a). In BALB/cA mice, which have an increased metabolic capacity for 1-bromopropane, absolute liver weights were significantly increased by 22% following exposure to 250 ppm 1-bromopropane for 4 weeks; no changes were observed at ≤110 ppm (Liu et al. 2009). In other mouse strains, liver weight was significantly increased by 13–43% following intermittent exposure to ≥300 ppm for 2–14 weeks; no exposure-related changes were observed at ≤250 ppm (Liu et al. 2009, 2010; NTP 2011).

The results of monitoring clinical chemistry parameters have been mixed and not always consistent with histopathological findings. Early, transient changes in clinical chemistry (decreased albumin, total protein, and alanine aminotransferase [ALT] activity) that were observed in rats intermittently exposed to 62.5–1,000 ppm for 14 weeks were attributed to the effects of 1-bromopropane on hepatic protein metabolism; however, the 25–30% increase in succinate dehydrogenase (SDH) activity in male rats exposed to ≥500 ppm might have been indicative of mild hepatotoxicity (NTP 2011). Serum activities of liver enzymes were significantly decreased in male rats exposed to ≥50 ppm for 8 weeks (Kim et al.

1999). In females, aspartate aminotransferase (AST) activity was not significantly affected, ALT was decreased at ≥300 ppm, and lactic dehydrogenase (LDH) was decreased at 300 ppm but not 1,800 ppm (Kim et al. 1999). The lack of a dose-response relationship, at least in females, is consistent with an apparent lack of dose-response reported for histological alterations in this study. No biologically significant exposure-related changes were observed in hepatic clinical chemistry parameters in male or female rats exposed up to 600 ppm 1-bromopropane for 13 weeks; this exposure concentration induced hepatocyte vacuolization in male rats (Albemarle Corporation 1997). In male rats, plasma ALT levels were significantly decreased by 27–49% following intermittent exposure to ≥700 ppm for 3–12 weeks, but no changes were observed in plasma AST; no histological examination of the liver was conducted in this study (Ishidao et al. 2002).

In a chronic-duration study, no exposure-related changes in non-neoplastic liver histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data available suggest that the liver is not a sensitive target for 1-bromopropane toxicity. However, animal data suggest that at high enough concentrations, the liver may be a target of 1-bromopropane toxicity.

Renal Effects. The available studies of humans exposed to 1-bromopropane suggest that inhaled 1-bromopropane did not significantly alter renal function under the exposure conditions. A significant trend for increased blood urea nitrogen (BUN) was reported in male and female Chinese workers exposed to 1-bromopropane in the study conducted by Li et al. (2010); however, all reported values for BUN (as well as serum creatinine) were within reported reference values (Ichihara et al. 2011). In the Li et al. (2010) study, median exposure concentrations for low-, mid-, and high-dose females (20/group) were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for low- and high-dose males (13/group) were 1.05 and 12.5 ppm, respectively. In the 2003 NIOSH survey described earlier under Hematological Effects, no exposure-related changes were observed in renal clinical chemistry values between adhesive-spray line workers exposed to a geometric mean (range) of 45.7 ppm (7–281 ppm) and 30 unexposed workers exposed to a geometric mean (range) of 1.1 ppm (0.1–4.9 ppm) (NIOSH 2003a). Similarly, in case studies, two women who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into their workplace had renal clinical chemistry and urinalysis parameters within normal ranges; however, one woman developed polyuria (Raymond and Ford 2007). The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm). It should be

mentioned that the women had been furniture gluers for ≥40 months prior to the introduction of 1-bromopropane into the workplace.

No information regarding renal effects was located in the available acute-duration studies in animals.

Intermediate-duration inhalation studies in animals provide information regarding kidneys' histological appearance, weight, and urinalysis parameters. Some animal studies suggest that exposure to high concentrations of 1-bromopropane may induce adverse renal effects.

Results of microscopic examination of the kidneys have been mixed. For instance, no significant alterations have been reported in rats at ≤600 ppm 1-bromopropane (Albemarle Corporation 1997; Kim et al. 1999; Yamada et al. 2003), but mild dilation of proximal tubules was seen in female rats exposed to 800 ppm (Yamada et al. 2003), tubule casts were reported in female exposed to 1,800 ppm for 8 weeks (Kim et al. 1999), and transitional renal epithelial hyperplasia and pelvic mineralization were reported in parental generation female rats exposed to 500 ppm 1-bromopropane (BSOC 2001a). In contrast, no exposure-related changes in kidney histology were observed in female rats exposed up to 2,000 ppm 1-bromopropane for 2–14 weeks (NTP 2011). Similarly, no exposure-related changes were observed in kidney histology in male rats at up to 2,000 ppm or mice at up to 500 ppm for 2–14 weeks (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011; Yu et al. 1998, 2001).

Results of monitoring kidney weight were mixed. The lowest LOAEL in rats was 125 ppm 1-bromopropane for a 20% increase in absolute kidneys weight in females in a 16-day study (NTP 2011), whereas the lowest LOAEL in mice was 500 ppm 1-bromopropane for a 12% increase in kidney weight in a 14-week study (NTP 2011). No NOAEL was identified in the rat study and the NOAEL in the mouse study was 250 ppm. Because other studies did not report significant alterations in kidney weights at higher exposure concentrations or effects were not dose-related, no generalizations can be made, suggesting that kidney weight is not a reliable biomarker of 1-bromopropane toxicity.

Two studies provided information regarding urinalysis in rats exposed to 1-bromopropane, and based on the results, it seems that exposure to 1-bromopronane did not induce toxicologically significant alterations. One 8-week study reported increased urobilinogen, bilirubin, ketone bodies, and leukocytes in females exposed to ≥300 ppm and decreased urobilinogen and increased ketone bodies in males exposed to 1,800 ppm (Kim et al. 1999). However, no data were shown, and the investigators stated that most values were within normal limits. In the other study, no exposure-related changes in urinalysis were

observed in male or female rats exposed up to 600 ppm 1-bromopropane (the highest concentration tested) for 13 weeks (Albemarle Corporation 1997).

In a chronic-duration study, no exposure-related changes in kidney histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data available suggest that the kidney is not a sensitive target for 1-bromopropane toxicity. Results from some animal studies suggest that at high enough concentrations, the kidney may be a target of 1-bromopropane toxicity. These concentrations, however, are considerably higher than those reported in occupational studies.

Endocrine Effects. A small number of human studies provide information on endocrine effects after exposure to 1-bromopropane. Based on these limited data, it appears that 1-bromopropane does not have endocrine effects in humans. In a study of Chinese workers exposed to 1-bromopropane conducted by Li et al. (2010), regression analyses that included exposure level and duration showed significant trends for increased serum TSH and follicle-stimulating hormone (FSH) in female workers. Neither serum estradiol levels in females nor serum testosterone levels in males were significantly associated with exposure to 1-bromopropane.

In a case study of female foam cushion gluers experiencing frank neurotoxicity following exposure to 1-bromopropane vapors 30–40 hours/week for ≥3 years, no exposure-related changes in serum TSH were observed (Majersik et al. 2007). The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range 91–176 ppm). Similarly, Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had normal thyroid function tests. The geometric mean air concentration in this case was 107 ppm for glue sprayers (range 58–254 ppm).

Studies in animals have examined mostly the microscopic appearance and weight of endocrine glands and, consistent with the limited human data, do not suggest that the endocrine system is a particularly sensitive target for 1-bromopropane toxicity.

The only relevant information in an acute-duration study is that no changes in adrenal weight or plasma corticosterone levels were observed in male rats exposed intermittently to concentrations up to 1,000 ppm 1-bromopropane for 1–4 weeks (Zhang et al. 2013).

Intermediate-duration studies identified a LOAEL of 500 ppm 1-bromopropane for moderate to marked necrosis of the adrenal cortex in female mice exposed for 14 weeks; the NOAEL was 250 ppm (NTP 2011). No exposure-related non-neoplastic changes were observed in other endocrine glands. Studies in several strains of rats exposed intermittently to up to 1,800 ppm 1-bromopropane did not report exposure-related histopathological lesions in endocrine glands (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011; Yamada et al. 2003).

Several intermediate-duration studies provide information on endocrine gland weight. The lowest LOAEL was 50 ppm 1-bromopropane for a 30% increase in relative weight of the left adrenal in male rats exposed for 8 weeks (Kim et al. 1999). However, exposure to higher concentrations did not show a clear dose-response relationship, and no significant changes occurred in the right adrenal or in the adrenal gland from females exposed to the same concentrations (Kim et al. 1999). Therefore, the significance of the effect is questionable at best. Other studies in rats that tested exposure concentrations in the range of 200–800 ppm 1-bromopropane also reported increases in adrenal weight in rats, but the results were inconsistent between studies, or no dose-response was apparent (Albemarle Corporation 1997; Yamada et al. 2003). In other intermediate-duration exposure studies, no exposure-related changes in adrenal or pituitary weight were observed in rats intermittently exposed to concentrations up to 1,000 ppm (Ichihara et al. 2000a; Zhang et al. 2013).

In chronic studies, no exposure-related, non-neoplastic changes were observed in endocrine glands from rats or mice intermittently exposed to concentrations up to 500 and 250 ppm 1-bromopropane, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data and the animal data available do not suggest that endocrine end points are particularly sensitive targets for 1-bromopropane toxicity.

Dermal Effects. No information was located regarding dermal effects in humans following inhalation exposure to 1-bromopropane.

No exposure-related non-neoplastic skin lesions were observed in intermediate-duration studies in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; Morgan et al. 2011; NTP 2011).

Ocular Effects. No information was located regarding ocular effects in humans following inhalation exposure to 1-bromopropane. However, symptoms of eye irritation were common among Chinese workers exposed to concentrations ≥56.9 ppm 1-bromopropane (Ichihara et al. 2004a). It is assumed that the eye irritation was due to vapors of 1-bromopropane making direct contact with the eye.

No exposure-related changes were observed in ophthalmic or microscopic examinations of the eyes of rats intermittently exposed to concentrations up to 600 ppm 1-bromopropane for 13 weeks (Albemarle Corporation 1997). Similarly, no exposure-related non-neoplastic lesions were observed in the eyes of rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm 1-bromopropane, respectively, for 14 weeks, or 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

Body Weight Effects. Studies in humans and in rats show that repeated exposure to 1-bromopropane can produce weight loss. Several single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane also reported body weight loss (Ichihara et al. 2002; Raymond and Ford 2007). In general, weight loss (11–25 pounds in some cases) occurred in a relatively short period of time prior to hospitalization for neurological symptoms. In one case, weight loss was accompanied by diarrhea and nausea/vomiting (Ichihara et al. 2002). In two additional cases, it was noted that the subjects complained of dysphagia (difficulty swallowing), which suggested a disorder of the glossopharyngeal nerve, vagus nerve, or medulla oblongata (Ichihara et al. 2002). The mean daily time-weighted exposure level in one workplace was 133±67 ppm (range 60–261 ppm). In cases reported by Raymond and Ford (2007), the geometric mean air concentration of 1-bromopropane was 107 ppm for glue sprayers (range 58–254 ppm).

In an acute 4-hour nose-only inhalation study in rats, exposure of males to 7,280 ppm 1-bromopropane or females to 7,029 ppm 1-bromopropane did not result in significant alterations in body weight over a 14-day observation period following exposure (Elf AtoChem S.A. 1997). Intermittent exposure of pregnant rats to 498 or 996 ppm 1-bromopropane on gestational days (GDs) 6–19 resulted in 14.3 and

24.6% reductions in net weight (weight at termination [GD 20] minus weight on GD 6), respectively; the NOAEL was 100 ppm 1-bromopropane (BSOC 2001b).

In intermediate-duration studies, body weight effects following inhalation exposure to 1-bromopropane differed between rat strains. In general, the relative strain susceptibility was Wistar > F-344 > Sprague Dawley. In male and female Wistar rats exposed intermittently for 1–14 weeks, final body weight decreases of 9.8–30% compared to controls were consistently reported at exposure concentrations ≥1,000 ppm 1-bromopropane, and decreased body weight was also occasionally observed in animals exposed to 700–800 ppm 1-bromopropane; no significant body weight effects were observed ≤400 ppm 1-bromopropane (Banu et al. 2007; Furuhashi et al. 2006; Honma et al. 2003; Huang et al. 2016; Ichihara et al. 2000a, 2000b; Ishidao et al. 2002; Subramanian et al. 2012; Wang et al. 2002, 2003; Yamada et al. 2003; Yu et al. 2001; Zhang et al. 2013). Male F-344 rats exposed intermittently to ≥1,000 ppm 1-bromopropane for 2–105 weeks showed decreases in final body weight of 12–27% relative to controls; no significant body weight effects were observed in F-344 males exposed to ≤500 ppm or in females exposed to ≤2,000 ppm (Morgan et al. 2011; NTP 2011; Sekiguchi et al. 2002). None of the studies in Wistar or F-344 rats provided information regarding food consumption. In Sprague-Dawley rats, no significant changes (≤10% compared to controls) in body weight or food consumption were observed in males or females intermittently exposed to concentrations up to 1,800 ppm for 8–13 weeks (Albemarle Corporation 1997; Kim et al. 1999; Sohn et al. 2002). However, male Sprague-Dawley from the parental generation in a 2-generation study exposed to 750 ppm 1-bromopropane were 12.8% lighter at termination than controls (BSOC 2001a). In addition, pregnant rats from the parental and F1 generations exposed to 500 ppm 1-bromopropane had body weights reduced 12–14% on GD 20; no significant effects were reported at 250 ppm 1-bromopropane (BSOC 2001).

No body weight effects were observed in four mouse strains intermittently exposed to concentrations up to 2,000 ppm for 2–14 weeks (Liu et al. 2009; NTP 2011; Zong et al. 2016). Similarly, no body weight effects were observed in mice exposed to concentrations up to 250 ppm for 105 weeks (Morgan et al. 2011; NTP 2011).

Human and rat studies indicate that exposure to 1-bromopropane can reduce body weight gain. Observed weight effects may be secondary to nausea and anorexia, or other neurological effects in exposed humans (see Section 3.2.1.4, Neurological Effects, for more details). In Wistar rats, exposure to ≥1,000 ppm 1-bromopropane has been reported to induce a decline in consciousness (Honma et al. 2003), so

decreased food intake due to sedation may explain, at least in part, the reported decreased weight gain at these exposure levels.

Metabolic Effects. Limited data from reports of workers experiencing frank neurotoxicity following exposure to 1-bromopropane do not suggest metabolic effects of 1-bromopropane. In the 2003 NIOSH survey previously described in the Hematological Effects section, no exposure-related changes were observed in electrolyte levels between adhesive-spray line workers exposed to a geometric mean of 45.7 ppm 1-bromopropane (range, 7–281 ppm) and 30 unexposed workers exposed to a geometric mean of 1.1 ppm 1-bromopropane (range, 0.1–4.9 ppm) (NIOSH 2003a). Similarly, Raymond and Ford (2007) reported normal electrolyte and glucose levels in four workers who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into the workplace. The geometric mean air concentration was 107 ppm for glue sprayers (range, 58–254 ppm). It should be mentioned that the workers had been furniture gluers for up to 18 years prior to the introduction of 1-bromopropane into the workplace. In a case study of a female foam cushion gluer experiencing frank neurotoxicity following exposure to 1-bromopropane vapors for 30–40 hours/week for ≥3 years, no exposure-related changes in glucose levels were observed (Majersik et al. 2007). The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range, 91–176 ppm).

Only one study in animals that assessed metabolic end points was located. No exposure-related changes in electrolyte or glucose levels were observed in male or female rats intermittently exposed up to 600 ppm 1-bromopropane for 13 weeks (Albemarle Corporation 1997).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1-bromopropane.

Only one study was located that evaluated immune function in animals exposed to 1-bromopropane via inhalation. In that study, the IgM plaque-forming response to immunization with SRBCs was reduced by up to ~60% in splenocytes harvested from female rats and mice exposed intermittently to 1,000 ppm and ≥125 ppm, respectively, for 4–10 weeks (Anderson et al. 2010). Other exposure-related changes observed in mice at ≥125 ppm included reduced absolute spleen weight, reduced spleen cellularity, decreased CD3+ cells in the spleen, and increased natural killer (NK) cells in the spleen. No mouse NOAEL was identified. In rats, several significant changes were observed in spleen cell subpopulations

in rats at ≥500 ppm, including decreased CD4−/CD8+, CD45/B220+, and CD3+ cells and increased NK cells. The NOAEL in rats was 250 ppm.

No other animal studies evaluating immune function were located. However, several studies examined immune organ weight or histology following inhalation exposure to 1-bromopropane; however, no exposure-related changes were observed in intermediate-duration studies in rats or mice exposed intermittently to concentrations up to 1,800 or 500 ppm, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999; Morgan et al. 2011; NTP 2011; Yamada et al. 2003).

The limited evidence from animal inhalation studies indicates that 1-bromopropane can suppress immune responses in two different species, indicating that immune suppression may be a concern following 1-bromopropane exposure in humans.

3.2.1.4 Neurological Effects

Exposure to 1-bromopropane can induce neurotoxicity in humans as evidenced by reports of exposure at work and occupational studies involving larger cohorts.

Neurological parameters were evaluated in Chinese 1-bromopropane production workers and unexposed controls (no monitoring data were available in the control factories, but these factories did not use 1-bromopropane) from the Li et al. (2010) occupational study described in the Hematological Effects section. Median exposure concentrations for the low-, mid-, and high-exposure females were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for the low- and high-dose males were 1.05 and 12.5 ppm, respectively. Comprehensive neurological evaluations were conducted that included measurements of motor and sensory parameters as well as performance in various neurobehavioral tests. Using regression analysis of median group exposure levels, adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls, significant trends were observed in tibial distal latency, vibration sense in the toes, and Benton test in female workers. Significant increases in tibial distal latency and vibration sense threshold were also associated with cumulative exposure in female workers. Regression analyses also showed impaired results in a test of motor coordination in males. When workers were stratified by exposure groups (control, low-, mid-, and high-exposure), analysis of variance (ANOVA) showed significant decreases in vibration sense, tibial distal latency, and sural

sensory nerve conduction velocity between exposed females and controls. The vibration sense threshold showed the clearest dose-related effect, with significant increases (indicative of decreased vibration sense) in all exposed female groups. No significant differences between controls and individual male groups were seen regarding neurological parameters in this analysis. No information was provided regarding work position, which could have contributed to numbness and decreased sensations. The minimal LOAEL of 1.28 ppm for reduced vibration sense in female workers was used as the basis for the chronic-duration inhalation MRL. However, the confidence in the MRL is low due to a number of limitations of the principal study. Key limitations identified by the investigators or pointed out by others (Smith et al. 2011) included: (1) the cross-sectional study design; (2) potential selection bias for the control group; (3) potential underestimation of 1-bromopropane exposure levels; (4) co-exposure to low levels of 2-bromopropane in the exposed group of workers; (5) lack of biomonitoring data for controls; (6) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (7) abnormally high control values for tibial nerve distal latency; (8) concerns regarding the sensitivity of the vibration sense measurement method utilized in the study; and (9) no data on menstrual cycle of females. However, after careful review of limitations and criticisms, as well as the available human and animal data, this study was considered to be the best available study on which to base the chronic MRL. In support, the most sensitive animal study yielded an MRL of 0.03 ppm (0.15 mg/m^3) based on respiratory lesions (Morgan et al. 2011; NTP 2011), which is essentially equivalent to the MRL based on the selected human study. The rationale for selecting the Li et al. (2010) study as the principal study for the derivation of the chronic inhalation MRL, despite acknowledged limitations, is discussed in more detail in Appendix A. The results of the neurological testing of 1-bromopropane workers from one of the three factories included in the Li et al. (2010) study had been published previously by Ichihara et al. (2004b).

Other occupational studies evaluating neurological effects include two NIOSH Health Hazard Evaluation reports of workers exposed to 1-bromopropane during the spray application of solvent-based adhesives (NIOSH 2002, 2003a). These studies, however, are limited due to small sample sizes, lack of control for potential confounding factors (e.g., age), and/or lack of unexposed referent group. In the first report, study subjects were exposed to a geometric mean (range) 168.9 ppm (60–381.2 ppm) 1-bromopropane. All workers surveyed (n=42) presented with symptoms suggestive of excessive exposure to solvents. Those exposed to the higher levels of 1-bromopropane (169.8–197 ppm) reported more frequently having a headache at least once per week, having painful tingling in the hands, having a tremor, and “feeling drunk” when not drinking than those with the lower exposure levels. Thirty-two persons were subjected to further analyses of symptoms. The results showed that for each of the symptoms evaluated, the

concentrations of 1-bromopropane in air were not statistically different between those individuals reporting the symptom compared to those not reporting the symptom. In the second NIOSH report, the cohort included 10 female and 3 male workers exposed to a geometric mean (range) of 45.7 ppm (7–281 ppm) and 30 unexposed workers exposed to a geometric mean (range) of 1.1 ppm (0.1–4.9 ppm). Exposed workers complained more frequently of tremor, headache, feeling "drunk," fatigue, and anxiety; using personal breathing zone (PBZ) data, employees reporting anxiety, headache, and feeling "drunk" had statistically significant higher PBZ concentrations of 1-bromopropane compared to those not reporting those symptoms. Nerve conduction studies performed in 29 individuals were judged by a physician to be normal, 4 were incomplete but without abnormalities, and 4 were considered borderline. The remaining five tests were considered abnormal; two of them were among the workers exposed to 1-bromopropane, but neither one was among the most heavily exposed workers. This yielded a prevalence ratio of 1.5 (95% CI, 0.3–7.9) for abnormal nerve conduction. Assessment of the combined (n=9) borderline tests (n=4) and abnormal tests (n=5) showed that only two of them were exposed to 1-bromopropane and seven were not. Overall, the results of this survey found no relationship between abnormal nerve conduction and exposure to 1-bromopropane.

Case reports have described neurological effects in subjects exposed to 1-bromopropane for periods ranging from a few weeks to years. In most cases, dermal exposure could have been significant since often no gloves were used when handling 1-bromopropane, or the use of gloves, as noted in some reports, may have enhanced dermal uptake of 1-bromopropane by occlusion effect. In an early case described by Sclar (1999), a subject exposed for 2 months to a solvent containing mainly 1-bromopropane developed numbness and progressive weakness of the extremities. Nerve conduction studies showed evidence of primary, symmetric demyelinating polyneuropathy. Samukawa et al. (2012) reported that a subject who used 1-bromopropane as a cleaning agent for metal parts for 18 months complained of numbness and pain of the lower extremities, weakness, and gait disturbance. Conduction velocity was decreased in motor and sensory nerves. Examination of a biopsy of the sural nerve showed axonal damage. The mean TWA level of exposure for this subject was estimated to be 553 ppm 1-bromopropane (range, 353–663 ppm). Others have reported similar effects (Ichihara et al. 2002; Majersik et al. 2007; MMWR 2008; Raymond and Ford 2007; Wang et al. 2015). Diarrhea, urinary incontinence, and abnormal sweating were signs reported in the three cases described by Ichihara et al. (2002), suggesting alterations in the autonomic nervous system. The daily exposure concentration measured with a passive sampler attached to one subject for 11 days was 133±67 ppm (mean ± SD). Majersik et al. (2007) reported six cases of neurotoxicity occurring in foam cushion gluers exposed to 1-bromopropane vapors from spray adhesives. Five patients were exposed 30–40 hours/week over a period of 3 years, whereas the sixth patient had been

employed for 3 months; none used protective clothing. Lower extremity pain or paresthesias developed subacutely in all of the patients. Five of them complained of difficulty walking and, upon examination, had spastic paraparesis, distal sensory loss, and hyperreflexia. Analysis of air samples collected at the workplace during gluing operations revealed a mean concentration of 1-bromopropane of 130 ppm (range, 91–176 ppm) with a 7-hour TWA of 108 ppm (range, 92–127 ppm). A 2-year follow-up of three of the patients revealed persistent symptoms that included headache, decreased memory, decreased mood, lower extremities numbness, cramping, paresthesias, weakness, and difficulty walking/poor balance. Clinical signs noted in these individuals included decreased cognition, lower extremities spasticity and weakness, gait ataxia, hyperreflexia, and decreased lower extremities sensation. Majersik et al. (2007) suggested that the pathogenesis of 1-bromopropane neurotoxicity in humans may reflect a central distal axonopathy syndrome. It should be noted that decreased vibration sense, particularly in the lower extremities, was reported in several of the cases described above (Ichihara et al. 2002; Majersik et al. 2007; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Vibration sense in the toes appeared to be the most sensitive neurological end point in 1-bromopropane workers studies by Li et al. (2010), and was significantly decreased in workers exposed to a median concentration ≥1.28 ppm 1-bromopropane.

Many studies have examined the effects of 1-bromopropane on the nervous system of animals. These studies have provided information regarding biochemical, morphological, and physiological aspects of both the peripheral nervous system and the central nervous system. For the most part, these studies support the findings in humans.

A study aimed at determining an LC_{50} for 1-bromopropane in rats reported decreased activity and ataxia within 1 hour after a 4-hour exposure to ≥11,000 ppm 1-bromopropane (Kim et al. 1999). The same investigators reported that male and female rats exposed to 1,800 ppm 1-bromopropane for 6 hours showed decreased activity and mild ataxia after 1 hour of exposure; no such signs were observed in rats exposed to 300 ppm 1-bromopropane. In another study, daily exposure of male rats to 1,000 ppm 1-bromopropane 8 hours/day for 14 days significantly reduced forelimb grip strength, but no significant effect was seen at ≤200 ppm 1-bromopropane or at 1,000 ppm when tested following exposure on day 1 or 7 (Honma et al. 2003). The Honma et al. (2003) study was used to derive an acute-duration inhalation MRL for 1-bromopropane. A more detailed description of the Honma et al. (2003) study can be found in Appendix A.

An acute-duration study in male rats examined neurochemical (8 rats/group) and morphological effects (1 rat/group) of 1-bromopropane in rats exposed up to 800 ppm 1-bromopropane 8 hours/day for 7 days

(Wang et al. 2002). Observed morphological alterations included the preterminal axon swelling with thin myelin sheath in the gracile nucleus of the medulla oblongata and swelling and masses of myelin sheath, hypertrophy of Schwann cell cytoplasm, and decreased frequency of Schmidt-Lanterman incisures in the posterior tibial nerve. Morphological changes were not observed in the medulla or tibial nerve at ≤400 ppm or the cerebellum, dorsal root ganglion, or thoracic spinal cord at ≤800 ppm. It should be mentioned, however, that only 1 rat per group (n=9) was used for morphological analyses, therefore, the findings may not be representative. Biochemical findings in this study included decreased creatine kinase (CK) activity in the brain stem and spinal cord at ≥200 ppm, increased total glutathione through the central nervous system at ≥200 ppm, and reduced levels of the neuronal marker protein γ-enolase in the cerebrum and cerebellum at ≥400 ppm. These findings suggest that biochemical end points are affected at lower exposures than morphological structures if the morphological findings are representative of the various exposure groups.

In intermediate-duration studies, the lowest LOAEL for neurological effects was 50 ppm 1-bromopropane for increased spontaneous locomotor activity in male F-344 rats exposed intermittently for 3 weeks; the NOAEL was 10 ppm 1-bromopropane (Honma et al. 2003). The increase in spontaneous locomotor activity was used to derive an intermediate-duration inhalation MRL for 1-bromopropane. Other effects occurring at higher exposure concentrations included increased ambulation and rearing, altered performance in a water maze test, and decreased muscle strength; however, concentrations up to 1,000 ppm did not significantly alter passive avoidance behavior, preening behavior, or motor coordination (Honma et al. 2003). Other studies in rats have reported reduced limb grip strength at ≥200 ppm 1-bromopropane and altered gait at ≥800 ppm (Ichihara et al. 2000b; Yu et al. 1998, 2001). Male rats exposed to 1,500 ppm 1-bromopropane intermittently for 4 weeks showed frank effects such as ataxic gait and convulsions (Fueta et al. 2002). A study that assessed the reversibility of the effects of 1-bromopropane reported a significant decrease (about 68%) in hindlimb muscle strength in male Wistar rats following exposure to 1,000 ppm 1-bromopropane for 6 weeks, which was still evident (about 40% reduction) 14 weeks after exposure terminated (Banu et al. 2007). In a 13-week study in rats, however, no exposure-related changes were observed in motor activity or a functional observation battery assessed during weeks 4, 8, and 13 of exposure to 1-bromopropane at concentrations up to 600 ppm (Albemarle Corporation 1997). No significant histopathological changes were observed in rats or mice exposed at up to 1,800 or 500 ppm, respectively, 1-bromopropane 6 hours/day, 5 days/week for 8–14 weeks (Kim et al. 1999; NTP 2011; Sohn et al. 2002). Neurobehavior was not assessed in these studies.

Some functional deficits described above could be explained by basic electrophysiological changes such as alterations in nerve conduction velocity. For example, motor nerve conduction velocity was significantly decreased and distal latency was increased in male Wistar rats after several weeks of exposure to ≥800 ppm 1-bromopropane (Ichihara et al. 2000b; Yu et al. 2001). In turn, decreased nerve conduction velocity could be due to morphological changes such as swelling of the axons and alteration of the myelin sheath, as observed by Ichihara et al. (2000b) and Yu et al. (1998, 2001). In Sprague-Dawley rats, a strain in which no functional deficits or morphological alterations of the brain were found by Albemarle Corporation (1997) and BSOC (2001a), a study of similar duration and exposure conditions as those used by Ichihara et al. (2000b) and Yu et al. (2001) reported no morphological alterations in peripheral nerves of male or female rats exposed to up to 1,250 ppm 1-bromopropane; however, no nerve conduction velocity experiments were conducted (Sohn et al. 2002). The mechanism(s) underlying the apparent strain differences are unknown.

Studies have also examined morphological and biochemical alterations in various brain areas following exposure to 1-bromopropane. For example, intermittent exposure of male rats to ≥800 ppm 1-bromo-propane vapors for 4 weeks resulted in a significant reduction in the density of noradrenergic axons in the dorsal and ventral medial prefrontal cortex and the amygdala but induced no significant changes in the dentate gyrus in the hippocampus (Mohideen et al. 2011). In contrast, exposure to 1-bromopropane did not affect the density of serotonergic neurons in any of the three areas studied. A more recent study in rats reported that exposure to 1,000 ppm 1-bromopropane for 4 weeks produced pyknosis and shrinkage of Purkinje cells and nuclei of granular cells of the cerebellum (Mohideen et al. 2013). Immunostaining showed that exposure to ≥400 ppm 1-bromopropane significantly increased the number of astrocytes in the middle cerebellar peduncle, suggesting astrocyte activation. Exposure to 1-bromopropane also induced significant elongation of processes in astrocytes in the cerebellum in all exposed groups. There was no clear demyelination in the cerebellum or hippocampus. Cerebellar glia cells were also affected in a study in male rats exposed to 1,000 ppm 1-bromopropane 8 hours/day, 7 days/week for 4 weeks (Subramanian et al. 2012). In these rats, microglia appeared larger and had longer ramified processes in the high-dose group. Microscopy also showed shrinkage of Purkinje cells in the high-dose group. No such effects were reported in rats exposed to 800 ppm 1-bromopropane. Morphological changes were paralleled by exposure-concentration-related increases in markers of oxidative stress in the cerebellum, as well as reactive oxygen species and nitric oxide content, suggesting that these biochemical changes may play a role in the neurotoxicity of 1-bromopropane. Other biochemical changes observed in various brain regions following exposure to ≥200 ppm 1-bromopropane for 1–4 weeks included alterations in amino acids involved in transamination and alterations in levels of neurotransmitters or their metabolites or

precursors from the gamma-aminobutyric acid (GABA), serotonergic, dopaminergic, noradrenergic, and glutamatergic systems (Suda et al. 2008; Zhang et al. 2013); see Section 3.4.2, Mechanisms of Toxicity, for more details, in particular the possible role of the hippocampus in 1-bromopropane-induced neurotoxicity.

In a chronic-duration inhalation study of 1-bromopropane, exposure of male and female rats to up to 500 ppm 1-bromopropane or of male and female mice to up to 250 ppm 1-bromopropane did not induce gross or microscopic alterations in brain (Morgan et al. 2011; NTP 2011). No other neurological end points were assessed in these studies.

The available data clearly indicate that the nervous system is a target for 1-bromopropane toxicity in humans and animals. Data in humans show that 1-bromopropane can induce morphological alterations in neurons, which may lead to motor and sensory deficits. Studies in animals show that 1-bromopropane can induce biochemical, morphological, electrophysiological, and neurobehavioral alterations by mechanisms yet to be elucidated.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Due to unclear adversity of biochemical changes in the nervous system, these end points were not used as the basis of NOAEL/LOAEL determinations unless they were clearly associated with an apical end point (e.g., neurobehavioral change, histopathological lesion, etc.).

3.2.1.5 Reproductive Effects

Available information regarding reproductive effects of 1-bromopropane in humans is limited. In two NIOSH health hazard reports, no exposure-related reproductive effects were reported by workers exposed to 1-bromopropane in response to the questions regarding whether they had been diagnosed with a reproductive or fertility problem, had ever seen a doctor for reproductive or fertility problems, or had failed to have a child after attempting for a full year (NIOSH 2002, 2003a). The geometric means for 1-bromopropane exposure levels were 168.9 and 45.7 ppm for the 2002 and 2003 report, respectively. In the 2003 report, a limited number of individuals (three exposed males, nine unexposed males) were evaluated for sperm parameters (NIOSH 2003a). There was no evidence of exposure-related changes in sperm count, motility, or morphology. In preliminary health surveys, female workers from a Chinese 1-bromopropane factory (n=23) did not report more menstrual abnormalities than age-matched referents

from a beer factory (Ichihara et al. 2004a, 2004b). The 8-hour shift TWA median exposure was 1.61 ppm 1-bromopropane. Survey results were not included in the more comprehensive health survey from this and two other factories in China (Li et al. 2010).

Animal studies that evaluated sperm/estrous cycle parameters, reproductive organ weight and histology, and reproductive hormone levels were available for review. While the available human data are inadequate to assess the reproductive toxicity of 1-bromopropane, animal data suggest that the reproductive system may be a potential target of concern for 1-bromopropane toxicity in humans.

Alterations in sperm parameters have been consistently reported in rats and mice following intermittent, intermediate-duration inhalation exposure to 1-bromopropane at concentrations as low as 250 and 50 ppm, respectively. Observed effects in F-344 rats exposed to ≥250 ppm and rats exposed to ≥400 ppm included a 25–70% decrease in sperm count, a 7–58% decrease in sperm motility, and a 7–98.5% increase in percent of abnormal sperm (including tailless sperm and banana-like sperm heads); no sperm alterations were observed in rats exposed to ≤200 ppm 1-bromopropane (Ichihara et al. 2000a; NTP 2011). In Wistar rats, exposure to 400 ppm 1-bromopropane for 6 weeks results in a 23% decrease in epididymal sperm count and exposure to 1,000 ppm significantly reduced sperm motility and sperm count even 14 weeks after the 6-week exposure period ceased (Banu et al. 2007). The investigators suggested that different mechanisms operate at different exposure concentrations based on the observed failure of spermiation at 400 ppm 1-bromopropane and spermatogenic cell depletion at 1,000 ppm 1-bromopropane. In three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA), the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible, showing a 27–78% decrease in sperm count, a 24–39% decrease in percent of motile sperm, and a 15–24% increase in the percent of abnormal sperm (2-tail sperm, banana-like sperm) at concentrations ≥50 ppm 1-bromopropane (lowest concentration tested) (Liu et al. 2009). Garner et al. (2007) had earlier reported that CYP2E1-null mice exposed to 800 ppm for 6 hours had a lower reduction (12%) in sperm motility than similarly exposed wild mice (37%). In B6C3F1 mice, sperm count was decreased 28% and sperm motility was decreased 3% at 500 ppm 1-bromopropane; no sperm alterations were observed at concentrations ≤250 ppm (NTP 2011).

Multiple studies reported alterations in the estrous cycle in rats and mice intermittently exposed to 1-bromopropane vapors at concentrations ≥250 and 500 ppm, respectively, for 12–14 weeks. Observed alterations included an increase in the number of irregular cycles or lack of estrous cycling in rats exposed to ≥400 ppm (Yamada et al. 2003), extended estrus period and decreased diestrus period during normal-

length estrous cycles in F-344 rats exposed to ≥250 ppm for 14 weeks (NTP 2011), and a 10% increase in estrous cycle length in mice exposed to 500 ppm 1-bromopropane for 14 weeks (NTP 2011). No significant changes in the estrous cycle were observed in rats at ≤200 ppm or mice at ≤250 ppm (NTP 2011; Yamada et al. 2003). In a shorter intermediate-duration study in rats exposed intermittently to up to 1,000 ppm 1-bromopropane for 20 days, there were no exposure-related changes in the number of estrous cycles per group, number of cycles per rat, cycle days, number of rats with cycles >6 days in duration, or number of ovulated ova in the oviduct at sacrifice (during estrous) (Sekiguchi et al. 2002).

An acute inhalation study in male rats did not reveal histological lesions in the testes following a 4-hour nose-only exposure to up to 8,500 ppm 1-bromopropane (Elf AtoChem S.A. 1997).

Histopathological lesions in the reproductive organs were infrequently reported in longer-term studies. One intermediate-duration study reported several alterations in reproductive organ histology in male Wistar rats following intermittent exposure to 800 ppm 1-bromopropane for 12 weeks (Ichihara et al. 2000a). Histological alterations were described qualitatively only, and included alterations in the testes (increased number of degenerated spermatocytes and retention of elongated spermatids in the seminiferous tubules), epididymides (decreased diameter of the epididymal duct cavity, increased interstitial space, increased height of the epithelial cells, and presence of neutrophil leukocytes or degenerated epithelial cell-like profiles in the epididymal duct), and the prostate and seminal vesicles (smaller alveoli and many degenerated cells in the vesicular cavity of the seminal vesicles). With the exception of retention of elongated spermatids in the seminiferous tubules at 400 ppm, no histopathological changes were observed at concentrations ≤400 ppm 1-bromopropane (Ichihara et al. 2000a). A more recent study from the same group of investigators reported degenerative changes in the reproductive organs of male Wistar rats exposed to 1,000 ppm 1-bromopropane for 6 weeks (Banu et al. 2007). Fourteen weeks after exposure ceased, the appearance of the prostate and seminal vesicles had returned to normal, but the testes and epididymides still showed histological alterations (Banu et al. 2007). In females, one intermediate-duration study reported follicular changes in the ovaries of rats intermittently exposed to concentrations ≥200 ppm 1-bromopropane for 12 weeks, including a significant 33–75% decrease in the number of antral and growing follicles (Yamada et al. 2003). In this study, no histological changes were observed in the uterus or vagina at exposures up to 800 ppm 1-bromopropane (Yamada et al. 2003). However, no significant histopathological changes were reported in the reproductive organs in intermediate-duration studies in rats or mice exposed to up to 1,800 or 500 ppm 1-bromopropane, respectively (Albemarle Corporation 1997; Kim et al. 1999; NTP 2011; Yu et al. 1998,

2001), or in chronic duration studies in rats or mice at concentrations up to 1,000 or 500 ppm, respectively (Morgan et al. 2001; NTP 2011).

Reproductive organ weight changes have been inconsistently reported in intermediate-duration studies with intermittent exposure to 1-bromopropane. Testes weight was significantly decreased by 12.5% in mice exposed to 250 ppm, but not ≤110 ppm 1-bromopropane (Liu et al. 2009); however, no other intermediate-duration study reported decreased testicular weight in mice or rats exposed to concentrations up to 500 and 1,800 ppm, respectively (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; Liu et al. 2009; NTP 2011). A study aimed at determining an LC_{50} for 1-bromopropane in rats did not report altered testes weight after the 14-day observation period at up to 8,500 ppm (Elf AtoChem S.A. 1997). Epididymides weight was significantly reduced by 11–28% in rats exposed to ≥400 ppm 1-bromopropane (Ichihara et al. 2000a) and by 14–19% in rats exposed to 1,000 ppm (but not ≤500 ppm) (NTP 2011); however, no changes in epididymides weight were reported in mice exposed to concentrations up to 500 ppm (Liu et al. 2009; NTP 2011). Significant reductions of 18–47% in weight of the seminal vesicles have been reported in rats and C57Bl/6J mice at ≥200 and 250 ppm, respectively; however, seminal vesicle weights were not altered in DBA/2J or BALB/cA mice exposed to concentrations up to 250 ppm (Ichihara et al. 2000a; Liu et al. 2009). In addition, one study reported a 32% decreased in prostate weight in rats at 800 ppm, but not ≤400 ppm (Ichihara et al. 2000a). A study that examined the reversibility of the effects of 1-bromopropane reported significant reductions in absolute weight of the prostate (56%), seminal vesicles (56%), testes (33%), and epididymides (28%) after 6 weeks of exposure to 1,000 ppm 1-bromopropane; no significant changes occurred at 400 ppm 1-bromopropane (Banu et al. 2007). Fourteen weeks after exposure ceased, the weight of the testes and epididymides were still significantly reduced compared to controls (Banu et al. 2007). One intermediate-duration study reported a significant 27–30% increase in the relative weight of the right and left ovaries in rats exposed to 1,800 ppm 1-bromopropane for 8 weeks; no changes were observed at concentrations ≤300 ppm (Kim et al. 1999). In other intermediate-duration studies, no changes were observed in female reproductive organ weights in rats exposed to concentrations up to 1,000 ppm (Albemarle Corporation 1997; Sekiguchi et al. 2002; Yamada et al. 2003).

Three intermediate-duration studies evaluated reproductive hormones in animals exposed to 1-bromopropane. Plasma testosterone levels were significantly decreased by 36% in male rats exposed to 800 ppm for 12 weeks (Ichihara et al. 2000a). Exposure to 1,000 ppm 1-bromopropane for 6 weeks resulted in a 56% reduction in serum testosterone in male Wistar rats (Banu et al. 2007). After a 4-week recovery period, serum testosterone was reduced 27% relative to controls, and returned to control values

after a 14-week recovery period; no significant changes were reported at 400 ppm 1-bromopropane. No changes were observed in testosterone levels at ≤400 ppm or in plasma luteinizing hormone (LH) or FSH at concentrations up to 800 ppm 1-bromopropane (Ichihara et al. 2000a). No changes were observed in serum LH or FSH in female rats following intermittent exposure at concentrations up to 800 ppm 1-bromopropane for 12 weeks (Yamada et al. 2003).

A comprehensive 2-generation reproductive study defined a NOAEL and LOAEL of 100 and 250 ppm 1-bromopropane, respectively, for reproductive effects in rats (BSOC 2001a). Exposure to 250 ppm 1-bromopropane resulted in a significant reduction (14%) in absolute prostate weight in F0 males and increased length of the estrous cycle (9%) in F1 females. Other reported effects included 48% reduction of fertility at 500 ppm and complete infertility at 750 ppm in the F0 generation. The mating index was also significantly reduced at 750 ppm, and time between paring and coitus was increased in groups exposed to ≥500 ppm 1-bromopropane. Males in the F0 generation exposed to ≥500 ppm 1-bromopropane had significantly reduced sperm motility and reduced morphologically normal sperm; this was also observed in F1 males exposed to 500 ppm. The number of implantation sites was significantly reduced in F0 dams exposed to 500 ppm 1-bromopropane. Examination of the ovary of F0 females showed significantly decreased corpora lutea at 500 and 750 ppm and increased follicular cysts and interstitial cell hyperplasia at 750 ppm. Ovaries of 500 ppm-exposed F1 females also showed an increased incidence of cysts and interstitial cell hyperplasia. No significant histological alterations were reported in the testes from male rats in the F0 or F1 generation. It should be noted, however, that exposure of rats to ≤996 ppm 1-bromopropane (highest concentration tested) during GDs 6–19 did not significantly affect pregnancy rates (pregnancy at termination), uterus weight, mean number of corpora lutea, pre- and post-implantation loss, or mean number of early and late resorptions (BSOC 2001b).

Some of the reproductive effects in rats reported by Albermarle Corporation (2001) were also reported in a study in which pregnant female rats were exposed to 1-bromopropane from conception to the end of lactation (Furuhashi et al. 2006). In the latter study, male offspring from rats exposed to 400 ppm 1-bromopropane showed no exposure-related changes in the epididymal sperm count or the percent motile sperm at postnatal day (PND) 50, but the rate of sperm arrival at cauda epididymides (the tail or inferior portion leading into the ductus deferens) was significantly lower than in controls. At 100 ppm (lowest concentration tested) and 400 ppm, testes showed fewer cells in the seminiferous tubules and fewer cell layers at PND 21 and a delay in thickening and differentiation of seminiferous tubules at day 33 (no quantitative data reported). Evaluation of sexual maturation in female offspring showed no

exposure-related changes, as assessed by the timing of the first diestrous. No changes were observed in male or female reproductive organ weights at PND 21, 33, or 50.

Overall, the available human data are inadequate to assess the reproductive toxicity of 1-bromopropane. However, the available animal data suggest that the reproductive system may be a potential target of concern for 1-bromopropane toxicity in humans.

3.2.1.6 Developmental Effects

No studies were located for developmental effects in humans after inhalation exposure to 1-bromopropane.

Limited information regarding developmental effects in animals indicate that perinatal exposure to 1-bromopropane can lead to altered growth in rats, but the relevance of this information to exposure of humans is unclear.

Reduced fetal weight was reported in a gestational intermittent exposure study in rats (BSOC 2001b). On GD 20, fetal body weights (male and female combined) from dams exposed to 100, 498, or 996 ppm 1-bromopropane were reduced 2.5, 4.9, and 7.4% relative to controls, respectively. Exposure to 1-bromopropane did not significantly affect the mean number of live fetuses per rat or sex ratio. Exposure to 1-bromopropane also did not induce external, visceral, or skeletal malformations. There was a significant increased dose-related incidence of delayed ossification in fetuses from the mid- and high-exposure concentration groups, which the investigators suggested was probably associated with maternal toxicity (reduced food consumption and body weight) and reduced fetal weight. Reduced body weight in the offspring was also reported in another study in which rats were exposed intermittently to 700 ppm 1-bromopropane (only exposure concentration tested) on GDs 1–20 (Fueta et al. 2015). Offspring body weight on PND 14 (only time measured) was reduced 7.5–9.5% compared to controls; no maternal toxicity was reported in this study. Fueta et al. (2015) also reported that maternal exposure to 1-bromopropane resulted in suppression of a shaking behavior in 14-day-old pups induced by injection of kainate, but not of a scratching behavior induced by kainate; the relevance of these findings to human health is unknown.

In the 2-generation study by BSOC (2001a) summarized above, the number of F1 and F2 pups born and litter size from the group exposed to 500 ppm 1-bromopropane were significantly reduced compared to

controls; no significant differences were seen at 250 ppm 1-bromopropane. F1 and F2 viability during lactation was not significantly affected by exposure to 500 ppm. F1 male pups exposed to 500 ppm had significantly reduced weight (13.7%) on PND 28. Male and female F1 pups necropsied on PND 21 or 28 showed no significant gross alterations in tissues or organs or alterations in selected organ weights (brain, spleen, thymus). A significant delay in F1 preputial separation occurred at 500 ppm; this was attributed to reduced body weights. Vaginal patency was not affected in F1 females. F2 male and female pup weights on PNDs 14 and 21 were significantly reduced (14–18%) at 500 ppm. Gross necropsy of F2 on PND 21 did not show treatment-related gross alterations or alterations in the brain, spleen, or thymus.

In a study in which rats were exposed to 1-bromopropane from conception to the end of lactation, survival of offspring during lactation was decreased in a dose-dependent fashion by ~5, 30, and 70% at 100 (lowest concentration tested), 400, and 800 ppm, respectively (Furuhashi et al. 2006). Decreased survival, however, was only statistically significant at 800 ppm. In order to determine if decreased survival and body weight gain in offspring were due to gestational or lactational exposure, a cross-foster experiment was also conducted with 0 or 800 ppm 1-bromopropane. The results showed that gestation and lactation exposure had comparable effects on survival rate, but lactation exposure played a greater role on growth of the offspring. Additionally, F1 animals were assessed for their ability to produce F2 offspring. Mated offspring from the lactation-only exposure group produced a significantly greater number of dead F2 offspring, compared with control. However, no exposure-related effects were observed in the F2 litter for gestational-only exposure. This suggested that lactation exposure may have played a greater role in sexual maturation of the offspring.

No teratogenic effects were reported by either BSOC (2001a, 2001b) or Furuhashi et al. (2006).

3.2.1.7 Cancer

No studies of cancer in humans exposed to 1-bromopropane by the inhalation route were located in the literature.

The potential carcinogenicity of 1-bromopropane has been examined in bioassays in rats and mice (Morgan et al. 2011; NTP 2011). In both bioassays, animals were exposed 6 hours/day, 5 days/week for up to 105 weeks. Rats were exposed to 0, 125, 250, or 500 ppm 1-bromopropane vapors, while mice were exposed to 0, 62.5, 125, 250, or 500 ppm 1-bromopropane vapors. 1-Bromopropane was a multi-site carcinogen in rats, significantly increasing the incidence of large intestine adenomas in females

(500 ppm), skin keratoacanthoma in males (≥250 ppm), skin keratoacanthoma, basal cell adenoma, or squamous cell carcinoma in males (≥125 ppm), malignant mesothelioma in males (500 ppm), and pancreatic islet adenoma in males (≥125 ppm). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females (≥62.5 ppm).

Based on the information available, the Department of Health and Human Services (DHHS) has classified 1-bromopropane as "*reasonably anticipated to be a human carcinogen"* (NTP 2016). Based on the findings in animals, ACGIH has assigned 1-bromopropane a classification of "*A3 – Confirmed animal carcinogen with unknown relevance to humans"* (ACGIH 2104, 2016). The International Agency for Research on Cancer (IARC) and the EPA have not evaluated the carcinogenicity of 1-bromopropane (IARC 2014; IRIS 2014).

3.2.2 Oral Exposure

3.2.2.1 Death

No reports of death in humans due to oral exposure to 1-bromopropane were located in the available literature.

In male and female rats exposed once to concentrations of 2,000 mg 1-bromopropane/kg via gavage, 0/5 males and 1/5 females died during the 14-day observation period; the LD_{50} was determined to be greater than 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1993). Necropsy did not reveal gross alterations. Although there are no monitoring data for 1-bromopropane in water or soil, it is unlikely that humans would be orally exposed to these high levels of 1-bromopropane.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, endocrine, dermal, ocular, or metabolic effects in humans or in animals following oral exposure to 1-bromopropane. In addition, no studies were located regarding hepatic and body weight effects in humans exposed orally to 1-bromopropane.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	once (G)	Bd Wt	2000			Elf Atochem S.A. 1993 1-Bromopropane	
2	Rat (Wistar)	12 d 1 x/d (GO)	Bd Wt	800 M			Guo et al. 2015 1-Bromopropane	
3	Rat (Wistar)	12 d 1 x/d (GO)	Bd Wt	400 M	800 M (13% decrease in final body weight)		Zhong et al. 2013 1-Bromopropane	
4	Mouse (BALB/c)	once (GO)	Hepatic	200 F	500 F (centrilobular hepatocyte swelling)		Lee et al. 2007 1-Bromopropane	Congestion, hemorrhage, cellular swelling and vacuolization of hepatocytes was observed at 1,000 ppm
			Bd Wt	1000 F				
5	Mouse (ICR)	10 d 1 x/d (GO)	Bd Wt	600 M			Yu et al. 2008 1-Bromopropane	
Immuno/ Lymphoret								
6	Mouse (BALB/c)	once (GO)			200 F (reduced antibody response to T-dependent antigen)		Lee et al. 2007 1-Bromopropane	

Table 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
7	Rat (Sprague-Dawley)	once (G)				2000 (sedation)	Elf Atochem S.A. 1993 1-Bromopropane	
8	Rat (Wistar)	12 d 1 x/d (GO)		100 M	200 M (impaired spatial memory and learning ability)		Guo et al. 2015 1-Bromopropane	
9	Rat (Wistar)	12 d 1 x/d (GO)			200[b] M (impaired spatial learning and memory)		Zhong et al. 2013 1-Bromopropane	
Reproductive								
10	Mouse (ICR)	10 d 1 x/d (GO)			600 M (degeneration of pachytene spermatocytes)		Yu et al. 2008 1-Bromopropane	

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration (14 days or less) oral minimal risk level (MRL) of 0.2 mg/kg/day for 1-BP. Using benchmark-dose modeling, a BMD1SD and BMDL1SD of 148.37 and 19.75 mg/kg/day, respectively, were calculated for decreased spatial memory in rats on Day 5 of the Morris water maze task from the selected model (Hill). The BMDL1SD was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive the MRL of 0.2 mg/kg/day.

Bd Wt = body weight; d = day(s); F = Female; (G) = gavage; (GO) = gavage in oil; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; x = time(s)

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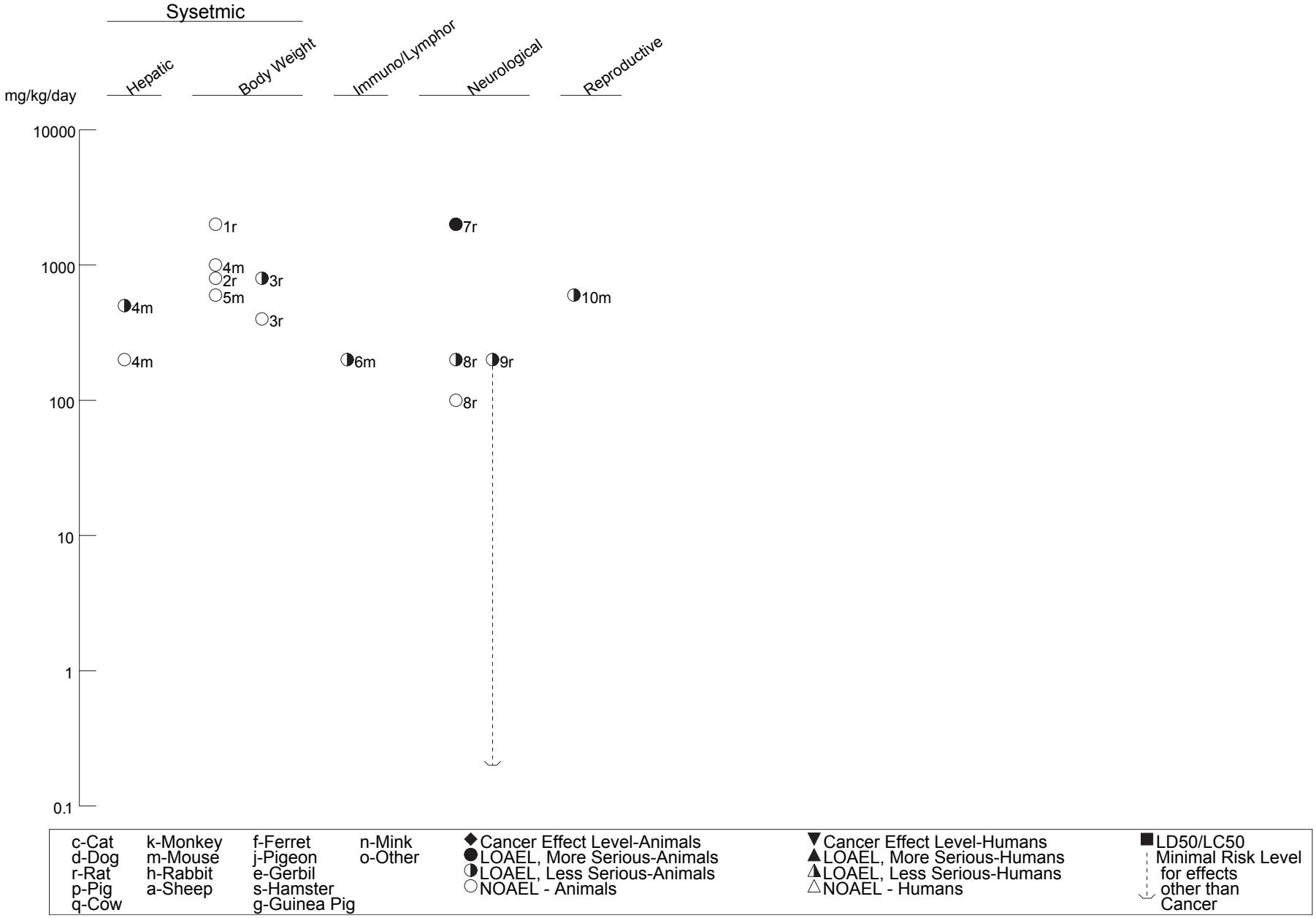
Figure 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral

Acute (≤14 days)



Hepatic Effects. Data from a single acute-duration oral study in mice suggest that exposure to high oral doses of 1-bromopropane may induce severe liver effects, although further studies are needed to validate these data. Gavage administration of a single dose of 500 mg 1-bromopropane/kg to female mice induced centrilobular swelling of hepatocytes, and a single dose of 1,000 mg 1-bromopropane/kg induced liver congestion, hemorrhage, cellular swelling, and vacuolization assessed 12 hours after dosing and increasing in severity at later times (assessed up to 48 hours post-exposure) (Lee et al. 2007); no significant effects were reported in mice dosed with 200 mg 1-bromopropane/kg. These morphological changes were accompanied by increased serum ALT activity (maximally 380-fold 24 hours after dosing with 1,000 mg 1-bromopropane/kg). Biochemically, treatment with 1-bromopropane caused depletion of GSH and increased the formation of GSH conjugates, possibly leading to increased oxidative stress, as evidenced by increased levels of malondialdehyde and decreased catalase activity.

Body Weight Effects. Limited data in animals preclude drawing meaningful conclusions regarding effects from oral 1-bromopropane exposure on body weight. Body weight was not affected in male or female rats administered a single dose of 2,000 mg 1-bromopropane/kg and observed for up to 14 days (Elf Atochem S.A. 1993) or in female mice administered a single dose of 1,000 mg 1-bromopropane/kg and observed for up to 48 hours (Lee et al. 2007). In repeated-dose studies, administration of 800 mg 1-bromopropane/kg/day to male rats for 12 consecutive days resulted in a 13% decrease in terminal body weight; no significant effect was reported at 400 mg 1-bromopropane/kg/day (Zhong et al. 2013). No data on food consumption were provided in the latter study. In a similar study, 10 consecutive doses of up to 600 mg 1-bromopropane/kg/day did not significantly affect body weight in male mice (Yu et al. 2008).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following oral exposure to 1-bromopropane.

A single mouse study provides relevant information, although it is insufficient to determine whether the immunological system might be a target for oral exposure to 1-bromopropane. Female mice dosed once by gavage with ≥200 mg 1-bromopropane/kg and immunized intraperitoneally with SRBC 30 minutes later showed a significant reduction in the antibody response to the T-dependent antigen of up to 60% 4 days later (Lee et al. 2007). It was also reported that ≥200 mg 1-bromopropane/kg/day significantly reduced the number of $CD4^{+}IL\text{-}2^{+}$ cells in response to ConA by up to ~30%. Flow cytometry showed that

1-bromopropane reduced the absolute number of all splenocyte subpopulations. The investigators also reported that exposure to 1-bromopropane decreased spleen GSH content while increasing a GSH conjugation product, and suggested that immunotoxicity might be related to increased oxidative stress.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to 1-bromopropane.

The limited number of studies in animals showed that high oral doses of 1-bromopropane can produce sedation, and repeated lower doses can affect learning and memory.

Clinical signs of neurotoxicity, including marked decrease in spontaneous activity (sedation), piloerection, and dyspnea, were observed in male and female rats within 4 hours of receiving a single gavage dose of 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1993). Surviving animals (9/10) fully recovered by day 2 of the 14-day post-exposure observation period.

Limited data are available in a study that examined the effects of 1-bromopropane on cognitive function in male rats and the possible role of oxidative stress (Zhong et al. 2013). On days 8–12 of a 12-day treatment with 200, 400, or 800 mg 1-bromopropane/kg/day, cognitive function (spatial learning and memory) was assessed with the Morris water maze test. Some rats dosed with 400 and 800 mg 1-bromopropane/kg/day showed irritability at the start of dosing. After 1 week of dosing, rats in the 800 mg 1-bromopropane/kg/day group showed slow response and sluggishness. Dose-related impairments were observed in learning and memory measures in the Morris water maze task. During the 4-day learning phase, the escape latency was significantly increased in the 800 mg 1-bromopropane/kg/day group and the total swimming distance was increased at ≥200 mg 1-bromopropane/kg/day. Time spent in different swimming "search" patterns (direct finding, approaching target, random searching, and thigmotaxis) differed significantly in all exposed groups, compared with controls, with exposed animals showing increased thigmotaxis (time spent in periphery of tank). On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times that they crossed the former location of the target platform; rats exposed to 800 mg 1-bromopropane/kg/day also showed a significant decrease in time spent in the target quadrant. Assessment of biochemical indices in the brain showed an increase in oxidative stress (increased malondialdehyde and oxidized GSH, reduced GSH, and reduced GSH reductase activity) for the most part in the mid- and high-dose groups.

Tests with specific monoclonal antibodies also showed increased total levels of reactive aldehyde modified proteins in the cerebral cortex. A more recent study by the same groups of investigators (Guo et al. 2015) confirmed the findings of Zhong et al. (2013) and proposed that 1-bromopropane-induced reduction of a novel neuroglobin (Ngb) with antioxidant properties might be involved in the neurotoxicity induced by 1-bromopropane. In another similar study, it was reported that melatonin, administered simultaneously with 1-bromopropane (600 mg/kg/day for 27 consecutive days) to rats, ameliorated the 1-bromopropane-induced impairment of learning and memory and loss of hippocampal neurons (Xu et al. 2016). The investigators suggested that melatonin acts by scavenging reactive oxygen species and reducing oxidative stress. Data from Zhong et al. (2013) were used to derive an acute-duration oral MRL for 1-bromopropane.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to 1-bromopropane.

Only one animal study with relevant information was identified; the results do not suggest that 1-bromopropane is a reproductive toxicant by the oral route.

The available study examined the effect of 1-bromopropane on dominant lethality in male mice (Yu et al. 2008) (see Section 3.3, Genotoxicity). Administration of 600 mg 1-bromopropane/kg/day (only dose level tested) for 10 consecutive days did not significantly affect serum testosterone levels, as assessed 5 weeks after treatment. At that time, microscopic examination of the testes showed degeneration of pachytene spermatocytes in the treated males. Evaluation of sperm parameters in cauda epididymides showed somewhat reduced motility in the treated group but the difference with controls was not statistically significant. All other sperm parameters in treated mice were comparable to controls (path velocity, straight line velocity, curvilinear velocity, lateral head displacement, and beat cross frequency). Further studies seem necessary to validate these findings.

No studies were located regarding the following effects in humans or animals following oral exposure to 1-bromopropane:

3.2.2.6 Developmental Effects
3.2.2.7 Cancer

3.2.3 Dermal Exposure

Only one human study was located with relevant information. An occupational study reported that workers exposed to concentrations of 1-bromopropane in the air ≥56.9 ppm experienced symptoms of nose, eye, and throat irritation (Ichihara et al. 2004a). It is assumed that this occurred due to direct contact of vapors of the chemical with the tissues. It should be noted, however, that the measured concentrations included 1-bromopropane as well as 2-bromopropane, since the analytical method could not differentiate between the two compounds. In addition, no appropriate controls were used. Finally, given the nature of the complaints, it is reasonable to assume that no protective masks were used.

No animal studies were located with information that would support or refute the findings of the occupational study mentioned above. However, one animal study was located, in which application of 2,000 mg 1-bromopropane/kg to the skin of male and female rats under a semi-occlusive dressing for 24 hours did not induce mortalities, clinical signs of toxicity, cutaneous reactions, body weight effects, or gross abnormalities at necropsy during a 14-day post-exposure observation period. (Elf Atochem S.A. 1995).

3.3 GENOTOXICITY

Only one study was located regarding genotoxic effects in humans exposed to 1-bromopropane. The study was conducted in 63 workers at two facilities (facility A: 41 workers; facility B: 22 workers) where 1-bromopropane was used as a solvent for spray adhesives in foam cushions (Toraason et al. 2006). 1-Bromopropane TWA concentrations assessed from personal breathing zone samples ranged from 0.2 to 271 ppm at facility A and from 4 to 27 ppm at facility B. In general, exposures at facility A were estimated to be 4-fold higher than in facility B. Assessment of DNA damage in peripheral leukocytes from workers using the comet assay revealed no significant difference in DNA damage between sprayers and non-sprayers at either facility. However, results from multiple linear regression models that controlled for sex, age, smoking status, facility, and two glutathione *S*-transferase [GST] polymorphisms showed increased comet tail moment dispersion coefficients in sprayers at facility A at the end of the week. The covariates that had a significant effect in the models were GSTM1, facility, and sex. No conclusions can be drawn regarding the genotoxicity of 1-bromopropane in humans based on the results of a single study.

Results from *in vivo* and *in vitro* studies of 1-bromopropane genotoxicity are summarized in Tables 3-3 and 3-4, respectively. *In vivo* studies in animals have yielded negative results in tests for induction of

Table 3-3. Genotoxicity of 1-Bromopropane *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells			
Human peripheral leukocytes	DNA damage and repair, strand breaks	(+)	Torasson et al. 2006
Mouse peripheral blood	Micronuclei	–	NTP 2011
Male rat	Dominant lethal	–	Saito-Suzuki et al. 1982
Male mouse	Dominant lethal	–	Yu et al. 2008

– = negative result; (+) = weak positive

Table 3-4. Genotoxicity of 1-Bromopropane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	– (open test system)	– (open test system)	Barber et al. 1980, 1981
S. typhimurium TA100, TA1535	Reverse mutation	+ (closed test system)	+ (closed test system)	Barber et al. 1980, 1981
S. typhimurium TA97, TA98, TA100, TA 1535	Reverse mutation	–	–	NTP 2011
Escherichia coli Wp2 uvrA/pKM101	Reverse mutation	–	–	NTP 2011
Mammalian cells:				
Peripheral leukocytes	DNA damage		+	Toraason et al. 2006
Human hepatoma cell-line (HepG2)	DNA damage and repair, single strand breaks		–	Hasspieler et al. 2006
Human hepatoma cell-line (HepG2)	DNA damage and repair, repair activity		–	Hasspieler et al. 2006

+ = positive results; – = negative results

micronuclei and dominant lethality. Exposure via inhalation to 62.5–500 ppm 1-bromopropane for 3 months did not increase the frequency of micronucleated normochromatic or polychromatic erythrocytes in the peripheral blood of male or female mice (NTP 2011). Gavage administration of 300 or 600 mg 1-bromopropane/kg to male ICR mice for 10 days before mating revealed no dominant lethal mutations in germ cells (Yu et al. 2008). In addition, no dominant lethal mutations were observed in male rats gavaged with 400 mg 1-bromopropane/kg for 5 days before mating (Saito-Suzuki et al. 1982).

Studies of the genotoxic potential of 1-bromopropane *in vitro* yielded mixed results. In two studies conducted by NTP (2011), 1-bromopropane did not induce mutations in *Salmonella typhimurium* or *Escherichia coli* with or without exogenous metabolic activation. However, when tested in a closed system to control for volatility, 1-bromopropane was mutagenic to *S. typhimurium* strains TA100 and TA1535 (Barber et al. 1980, 1981). In this same study, using a conventional (or open) test system yielded negative results for all tested *Salmonella* strains.

An *in vitro* study in peripheral leukocytes from unexposed volunteers yielded positive results for DNA damage at the highest concentration tested (1 mM) (Toraason et al. 2006). However, because lower concentrations (≥0.1 mM) increased the incidence of apoptotic cells, the DNA damage may reflect general cell toxicity. In studies using the ethoxyresorufin O-deethylase (EROD) bioassay, 1-bromopropane did not induce DNA single-strand breaks or DNA repair in human hepatoma cell-line HepG2 at concentrations between 25 and 500 ppm. However, cytotoxicity was evident at 500 ppm (Hasspieler et al. 2006).

3.4 TOXICOKINETICS

3.4.1 Absorption

The detection of carbon-containing metabolites and elevated bromide ion concentrations in urine samples of workers exposed to 1-bromopropane by inhalation and dermal contact provides qualitative evidence that 1-bromopropane is absorbed by the respiratory tract and the skin in humans (Hanley et al. 2006, 2009, 2010; Valentine et al. 2007). In addition, reports of neurological and other effects in occupationally exposed subjects provide indirect evidence of absorption of 1-bromopropane (Ichihara et al. 2002; Majersik et al. 2007; MMWR 2008; NIOSH 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999).

Dermal absorption characteristics estimated in human epidermal membranes mounted on static diffusion cells included steady-state fluxes averaging 625–960 µg cm^{-2} $hour^{-1}$ with pure 1-bromopropane and 441–722 µg cm^{-2} $hour^{-1}$ with a commercial dry cleaning solvent, an average dermal penetration of about 0.2% from an applied dose of 13.5 mg/cm^2 under non-occluded conditions, and a dermal permeability coefficient for 1-bromopropane in water of 0.257 cm/hour (Frasch et al. 2011).

Qualitative evidence of absorption by the gastrointestinal and respiratory tracts comes from animal studies (Garner et al. 2006, 2015; Jones and Walsh 1979). ^{13}C-labeled metabolites were detected in urine collected from rats and mice exposed by inhalation to 800 ppm [1,2,3-^{13}C]-1-bromopropane for 6 hours (Garner et al. 2006). Indicative of rapid and extensive absorption by the respiratory tract, rats placed in closed chambers with concentrations ranging from 70 to 2,700 ppm rapidly decreased the chamber concentrations within 2 hours, followed by a more gradual decrease in 2–8 hours (Garner et al. 2015). At the lower end of the initial chamber air concentration range, the decrease was almost complete within 3–6 hours (Garner et al. 2015). A number of mercapturic acid derivative metabolites were detected in pooled urine samples collected from rats given oral doses of 200 mg 1-bromopropane/kg/day in arachis oil for 5 days (Jones and Walsh 1979).

No other human or animal studies were located that determined the rate or extent of absorption of 1-bromopropane following inhalation, oral, or dermal exposure.

3.4.2 Distribution

Simulations with a preliminary human PBPK model for inhaled 1-bromopropane predicted some accumulation of the parent material in blood following exposure for 8 hours/day for 5 days (Garner et al. 2015; see Section 3.4.5 for more discussion of the development and limitations of this model).

Results from metabolic disposition studies with rats and mice exposed to 1-bromopropane by intravenous injection or inhalation indicate that 1-bromopropane is rapidly and widely distributed by the blood, especially to highly perfused tissues like the brain, followed by a rapid clearance mediated by exhalation of parent material or metabolically produced CO_2 and urinary excretions of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). For example, following intravenous injection of [1-^{14}C]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al. 2006). In these

studies, most of the administered radioactivity was exhaled as parent material or metabolized CO_2 or excreted as metabolites in the urine. Distribution and accumulation of parent material in fatty tissue is limited with short-term exposure scenarios, but some accumulation with repeated exposures may occur (Garner and Yu 2014; Garner et al. 2006, 2015).

A cross-fostering study was conducted in rats to examine the disposition of bromine ion in the brain of rats and their offspring (Ishidao et al. 2016). Rats were exposed to 700 ppm 1-bromopropane 6 hours/day on GDs 1–20. On GD 20, bromine was significantly more concentrated (approximately 47% higher concentration) in the brain of exposed virgin rats than in the brain of exposed pregnant rats, which the investigators suggested could have been due to a dilution effect in the pregnant rats because of increasing body weight. On GD 20, brains from fetuses had significantly more bromine (approximately 68% higher concentration) than brains from the dams, indicating easy transfer of bromine to the fetus via the placenta. Analyses of the brains from pups from the different exposure groups showed that uptake of bromine via the milk was higher than through the placenta.

3.4.3 Metabolism

The metabolism of 1-bromopropane in mammals involves: (1) conjugation, principally with glutathione, leading to release of the bromide ion and formation of mercapturic acid derivatives and (2) oxidation (catalyzed by cytochrome P-450) of parent material and metabolites leading to metabolites with hydroxyl, carbonyl, and sulfoxide groups, and to CO_2. These concepts are based on studies of urinary metabolites in workers exposed to 1-bromopropane (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012; Valentine et al. 2007), *in vivo* metabolic disposition studies in rats and mice (Barnsley et al. 1966; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979), and *in vitro* metabolism studies with rat liver preparations (Jones and Walsh 1979; Kaneko et al. 1997; Tachizawa et al. 1982). There is evidence that mice have a higher capacity for oxidative metabolism of 1-bromopropane than rats (Garner and Yu 2014; Garner et al. 2006, 2007).

Occupational studies have identified multiple urinary metabolites of 1-bromopropane. N-Acetyl-S-(n-propyl)-L-cysteine has been identified in urine samples from workers in a 1-bromopropane manufacturing plant (Valentine et al. 2007), in foam fabricating plants using spray adhesives containing 1-bromopropane (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012), and in degreasing operations in plants using 1-bromopropane as a cleaning solvent in the manufacture of aerospace components, hydraulic equipment, optical glass, and printed electronic circuit assemblies (Hanley et al. 2010). Other

urinary metabolites identified in 1-bromopropane workers are the bromide ion (Hanley et al. 2010) and three oxygenated metabolites present at lower urinary concentrations than N-acetyl-S-(n-propyl)-L-cysteine: N-acetyl-S-propylcysteine-S-oxide (also known as N-acetyl-3-(propylsulfinyl) alanine), N-acetyl-S-(2-carboxyethyl) cysteine, and N-acetyl-S-(3-hydroxy-propyl) cysteine (Cheever et al. 2009; Hanley et al. 2009). The correlations between time weighted average workplace air concentrations of 1-bromopropane and urinary levels of bromide and N-acetyl-S-(n-propyl)-L-cysteine (Hanley et al. 2006, 2009, 2010; Valentine et al. 2007) support the hypothesis that conjugation with glutathione is a quantitatively important pathway in humans (see Figure 3-3). The detection of oxygenated metabolites in urine samples indicates that oxidation pathways also exist in humans (see Figure 3-4 for structures of identified oxygenated metabolites).

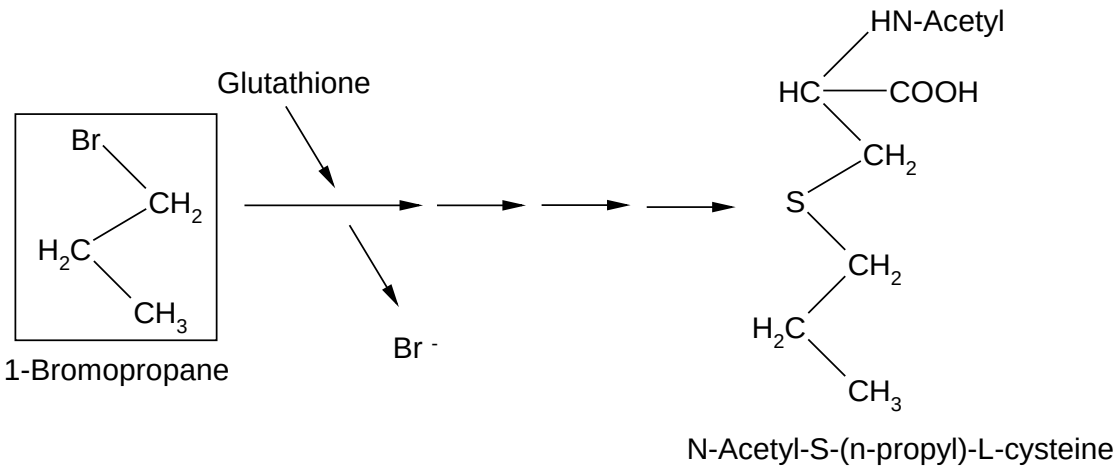
Results from metabolic disposition studies in rats and mice illustrate that the metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. Figure 3-5 presents proposed metabolic pathways based on results from studies of F-344 rats and B6C3F1 mice exposed to [1-^{14}C]-1-bromopropane by intravenous injection or [1,2,3-^{13}C]-1-bromopropane by inhalation or intravenous injection (Garner et al. 2006).

The metabolic scheme shows an oxidation path to CO_2 involving cytochrome P450 (CYP) oxidation steps to 1-bromo-2-propanol and bromoacetone. This path is proposed based on several findings:

1. Following intravenous injection of ^{14}C-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO_2 exhaled in 48 hours accounted for approximately 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al. 2006). (These data also indicate that oxidative metabolism of 1-bromopropane in rats is more dependent on dose than oxidative metabolism in mice; the decrease in percentage dose exhaled as CO_2 at the highest dose is greater in rats than mice.)

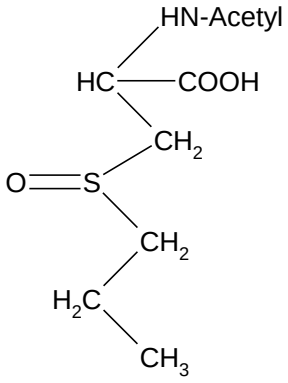
2. Pretreatment of rats with 1-aminobenzotriazole (ABT) before administration of single intravenous doses of ~20 mg/kg ^{14}C-1-bromopropane or inhalation exposure to 800 ppm ^{13}C-1-bromopropane for 6 hours caused decreased exhalation of radioactivity as CO_2 and decreased formation of oxidative urinary metabolites (Garner et al. 2006). ABT is an inhibitor of a number of CYP enzymes (Emoto et al. 2003).

Figure 3-3. Formation of N-Acetyl-S-(n-propyl)-L-cysteine from 1-Bromopropane via Conjugation with Reduced Glutathione (GSH)

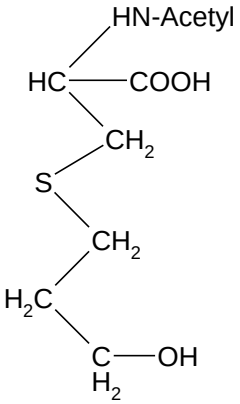


Sources: Hanley et al. 2009, 2010; Valentine et al. 2007

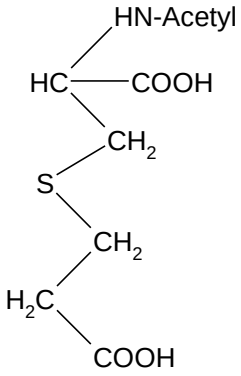
Figure 3-4. Mercapturic Acid Metabolites with a Sulfoxide Group or a Hydroxyl or Carbonyl Group on the Propyl Residue Identified in Urine Samples of 1-Bromopropane-Exposed Workers



N-Acetyl-S-propylcysteine-S-oxide
[also known as
N-acetyl-3-(propylsulfinyl)alanine]



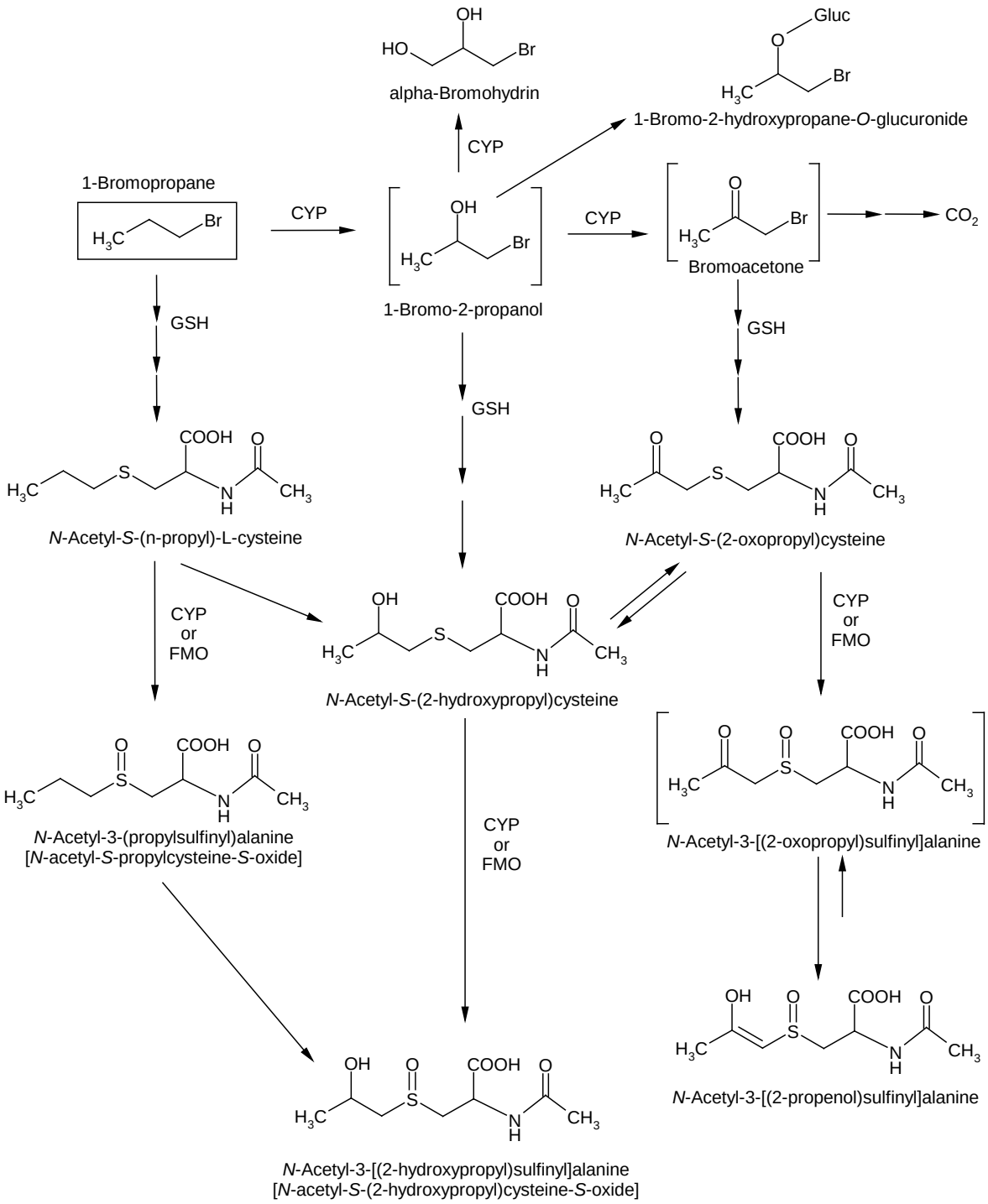
N-Acetyl-S-(3-hydroxypropyl)cysteine



N-Acetyl-S-(2-carboxyethyl)cysteine

Sources: Cheever et al. 2009; Hanley et al. 2009; Mathias et al. 2012

Figure 3-5. 1-Bromopropane Metabolism in Male F-344 Rats and B6C3F1 Mice Following Inhalation Exposure or Tail Vein Injection*



*Structures in brackets are proposed intermediates and were not isolated in urine.

CYP = cytochrome P450 monooxygenase; FMO = flavin-containing monooxygenease; GSH = glutathione

Sources: Garner et al. 2006, 2007; NTP 2013

3. Urinary metabolites derived from 1-bromo-2-propanol accounted for over half of all carbon-containing urinary metabolites identified in rats and mice exposed by inhalation or intravenous injection of ^{13}C-1-bromopropane. No 1-bromo-2-propanol-derived metabolites were found in urine of ABT-pretreated rats exposed to ^{13}C-1-bromopropane (Garner et al. 2006). 1-Bromo-2-propanol and bromoacetone themselves were not detected in urine of 1-bromopropane-exposed rats, but their presence was detected in preparations of rat liver homogenates incubated with 1-bromopropane (Garner et al. 2006).

4. N-Acetyl-S-(2-hydroxypropyl) cysteine was identified in urine of rats given subcutaneous doses of 1-bromopropane (1 mL of a 40% solution of 1-bromopropane in arachis oil per rat) (Barnsley et al. 1966).

Based on urinary metabolites identified with nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-tandem mass spectrometry (LC-MS/MS), and high-performance liquid chromatography (HPLC) radiochromatography (Garner et al. 2006), the scheme in Figure 3-5 also shows an initial conjugation of 1-bromopropane with glutathione leading to N-acetyl-S-(n-propyl)-L-cysteine, an oxidation step from 1-bromo-2-propanol to alpha-bromohydrin, a glucuronic acid conjugation step from 1-bromo-2-propanol to 1-bromo-2-hydroxypropane-O-glucuronide, and glutathione conjugation of 1-bromo-2-propanol and bromoacetone followed by oxidation steps leading to metabolites with sulfoxide groups (e.g., N-acetyl-3-[(2-hydroxypropyl)sulfinyl] alanine). The steps involving oxidation of sulfur in the glutathione conjugate derivatives were proposed to be catalyzed by CYP oxygenases or flavin-containing monooxygenases (FMO) as suggested by Krause et al. (2002).

Catalysis of the oxidation steps by a number of CYP isozymes is supported by results from metabolic disposition studies in wild-type and *Cyp2e1-/-* knock-out mice (F1 hybrids of 129/Sv and C57BL/6N strains) exposed by inhalation to 800 ppm ^{13}C-1-bromopropane for 6 hours (Garner et al. 2007). Three major metabolites were identified in urine collected from wild-type mice during exposure: N-acetyl-S-(2-hydroxypropyl) cysteine (34 µmoles in collected urine), 1-bromo-hydroxypropane-*O*-glucuronide (5 µmoles), and N-acetyl-S-(n-propyl)-L-cysteine (8 µmoles). In *Cyp2e1-/-* mice, the amounts of these metabolites in collected urine were changed to 21, 2, and 24 µmoles, respectively. The ratio of 2-hydroxylated metabolites to N-acetyl-S-(n-propyl)-L-cysteine was approximately 5:1 in wild-type and 1:1 *Cyp2e1-/-* mice. The results indicate that the deletion of CYP2E1 increased the relative importance of the glutathione conjugation pathway but did not eliminate the formation of oxygenated metabolites, suggesting the involvement of other CYP enzymes, in addition to CYP2E1, in oxidation steps as illustrated in Figure 3-5.

Evidence for the initial conjugation of 1-bromopropane with glutathione leading to the formation of N-acetyl-S-(n-propyl)-L-cysteine comes from a number of studies in rats and mice (Garner et al. 2006, 2007; Jones and Walsh 1979; Khan and O'Brien 1991).

1. N-Acetyl-S-(n-propyl)-L-cysteine was detected in the urine of wild-type and *Cyp2e1-/-* mice exposed to 800 ppm 1-bromopropane for 6 hours, at molar ratios to hydroxylated metabolites of 5:1 and 1:1, respectively (Garner et al. 2007).

2. N-Acetyl-S-(n-propyl)-L-cysteine and N-acetyl-3-(propylsulfinyl) alanine (i.e., N-acetyl-S-propylcysteine-S-oxide) accounted for approximately 39 and 5% of excreted urinary metabolites, respectively, in urine collected for 24 hours after inhalation exposure of rats to 800 ppm 1-bromopropane for 6 hours (Garner et al. 2006).

3. N-Acetyl-S-(n-propyl)-L-cysteine was a relatively minor urinary metabolite in rats given single 5-mg 1-bromopropane/kg intravenous doses, but accounted for >80% of urinary metabolites following administration of 100 mg 1-bromopropane/kg (Garner et al. 2006).

4. N-Acetyl-S-(n-propyl)-L-cysteine and N-acetyl-S-propylcysteine-S-oxide were among the six mercapturic acid derivatives identified in urine from rats given 200 mg 1-bromopropane/kg by gavage (in arachis oil) for 5 days (Jones and Walsh 1979). The structures of the other four mercapturic acid derivatives identified were consistent with glutathione conjugation of oxygenated metabolites of 1-bromopropane, rather than 1-bromopropane itself. These included N-acetyl-S-(2-hydroxypropyl) cysteine, N-acetyl-S-(3-hydroxypropyl) cysteine, and N-acetyl-S-(2-carboxyethyl) cysteine (Jones and Walsh 1979). The techniques used in this study did not determine the relative amounts of the urinary mercapturic acid derivatives.

5. Isolated hepatocytes incubated for 60 minutes with 1-bromopropane showed a decrease in glutathione content (from 58.4 to 40.8 nmol/10^6 cells), consistent with the importance of glutathione conjugation in metabolic disposition of 1-bromopropane in mammals (Khan and O'Brien 1991).

Other studies have identified other metabolites, not included in Figure 3-5, in urine from rats and mice exposed to 1-bromopropane (Ishidao et al. 2002; Jones and Walsh 1979) and in *in vitro* systems (Jones and Walsh 1979; Kaneko et al. 1997; Tachizawa et al. 1982). Jones and Walsh (1979) reported detecting metabolites in urine from rats orally exposed to 1-bromopropane that are consistent with the initial oxidation of the 3-C of 1-bromopropane: N-acetyl-S-(3-hydroxypropyl) cysteine, 3-bromopropionic acid, and N-acetyl-S-(2-carboxyethyl) cysteine. Garner et al. (2006) were not able to detect these metabolites in urine following administration of single intravenous doses up to 100 mg 1-bromopropane/kg in rats or exposure to 800 ppm for 6 hours in rats or mice. Garner et al. (2006) proposed that the apparent discrepancy may have been due to an amplification of minor metabolites from the pooling, concentration, and acid hydrolysis processes used in the earlier study. Glycidol (1,2-epoxy-3-propanol) was detected in urine of Wistar rats exposed by inhalation 6 hours/day to 700 ppm for 3 or 4 weeks or 1,500 ppm for 4 or

12 weeks; however, no determination of the amount of this compound was made, and the report did not mention the detection of any other carbon-containing metabolites (Ishidao et al. 2002). Kaneko et al. (1997) monitored the formation of n-propanol during incubation of rat liver microsomes with 1-bromopropane. 3-Bromopropanol and 3-bromopropionic acid were detected when 1-bromopropane was incubated in an *in vitro* oxidizing system, but 1-bromopropane metabolism with rat liver homogenates was not examined due to the low water solubility of 1-bromopropane (Jones and Walsh 1979). Propene, 1,2-epoxypropane, 1,2-propanediol, and proprionic acid were detected when liver microsomes from phenobarbital-treated rats were incubated with 1-bromopropane, and the addition of glutathione to the reaction mixture led to formation of S-(1' propyl)glutathione and S-(2' hydroxyl-1'-propyl) glutathione (Tachizawa et al. 1982). Garner et al. (2006) reported that propene, propylene oxide, propanediol, and propionic acid were not detected in liver homogenate incubations with 1-bromopropane; they suggested that the use of phenobarbital as a CYP inducer may have resulted (in the Tachizawa et al. [1982] studies) in the formation of metabolites not generated by constitutive CYP enzymes.

3.4.4 Elimination and Excretion

Results from animal metabolic disposition studies indicate that 1-bromopropane is eliminated from the body by exhalation of the parent material and metabolically derived CO_2 and by urinary excretion of metabolites (Garner et al. 2006; Jones and Walsh 1979). There is evidence that differences of relative importance of different excretion pathways between mice and rats may reflect higher capacity for oxidative metabolism of 1-bromopropane in mice than in rats (Garner and Yu 2014; Garner et al. 2006, 2007).

Following single intraperitoneal injections of 200 mg/kg doses of [1-^{14}C]-1-bromopropane in rats, about 60% of the administered radioactivity was eliminated as unchanged 1-bromopropane in the expired air within 4–6 hours, about 1.4% of the administered radioactivity was exhaled as $^{14}CO_2$ over 48 hours, and about 15% of the administered radioactivity was excreted in the urine within 48 hours. Following intravenous injection of [1-^{14}C]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO_2 exhaled in 48 hours accounted for about 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al. 2006). Radioactivity in exhaled parent material accounted for about 25, 32, and 71% of the administered dose in rats, and 45, 39, and 48% in mice (Garner et al. 2006). Radioactivity in urine collected for 48 hours accounted for about 17, 19, and 13% of the administered

dose in rats, and 23, 19, and 14% in mice (Garner et al. 2006). Radioactivity in feces accounted for <2% of administered doses, regardless of dose level, in both species (Garner et al. 2006).

Animal studies show that the elimination of 1-bromopropane from the body is rapid and only limited accumulation in the body is expected (Garner and Yu 2014; Garner et al. 2006; Ishidao et al. 2002). Following intravenous injection of [1-^{14}C]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al. 2006). Garner et al. (2006) proposed that radioactivity remaining in the carcass could represent covalently bound residues from reactive metabolites or incorporation of ^{14}C into cellular macromolecules from intermediate metabolic pathways. Following intravenous injection of 5 or 20 mg 1-bromopropane/kg doses into rats, the mean half-times of elimination of 1-bromopropane from the blood were 0.39 and 0.85 hours, respectively (Garner and Yu 2014). In gas uptake studies with male and female rats, calculated half-times of elimination for 1-bromopropane were rapid and increased with increasing air concentrations of 1-bromopropane (Garner and Yu 2014). Terminal elimination half-times were 0.5, 0.6, 1.1, and 2.4 hours for males, and 1.0, 1.0, 2.0, and 6.1 hours for females, exposed to initial air concentrations of 70, 240, 800, and 2,700 ppm, respectively. Pretreatment of female rats with ABT to inhibit CYP metabolism (intraperitoneal injection of 50 mg 1-bromopropane/kg 4 hours prior to gas uptake measurements) or buthionine sulfoxime, an inhibitor of glutathione synthesis (1,000 mg 1-bromopropane/kg/day orally for 3 days before gas uptake), resulted in longer elimination half-times: 9.6 hours with ABT and 4.1 hours with D,L-butionine(S,R)-sulfoximine (BSO), compared with 2.0 hours in untreated females at 800 ppm 1-bromopropane in the gas uptake chamber (Garner and Yu 2014). The results with the inhibitors show that both CYP mediated oxidative metabolism and glutathione conjugation play important roles in the elimination of 1-bromopropane. Levels of 1-bromopropane in blood decreased rapidly to detection limits within 0.7 hours after exposure stopped in Wistar rats exposed to 700 or 1,500 ppm 1-bromopropane 6 hours/day for ≥3 weeks (Ishidao et al. 2002). Clearance of the bromide ion from blood and urine, however, showed slower elimination kinetics: elimination half-times for bromide were 4.7–15.0 days in blood and 5.0–7.5 days in urine (Ishidao et al. 2002).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry

models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

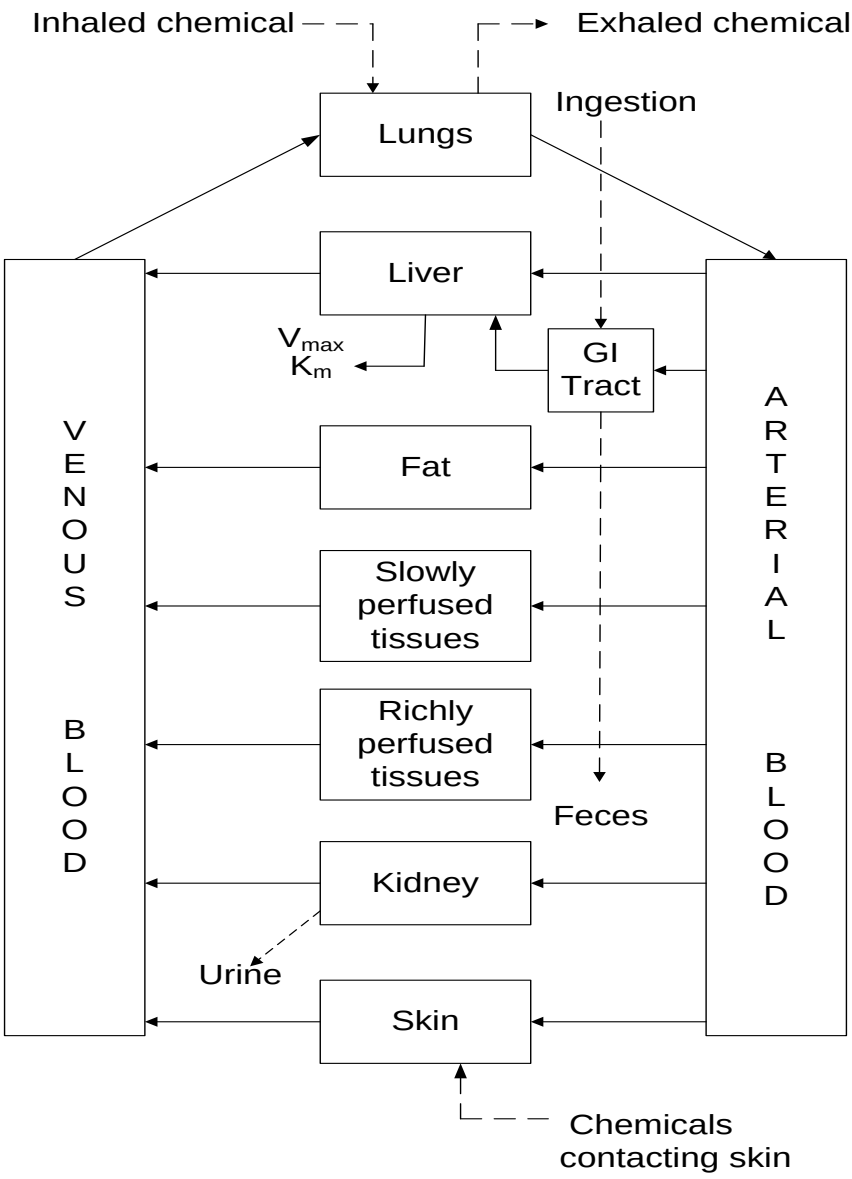
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-6 shows a conceptualized representation of a PBPK model.

If PBPK models for 1-bromopropane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Garner et al. (2015) developed male and female PBPK models for 1-bromopropane in F-344 rats, using data from gas uptake experiments at initial closed chamber concentrations of 70, 240, 800, and 2,700 ppm 1-bromopropane (Garner and Yu 2014). The models consisted of seven compartments: blood, lung, fat, rapidly perfused tissues, slowly perfused tissues, kidneys, and liver. The models assumed flow-limited distribution and metabolism in the liver via two competing initial steps: saturable CYP2E1-mediated oxidation (described by V_{max} and K_m kinetic constants) and GSH conjugation (described by a K_{gst} kinetic constant). Values for blood flow and tissue volume parameters were based on those used by Brown et al. (1997) and tissue partition coefficients were based on those reported by Gargas et al. (1989). Metabolic kinetic constants for the male and female rat models were estimated through optimization procedures involving visual assessment of fits to time-course data for closed chamber concentrations of 1-bromopropane, while holding other model parameters constant. Further validations or calibrations of the rat models were not conducted (e.g., comparing simulated blood concentrations versus observed blood concentration time-course data). Model simulations of blood concentrations indicated rapid attainment of maximal concentration after the start of 8-hour exposure periods, and rapid decline (within 30 minutes) after cessation of exposure. Simulations for a repeated exposure scenario (8 hours/day for 5 days) indicated no accumulative increase in blood concentrations at exposure levels of 20 and 800 ppm 1-bromopropane. A human PBPK model was developed from a general human model for volatile chemicals developed by Anderson et al. (2008) and body weight scaling of the rat metabolic parameters. Simulations with the human model for the repeated exposure scenario at 200 ppm indicated that the blood concentration at the end of the fifth day of exposure was increased by about 25% above the concentration at the end of the first day. Garner et al. (2015) speculated that simulated results showing that humans (but not rats) have accumulative increases in blood concentrations after a 5-day exposure scenario might be due to species differences in fat tissue volume (rat 7% and human 21.4%). Further development of the rat

Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

and the human models are necessary before they can be used to reliably extrapolate doses between rats and humans in the development of MRLs. Garner et al. (2015) noted that further development of the model to include metabolite concentrations in the model would be particularly useful for cross-species dosimetry purposes.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. As discussed in Section 3.1, 1-bromopropane is expected to be well absorbed by the gastrointestinal tract and the respiratory tract, but quantitative data on the extent of absorption are not available. *In vitro* studies with human epidermal explants have determined a dermal permeability coefficient of 0.25 cm/hour in water, dermal fluxes with pure compound and a commercial dry cleaning solvent ranging from 441 to 960 μg cm^{-2} $hour^{-1}$, and a low dermal penetration of about 0.2% under non-occluded conditions (Frasch et al. 2011). Results from gas uptake studies with rats in closed chambers indicated rapid and extensive absorption by the respiratory tract (Garner 2015). Like other volatile, lipophilic, noncharged gases, absorption of 1-bromopropane from the alveoli to the blood is thought to be mediated by passive diffusion (Lehman-McKeeman 2013).

Distribution. As discussed in Section 3.4.2, results from metabolic disposition studies with rats and mice exposed to 1-bromopropane by intravenous injection or inhalation indicate that 1-bromopropane is rapidly and widely distributed by the blood, especially to highly perfused tissues like the brain, followed by a rapid clearance mediated by exhalation of parent material or metabolically produced CO_2 and urinary excretion of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Distribution and accumulation of parent material in blood or fatty tissue is limited with short-term exposure scenarios, but some accumulation with repeated exposures may occur (Garner et al. 2006; 2015; Garner and Yu 2014).

Metabolism. As discussed in Section 3.4.3, and illustrated in Figures 3-3, 3-4, and 3-5, the metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. The balance between oxidative and glutathione-mediated metabolic pathways will determine whether 1-bromopropane is activated to reactive metabolites or degradation products are conjugated and eliminated in the urine (Garner and Yu 2014; Garner et al. 2015; Lee et al. 2010; Liu et al. 2009; Zong et al. 2016). Most urinary and exhaled metabolic products are debrominated leading to elevated levels of bromide ion in blood and

urine (Hanley et al. 2006, 2009, 2010; Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Valentine et al. 2007). Oxidation steps are mediated by CYP2E1 and other, as yet unspecified CYP monooxygenases. Reduced glutathione is the principal conjugating molecule for the parent compound, as well as for proposed oxygenated brominated intermediate metabolites (Garner et al. 2006, 2007; Jones and Walsh 1979). The most recent metabolic disposition studies in rats and mice indicate that oxidation at the 2-C of 1-bromopropane is the principal oxygenation site (Garner et al. 2006, 2007), but oxygenation at the 3-C of 1-bromopropane may be possible based on the identification of urinary metabolites, N-acetyl-S-(2-carboxyethyl) cysteine and N-acetyl-S-(3-hydroxypropyl) cysteine, in an earlier rat study (Jones and Walsh 1979) and in human workers (Cheever et al. 2009; Hanley et al. 2006). Proposed reactive intermediate metabolites include bromoacetone and alpha-bromohydrin (Garner et al. 2006, 2007), glycidol (Ishidao et al. 2002), and propene and 1,2-epoxypropane (Tachizawa et al. 1982).

Excretion. Results from animal studies indicate that 1-bromopropane is rapidly eliminated from the body by exhalation of the parent material and metabolically derived CO_2 and by urinary excretion of bromide ion and carbon-containing metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Forty-eight hours after single intravenous injections of doses of radiolabeled 1-bromopropane to rats and mice, residual radioactivity in the body accounted for <7% of administered doses (Garner et al. 2006). Gas uptake studies indicated that whole-body elimination half-times in rats increased with increasing air concentration, and were 2.4 and 6.2 hours at the highest tested concentration of 2,700 ppm (Garner and Yu 2014). Pretreatment of rats with inhibitors of CYP monoxygenases or glutathione synthesis prolonged whole-body elimination half-times indicating the importance of metabolism to the clearance of 1-bromopropane (Garner and Yu 2014). Elimination half-times for the bromide ion from the blood (~5–15 days) and urine (~5–8 days) were considerably longer than clearance of 1-bromopropane from the blood of rats repeatedly exposed by inhalation to 700 or 15,000 ppm; blood levels of 1-bromopropane were below levels of detection within 0.7 hours of the end of exposure (Ishidao et al. 2002).

3.5.2 Mechanisms of Toxicity

Overview. As summarized in Section 2.2 (Summary of Health Effects) and detailed in Section 3.2.1.4, Neurological Effects, the main target of concern following 1-bromopropane exposure in humans is the nervous system. The mechanisms for neurotoxicity have not been elucidated; however, proposed mechanisms include changes in neurotransmitter systems, electrophysiological alterations, decreased neurogenesis, glial activation, alteration of hippocampal proteins, and oxidative stress. Other potential

targets for 1-bromopropane toxicity include the respiratory, hepatic, renal, reproductive, immune, and hematological systems; however, evidence for these end points is limited. Likewise, mechanistic data for effects outside the nervous system are extremely limited. Available mechanistic data are summarized below.

Mechanisms of Neurotoxicity. Neurotoxic effects observed in humans range from subtle neurological deficits, such as decreased vibration sense and paresthesia, to frank neurotoxic effects, including ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002; Li et al. 2010; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Evidence from animal studies supports that exposure to 1-bromopropane can result in neurotoxicity (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Wang et al. 2002, 2003; Yu et al. 2001; Zhong et al. 2013).

Observed neurological effects may result from alterations in the gabanergic system following exposure to 1-bromopropane. A series of studies reported a decrease in paired pulse inhibition (PPI) of pyramidal cells of CA1 and granule cells of the dentate gyrus (DG) in hippocampal slices harvested from rats exposed to 1-bromopropane at ≥700 ppm intermittently for 4–12 weeks (Fueta et al. 2002, 2004). Granule cells, but not pyramidal cells, also showed decreased PPI at 400 ppm for 8–12 weeks; no effect was observed in either cell type at 200 ppm (Fueta et al. 2007; Ueno et al. 2007). Since no changes were observed in excitatory field potentials, changes in the PPI are likely caused by a reduction of recurrent inhibition (disinhibition) rather than changes in excitatory drives of principal neurons. In support, application of a γ-aminobutyric acid (GABA) receptor agonist (pentobarbital), a selective inhibitor of GABA transporter GAT 1 (Tiagabine), or a NMDA receptor antagonist (DL-2-amino-5-phosphono-pentanoic acid) led to an increase in PPI in the DG, indicating that 1-bromopropane exposure may lead to reduced GABA inhibition of N-methyl-D-aspartate (NMDA) receptors; the disinhibition in the hippocampal CA1 region appeared to have been caused by a different (unknown) mechanism (Fueta et al. 2002, 2004). Ueno et al. (2007) also showed that exposure to 1-bromopropane decreased the expression of the $GABA_A$ receptor β3 and δ subunit mRNA in the hippocampus from rats intermittently exposed to 400 ppm 1-bromopropane for 12 weeks. A significant reduction of mRNA expression of GABAal was also observed in the hippocampus of rats exposed to ≥800 ppm for 4 weeks; in the cortex, mRNA expression was significantly reduced after exposure to 800 ppm but not 1,000 ppm (Mohideen et al. 2009). In another study, a significant reduction in GABA neurotransmitter levels was reported in the hippocampus and cortex of rats intermittently exposed to 1,000 ppm 1-bromopropane for 3 weeks, compared with controls; no changes were observed at ≤200 ppm (Suda et al. 2008).

Other neurotransmitter systems have also been evaluated in rats following inhalation exposure to 1-bromopropane. Changes in levels of neurotransmitters or their metabolites or precursors from the serotonergic (5HT), dopaminergic (DA), noradrenergic (NE), and glutamatergic systems have been reported in various brain regions in rat intermittently exposed to 50–1,000 ppm 1-bromopropane for 3 weeks, compared with controls, when examined 2 and 19 hours after the final exposure (Suda et al. 2008). At 2 hours, significant observations in the 1,000 ppm group included decreased 5-hydroxy-indoleacetic acid (5HIAA; 5HT metabolite) in the striatum, decreased 3,4-dihydroxyphenylacetic acid (DOPAC; DA metabolite) in the hippocampus, and increased glutamine (glutamate precursor) in the hippocampus, midbrain, and cerebellum. 5HIAA was also significantly decreased at 200 ppm; no changes were observed at 2 hours in the 50 ppm group except for a significant decrease in DA in the striatum and in 5HIAA in the frontal cortex. At 19 hours, significant changes included decreased homovanillic acid (HVA; DA metabolite) and HVA/DA ratio in the striatum; decreased 3-methoxy-4-hydroxyphenylglycol (MHPG, NE metabolite), decreased MHPG/NE ratio, and increased 5HT in the occipital cortex; increased 5HIAA in the medulla; and increased glutamine in the frontal cortex, occipital cortex, hippocampus, striatum, midbrain, hypothalamus, and cerebellum. Alterations in the NE, DA, and 5HT neurotransmitter and/or metabolite levels were also reported in rats exposed to ≥200 ppm for 1–4 weeks (Zhang et al. 2013). At 1 week, observed effects included decreased NE and DOPAC/DA ratio in the striatum and a decreased HVA/DA ratio in the prefrontal cortex. At 4 weeks, observed effects included decreased NE and DA and increased HVA, HVA/DA, DOPAC/DA and (DOPAC + HVA)/DA ratio in the hippocampus; decreased NE, 5HIAA, HVA, and HVA/DA in the prefrontal cortex; and decreased NE in the striatum. In another study, several changes in the expression of serotonergic and dopaminergic receptor mRNA were reported in various brain regions of rats intermittently exposed to ≥400 ppm for 4 weeks (Mohideen et al. 2009). Significant changes included decreased 5HTr1a (cortex at 800 and 1,000 ppm, medulla at 400, 800, and 1,000 ppm), decreased 5HTr2a (cortex at 800 ppm, hippocampus at 1,000 ppm), increased 5HTr2c (cortex at 1,000 ppm), increased 5HTr3a (amygdala at 400 and 1,000 ppm), decreased D1R (cerebellum and cortex at 800 ppm), decreased D2R (hippocampus at 400, 800, and 1,000 ppm), and decreased 5HTr3a (pons/medulla at 400, 800, and 1,000 ppm). However, protein levels of D2 and 5HTr2a were not significantly altered in the cortex or hippocampus at up to 1,000 ppm; other receptor protein levels were not measured (Mohideen et al. 2009). Although the above studies show that exposure to 1-bromopropane can affect numerous neurotransmitter systems in various brain areas, these changes have not been associated with specific functional alterations; therefore, the biological significance of the changes is yet unknown.

1-Bromopropane may also cause neurotoxicity by interfering with neurogenesis, as a decrease in the number of BrdU-positive cells in the dentate gyrus of the hippocampus was observed in rats exposed to ≥800 ppm for 4 weeks (Zhang et al. 2013). Observed downregulation of hippocampal brain-derived neurotrophic factor (BDNF) and glucocorticoid receptor (GR) mRNA levels and low hippocampal NE levels may contribute to the reduced neurogenesis. Significant reductions in BDNF mRNA expression have also been observed in the U251 human astrocytoma cell line and mouse primary astrocytes (Yoshida et al. 2009). Yoshida et al. (2009) also show that DNA-binding and specific reporter activity of cAMP response element-binding transcription factor (CREB) and protein kinase A (PKA) activity were reduced in U251 cells, suggesting that BDNF downregulation may result from suppression of PKA activity (and subsequent decreased phosphorylation of CREB). Results of experiments by Huang et al. (2015) showed that exposure of rats to 1-bromopropane induced up- and down-regulation of proteins in the hippocampus involved in response to stimuli, metabolic processes, and apoptosis signaling.

1-Bromopropane has also been shown to cause glial activation (Mohideen et al. 2013; Subramanian et al. 2012), which suggests that neuroinflammation may contribute to observed neurotoxic effects. Immuno-staining showed that exposure to ≥400 ppm 1-bromopropane significantly increased the number of astrocytes in the middle cerebellar peduncle and induced significant elongation of processes in astrocytes in the cerebellum (Mohideen et al. 2013). In another study, cerebellar microglia cells appeared larger and had longer ramified processes in rats exposed to 1,000 ppm 1-bromopropane for 4 weeks, compared with controls; this effect was not observed at 800 ppm (Subramanian et al. 2012). Increased markers of oxidative stress (TBARs), as well as reactive oxygen species and nitric oxide (NO) content, were also observed in the cerebellum of rats exposed to 1,000 ppm, suggesting that oxidative stress may contribute to glial activation (and potential neuroinflammation) associated with 1-bromopropane exposure (Subramanian et al. 2012). Alterations in markers of oxidative stress (total and oxidized glutathione, glutathione reductase, thiol content, malondialdehyde, glutathione peroxidase) have also been reported in the brain and spinal cord of rats exposed to 200–1,000 ppm 1-bromopropane for 1–4 weeks (Guo et al. 2015; Huang et al. 2012; Wang et al. 2002, 2003; Zhong et al. 2013). Guo et al. proposed that 1-bromopropane-induced reduction of a neuroglobin with antioxidant properties might be involved in the neurotoxicity of 1-bromopropane. Additionally, studies in murine macrophages suggest that 1-bromopropane can cause dose-dependent induction of NO and proinflammatory proteins/genes, such as IL-1β, IL-6, TNF-α, COX-2, prostaglandin E_2, through nuclear factor-kappaB (NF-kB) transactivation via the Akt/ERK and p38 MAP kinase pathways (Han et al. 2008, 2012).

Human and animal studies have reported decreased nerve conduction velocities following 1-bromopropane exposure (Ichihara et al. 2000b; Li et al. 2010; Sclar 1999; Yu et al. 2001). Decreased nerve conduction velocity could be due to morphological changes such as swelling of the axons and alteration of the myelin sheath, which have been observed in rats exposed to ≥800 ppm for several weeks (Ichihara et al. 2000b; Wang et al. 2002; Yu et al. 2001). Mohideen et al. (2013) reported adverse effects on myelination in the cerebellum in rats exposed to 1,000 ppm 1-bromopropane for 4 weeks, including decreased levels of myelin basic protein (MBP) and decreased numbers of oligodendrocytes; however, the mechanisms underlying these changes have not been determined.

Protein expression studies have identified multiple systems/pathways in the brain that can be altered following 1-bromopropane exposure; however, strong conclusions regarding mechanisms of neurotoxicity from these studies cannot be made at this point. Decreased CK and isoenzyme (CK-B, CK-M) activity and increased heat-shock protein 27 levels were observed in the brain and/or spinal cord from rats exposed to ≥200 ppm 1-bromopropane for 1 or 12 weeks (Wang et al. 2002, 2003). These studies also indicated that modification of functional proteins containing a sulfhydryl base as a critical site might underlie mechanisms of neurotoxicity because 1-bromopropane exposure decreased levels of sulfhydryl bases of protein and nonprotein fractions in the cerebrum, cerebellum, and brain stem (Wang et al. 2002, 2003). Suda et al. (2008) reported a significant decrease in the level of the free amino acid taurine in several brain regions in rats exposed to ≥50 ppm 1-bromopropane for 3 weeks. Taurine is involved in many functions such as detoxification, cholesterol metabolism, neuromodulation, and transamination. Other amino acids involved in transamination were also altered, including cystathionine, serine, threonine, and β-alanine. In a proteomic analysis of hippocampal tissue obtained from rats intermittently exposed to 0, 400, or 1,000 ppm, 19 proteins were significantly altered after 1 and 4 weeks of exposure and 8 were altered in a dose-dependent fashion (Huang et al. 2011). Identified proteins were categorized into functional classes, including nucleocytoplasmic transport, immunity and defense, energy metabolism, ubiquitination-proteasome pathway, neurotransmitter, and purine metabolism, suggesting that hippocampal damage associated with 1-bromopropane exposure may involve oxidative stress, loss of ATP production, neurotransmitter dysfunction, and inhibition of the ubiquitination-proteasome system. Due to evidence of oxidative stress, another study by the same group of investigators specifically looked for proteins with increased carbonyl modification using the same protocol (Huang et al. 2012). Ten proteins with increased carbonyl modification were identified, including proteins involved in glycolysis, ATP production, tyrosine catabolism, GTP binding, guanine degradation, and neuronal metabolism of dopamine.

As summarized above, 1-bromopropane can induce neurological alterations by acting at multiple levels in the nervous system. The identity of the neurotoxic moiety(s), however, remains unknown.

Mechanisms of Hepatotoxicity. Hepatic effects have been observed in animal studies following inhalation exposure to 1-bromopropane, including histopathological changes (liver congestion, hemorrhage, cellular swelling, vacuolization of hepatocyte and/or degeneration) and increased liver weight (Albemarle Corporation 1997; Kim et al. 1999; Lee et al. 2007; Liu et al. 2010; NTP 2011; Yamada et al. 2003; Zong et al. 2016). Following exposure to ≥100 ppm for 28 days, *Nrf2*-null mice (lacking nuclear factor erythroid 2-related factor 2) showed significantly larger areas of hepatic necrosis relative to wild-type mice at the same exposure level (Liu et al. 2010). Since Nrf2 is a transcription factor that upregulates a battery of cytoprotective genes in response to oxidative stress and/or chemical exposure, these findings suggest that oxidative stress may play a role in hepatotoxic effects of 1-bromopropane. In wild-type mice, 1-bromopropane exposure at 300 ppm increased the mRNA levels of several cytoprotective genes regulated by Nrf2, including heme oxygenase-1 (HO-1), glutamate-cysteine ligase modifier subunit (GcLM), glutamate-cysteine synthetase (GcLc), glutathione reductase, and NAD(P)H:quinone oxidoreductase 1 (NQO1); these genes were not upregulated in *Nrf2*-null mice. Additionally, *Nrf2*-null mice have constitutively low mRNA expression levels of antioxidant enzymes and high malondialdehyde levels (Lui et al. 2010). Khan and O'Brien (1991) also suggested that oxidative stress plays a role in hepatotoxic effects of 1-bromopropane, reporting time-dependent glutathione depletion in isolated rat hepatocytes exposed to 100 µM 1-bromopropane. The role of oxidative stress in 1-bromopropane-induced liver toxicity is also suggested by the results of a study in three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) (Liu et al. 2009). Intermittent exposure of the mice induced concentration-related increases in hepatocellular degeneration and liver necrosis; the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to hepatic damage (Liu et al. 2009).

Mechanisms of Testicular Toxicity. Testicular effects have been observed in animal studies following inhalation or oral exposure to 1-bromopropane, including alterations in sperm parameters and degeneration of spermatocytes (Banu et al. 2007; Ichihara et al. 2000a; Liu et al. 2009; NTP 2011; Yu et al. 2008). While oral exposure to 400 ppm 1-bromopropane caused failure of spermiation in male Wistar rats, exposure to 1,000 ppm caused spermatogenic cell depletion (Banu et al. 2007), suggesting that different mechanisms operate depending on the exposure levels. Similarly, decreased epididymal sperm count was observed in rats injected with intraperitoneal doses of 1,000 mg 1-bromopropane/kg/day for

14 days (Xin et al. 2010). This finding was accompanied by a significant increase in the number of TUNEL-positive cells, indicating that increased apoptosis may be a mechanism of testicular toxicity. However, the apoptotic pathway is unclear because 1-bromopropane did not lead to significant changes in the expression of apoptosis-related genes and proteins (caspase-3, p53, Bax, Bcl-2, Fas, FasL). As with hepatotoxicity (see above), sperm toxicity appears to be, at least in part, caused by oxidative stress, based on findings of Garner et al. (2007) and Liu et al. (2009). The former showed that 1-bromopropane reduced sperm motility in CYP2E1-null mice to a much lesser extent than in wild type mice. Liu et al. (2009) exposed three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) and reported that the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to 1-bromoprapane-induced alterations in sperm parameters.

Mechanisms of Respiratory Toxicity. Limited human data from case reports suggest that exposure to 1-bromopropane can cause respiratory tract irritation at concentrations >100 ppm (Ichihara et al. 2002; Raymond and Ford 2007), and lesions of both the upper and lower respiratory tracts have been observed in rats and mice exposed to 1-bromopropane for intermediate and chronic durations (Morgan et al. 2011; NTP 2011). While studies specifically evaluating mechanisms of toxicity in the respiratory system have not been identified, Morgan et al. (2011) suggested that these lesions likely reflect the local irritant activity of 1-bromopropane, consistent with observations of other inhaled hydrocarbons.

Mechanisms of Carcinogenicity. 1-Bromopropane is a multisite carcinogen in rats and mice (Morgan et al. 2011; NTP 2011, 2013). While mechanisms of carcinogenicity for 1-bromopropane are unknown, Morgan et al. (2011) suggested possible mechanisms may include formation of reactive metabolites that can alkylate proteins or nucleic acids and/or oxidative stress due to glutathione depletion. *In vitro* incubation of 1-bromopropane with calf thymus DNA resulted in the formation of a N^7-guanine adduct (Thapa et al. 2016). Available data are insufficient to determine if 1-bromopropane can act by a genotoxic mode-of-action; see Section 3.3, Genotoxicity, for more details.

3.5.3 Animal-to-Human Extrapolations

Studies in rodents have shown species, strain, and sex differences in sensitivity to some 1-bromopropane-induced effects that are related to differences in the metabolic disposition of the chemical (Garner and Yu 2014; Garner et al. 2007; Liu et al. 2009). Differences in some toxicities of 1-bromopropane, such as hepatotoxicity and sperm toxicity, between rats and mice and between mice strains are related to

differences in oxidative capacity, specifically CYP2E1 protein levels, and differences in glutathione levels and GST activity in the liver. How the activities of the oxidative and conjugation pathways in humans compare to those in rats and mice in disposing of 1-bromopropane has not been determined. Therefore, the rodent model that is most appropriate to assess potential liver and sperm toxicity of 1-bromopropane in humans is unknown.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Limited human data do not suggest that 1-bromopropane is an endocrine disruptor. In the study of workers exposed to 1-bromopropane conducted by Li et al. (2010) discussed in Section 3.2.1, Inhalation Exposure, a significant trend for increased serum TSH was reported in females. Regression analyses that included exposure level and duration showed significant trends for increased serum TSH and FSH in female workers. However, neither serum estradiol in females nor serum testosterone levels in males were significantly associated with exposure to 1-bromopropane. A critical review of this study noted that because several of the measures in females experience temporal fluctuations related to the menstrual cycle, lack of appropriate control for these variables could have led to misleading results (Smith et al. 2011). Raymond and Ford (2007) reported that a 41-year-old woman who experienced adverse neurological effects after 2 weeks of working with a glue formulation containing 1-bromopropane had normal thyroid function tests results; the tests were performed about 2 months after she became ill. No further relevant information is available for humans.

In general, acute-, intermediate-, and chronic-duration inhalation studies in animals did not report significant gross or microscopic alterations in endocrine glands with the exception of moderate to marked necrosis of the adrenal cortex of female mice exposed intermittently to 500 ppm 1-bromopropane for 14 weeks (NTP 2011); the NOAEL was 250 ppm.

Two intermediate-duration studies evaluated reproductive hormones in animals exposed to 1-bromopropane. Plasma testosterone levels were significantly decreased by 36% in male Wistar rats exposed to 800 ppm 1-bromopropane for 12 weeks (Ichihara et al. 2000a). No significant changes were observed in testosterone levels at ≤400 ppm or in plasma LH or FSH at concentrations up to 800 ppm 1-bromopropane (Ichihara et al. 2000a). No changes were observed in serum LH or FSH in female Wistar rats following intermittent exposure at concentrations up to 800 ppm 1-bromopropane for 12 weeks (Yamada et al. 2003).

No *in vitro* studies were located regarding endocrine disruption of 1-bromopropane.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect

effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult.

Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information was located regarding health effects in children following exposure to 1-bromopropane. Since exposure to 1-bromopropane occurs mainly in occupational settings, children are not expected to experience exposures to 1-bromopropane.

No studies were located that exposed animals of different ages to 1-bromopropane to determine whether age might be a factor in the toxicity of 1-bromopropane. Therefore, it is not known whether younger animals are more susceptible to 1-bromopropane than older animals. However, because the nervous system is the main target for 1-bromopropane toxicity in humans and animals, it seems reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals, if such an exposure were to occur.

1-Bromopropane was a developmental toxicant in rats. Studies of rats exposed to ≥400 ppm 1-bromopropane during gestation and lactation reported decreased survival of offspring during lactation (Furuhashi et al. 2006). A cross-foster experiment actually showed that gestation and lactation exposure had comparable effects on survival rate of the neonates, but lactation exposure played a greater role on growth of the offspring. Additional experiments showed that mated F1 offspring from the lactation-only exposure group produced a significantly greater number of dead F2 offspring, compared with controls. However, no exposure-related effects were observed in the F2 litter for gestational exposure only. This suggested that lactation exposure played a greater role in growth and sexual maturation of the offspring. 1-Bromopropane has not shown teratogenicity in studies in animals (BSOC 2001a, 2001b).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids

(e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1-bromopropane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1-bromopropane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1-Bromopropane

Proposed biomarkers of exposure to 1-bromopropane include urinary levels of N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys), bromide, and 1-bromopropane itself. Field studies indicated that urinary levels of N-acetyl-S-(n-propyl)-L-cysteine and bromide were significantly correlated with time-weighted-average breathing zone air concentrations of 1-bromopropane in several groups of workers (Hanley et al. 2006, 2009, 2010). Use of N-acetyl-S-(n-propyl)-L-cysteine is expected to be more specific to 1-bromopropane than bromide due to the presence of the bromide ion in foods. Mathias et al. (2012) also reported a significant increase in urinary N-acetyl-S-(n-propyl)-L-cysteine and bromide ion levels in workers exposed to 1-bromopropane in a foam cushion manufacturing plant, compared with controls. The suitability of urinary levels of the metabolites 3-bromopropionic acid, N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine was also investigated by Mathias et al. (2012). There was no significant difference between urinary 3-bromopropionic acid levels between exposed and control workers, indicating that it is a poor biomarker. The analysis of the mercapturic acid metabolites N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine was discontinued due to low levels of

detection in urine samples (Mathias et al. 2012). In another study of workers involved in 1-bromopropane manufacturing, urinary 1-bromopropane concentrations were significantly correlated with TWA concentrations of 1-bromopropane in workplace air (Ichihara et al. 2004a). Valentine et al. (2007) studied blood and urine samples from workers and ambient air samples in a Chinese 1-bromopropane production plant in order to support the potential of urinary AcPrCys and globin S-propylcysteine (PrCys) adducts as biomarkers of exposure in humans. It was found that there was a significant increase in globulin PrCys adducts in exposed workers (1.52 pmol/mg globin) compared with that of control factory workers (0.11 pmol/mg globin). Also, an increase in urinary AcPrCys levels was directly related to an increase in ambient air exposure levels, which ranged from 0 to 170.54 ppm. In a study of Japanese workers exposed to 1-bromopropane in cleaning and painting workshops, urinary 1-bromopropane at the end of an 8-hour shift correlated closely with the exposure concentration (geometric mean 1.4 ppm) (Kawai et al. 2001). The investigators noted that an exposure concentration of 2 ppm could be readily biomonitored. Urinary bromide also correlated with 1-bromopropane in air, but the correlation was not as good as with urinary 1-bromopropane.

The distribution of the proposed biomarker N-acetyl-S-(n-propyl)-L-cysteine was evaluated in the general population in the National Health and Nutrition Examination Survey (NHANES) 2011–2012 (Jain 2015a). The study examined the distribution of urinary metabolites of volatile compounds by age, gender, race/ethnicity, and smoking status among 2,328 NHANES participants ≥20 years of age. Adjusted urinary geometric means of N-acetyl-S-(n-propyl)-L-cysteine were the same in males and females (5.3 ng/mL). Nonsmokers did not have statistically significantly different urinary levels of N-acetyl-S-(n-propyl)-L-cysteine than smokers. Non-Hispanic white subjects (3.9 ng/mL) had significantly lower levels of N-acetyl-S-(n-propyl)-L-cysteine than non-Hispanic black subjects (4.1 ng/mL) and non-Hispanic Asians (7.7 ng/mL). Non-Hispanic black subjects (4.1 ng/mL) had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than Hispanics (6.2 ng/mL) and non-Hispanic Asians (7.7 ng/mL). Evaluation of 417 children, 6–11 years of age, also participants in NHANES 2011–2012 showed no significant differences between genders (2.6 ng/mL in males and 3.3 ng/mL in females) (Jain 2015b). Non-Hispanic Asian children had the highest urinary levels of N-acetyl-S-(n-propyl)-L-cysteine (5.0 ng/mL) followed by non-Hispanic black children (3.4 ng/mL), non-Hispanic white children (2.4 ng/mL), and Hispanic children (2.1 ng/mL). Children had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than nonsmoking adults (3.4 versus 5.7 ng/mL).

Values similar to those reported by Jain (2015a, 2015b) were reported in pregnant women participants in the National Children's Vanguard Study (Boyle et al. 2016). The study included 488 women enrolled

from 2009 to 2010 from seven locations in the United States. N-Acetyl-S-(n-propyl)-L-cysteine was detected in urinary samples collected during the third trimester of pregnancy with a frequency of 99%; the median was 2.61 ng/mL and the 75th percentile value was 9.44 ng/mL.

The ubiquitous nature of N-acetyl-S-(n-propyl)-L-cysteine in the urine of the general population suggests that it may not be a specific biomarker for 1-bromopropane, as exposure to 1-bromopropane is expected to be primarily occupational with limited exposure in the general population (NTP 2011, 2016); see Section 6.5 for more details. It is unknown if other chemicals and/or endogenous metabolism contributed to the observed urinary levels of N-acetyl-S-(n-propyl)-L-cysteine in the studies by Jain (2015a) and Boyle et al. (2016). However, occupational studies indicate that N-acetyl-S-(n-propyl)-L-cysteine is likely to be the most predictive biomarker of exposure available at this time (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012; Valentine et al. 2007).

3.8.2 Biomarkers Used to Characterize Effects Caused by 1-Bromopropane

There are no specific biomarkers to characterize effects caused by 1-bromopropane in humans. As summarized in Section 3.2.1, Inhalation Exposure, the main target of 1-bromopropane toxicity in humans is the nervous system, as demonstrated in several cases of occupational exposure to 1-bromopropane. Symptoms commonly reported include, but are not limited to, headache, dizziness, numbness, pain, paresthesias and weakness of the lower extremities, and difficulty walking/poor balance (Majersik et al. 2007). Signs reported include spasticity and weakness of the lower extremities, difficulty with tandem gait, lower extremity hyperreflexia, decreased lower extremity sensation to vibration, proprioception, temperature, and light touch. Sclar (1999) noted that results from nerve conduction velocity studies were consistent with primary, symmetric demyelinating polyneuropathy. Symptoms suggesting involvement of mainly the central nervous system include anxiety, irritation, forgetfulness, difficulty in concentrating, and listlessness (Ichihara et al. 2002). Many of these signs and symptoms can occur in subjects overexposed to solvents in general, not even structurally-related to 1-bromopropane.

3.9 INTERACTIONS WITH OTHER CHEMICALS

The only information regarding interaction of 1-bromopropane with other chemicals is that pretreatment of rats with 1-aminobenzotriazole (an inhibitor of a number of CYP enzymes) before administration of single intravenous doses of ~20 mg/kg ^{14}C-1-bromopropane or inhalation exposure to 800 ppm ^{13}C-1-bromopropane for 6 hours caused decreased exhalation of radioactivity as CO_2 and decreased formation of oxidative urinary metabolites (Garner et al. 2006). In general, chemicals that interfere with

CYP enzymes or glutathione are likely to affect the metabolism of 1-bromopropane and increase or decrease toxicity.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1-bromopropane than will most persons exposed to the same level of 1-bromopropane in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1-bromopropane, or compromised function of organs affected by 1-bromopropane. Populations who are at greater risk due to their unusually high exposure to 1-bromopropane are discussed in Section 6.7, Populations with Potentially High Exposures.

No information was located in the available literature regarding human populations that may be unusually susceptible to toxic effects from 1-bromopropane. As discussed in Section 3.7 (Children's Susceptibility), children are not expected to experience exposures to 1-bromopropane since exposure occurs mainly in occupational settings.

Genetic differences in the ability to metabolize 1-bromopropane may confer differential susceptibility to toxic effects of 1-bromopropane. Following intermittent exposure to 50–250 ppm 1-bromopropane for 4 weeks, three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) showed dose-related increases in hepatocellular degeneration and liver necrosis; however, the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to hepatic damage (Liu et al. 2009). Mice are considerably more susceptible to 1-bromopropane-induced hepatotoxicity and spermatoxicity than rats (Liu et al. 2009, 2010; NTP 2011). The greater susceptibility of mice is likely due to higher CYP2E1-catalyzed production of cytotoxic metabolites. Lower reduced GSH levels in mice may also play a role in increased sensitivity to cellular injury.

Studies that evaluated more than one rat strain have not been identified; however, available single-strain studies suggest that Sprague-Dawley rats are less susceptible to neurotoxic effects of inhaled 1-bromopropane, compared with Wistar and F-344 rats (Albemarle Corporation 1997; Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Sohn et al. 2002; Yu et al. 2001). The mechanism(s) underlying the apparent strain differences are unknown.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1-bromopropane. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1-bromopropane. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to 1-bromopropane can be consulted for medical advice. No texts were located that provide specific information about treatment following exposure to 1-bromopropane; however, the following texts provide information about treatment following exposures to halogenated aliphatic hydrocarbons (or hydrocarbons in general):

Currance PL, Clements B, Bronstein, AC. 2007. Halogenated aliphatic hydrocarbons and related compounds. In: Currance PL, Clements B, Bronstein, AC, eds. Emergency care for hazardous materials exposure. 3rd edition. St. Louis, MO: Mosby, Inc., 216-223.

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Lewin NA, Goldfrank LR, et al., eds. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill Education, 1334-1345.

Thompson TM. 2014. Chapter 126: Hydrocarbons. In: Schafermeyer R, Tenenbein M, Macias CG, eds. Strange and Schafermeyer's pediatric emergency medicine. New York, NY: McGraw-Hill.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.11.1 Reducing Peak Absorption Following Exposure

1-Bromopropane is expected to be absorbed by the skin, gastrointestinal tract, and respiratory tract, but quantitative data on the extent of absorption are not available (Frasch et al. 2011; Garner et al. 2006; Hanley et al. 2006, 2009, 2010; Jones and Walsh 1979; Valentine et al. 2007). There are no known methods for reducing peak absorption following inhalation exposure. In cases of ingestion, the use of Activated charcoal has limited ability to reduce gastrointestinal absorption of hydrocarbons in general (Gummin 2015; Thompson 2014). Because it may also distend the stomach and predispose patients to vomiting and aspiration, the use of activated charcoal may be justified only in patients with mixed overdoses (Gummin 2015). Rapid rinsing of the skin with water or washing with soap and water will reduce the opportunity for dermal absorption. If the eyes are affected, proper rinsing procedures should be followed (Currance et al. 2007; HSBD 2013).

3.11.2 Reducing Body Burden

Results from animal studies indicate that 1-bromopropane is rapidly eliminated from the body by exhalation of the parent material and metabolically derived CO_2 and by urinary excretion of bromide ion and carbon-containing metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Following inhalation exposure, oxygen therapy and positive-pressure ventilation may be useful following inhalation exposure to 1-bromopropane to promote the loss of unmetabolized 1-bromopropane from the lungs (Currance et al. 2007; HSBD 2013). There are no known methods for reducing body burdens following oral or dermal exposure.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Since the mechanism(s) of toxicity for 1-bromopropane in humans is/are not yet elucidated, there are no known methods for interfering with the mechanism of action.

However, there is evidence that CYP2E1-catalyzed oxidation contributes to 1-bromopropane-induced spermatoxicity and hepatotoxicity in mice (Garner et al. 2006, 2007; Liu et al. 2009; Zong et al. 2016). The putative cytotoxic oxidative metabolites have not been identified, but CYP2E1 inhibition should be protective. An alternative therapeutic approach would be to administer antioxidants to inhibit lipoperoxidation. N-Acetylcysteine or another agent that will significantly enhance levels of reduced glutathione may also be beneficial. Whether these treatments would be beneficial in humans exposed to 1-bromopropane is unknown.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1-bromopropane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of 1-bromopropane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

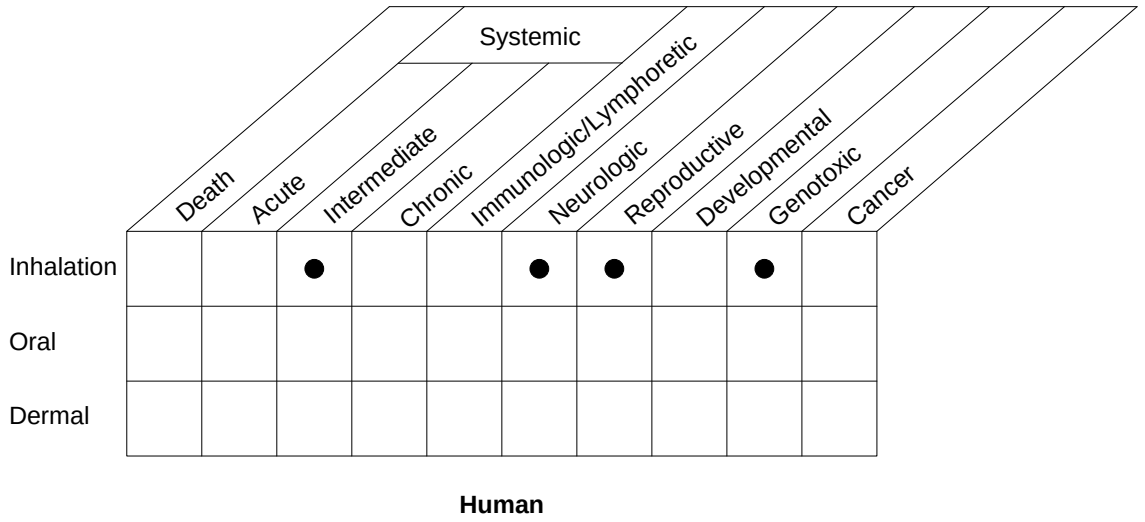
reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of 1-Bromopropane

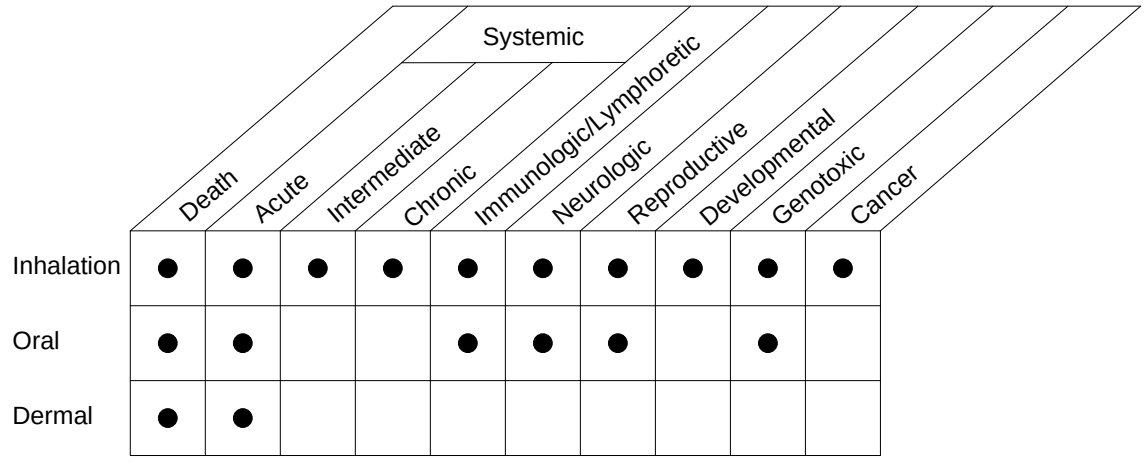
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1-bromopropane are summarized in Figure 3-7. The purpose of this figure is to illustrate the existing information concerning the health effects of 1-bromopropane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 3-7, there is a limited amount of data on the health effects of 1-bromopropane in humans following inhalation exposures. There are no oral or dermal data available for humans; however, these are not primary routes by which humans are exposed to 1-bromopropane. It should be noted that while exposure to 1-bromopropane occurred primarily via the inhalation route in the available human studies, dermal exposure may have also occurred. In most cases, it was not known whether or not the workers were using protective clothing and/or respirators, so the specific contribution of each route of exposure is not possible to determine. Figure 3-7 also shows that information on health effects of 1-bromopropane in animals is available for all effect categories, but is mainly limited to inhalation exposure studies in animals.

Figure 3-7. Existing Information on Health Effects of 1-Bromopropane



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The only acute-duration inhalation studies in humans were a few case studies reporting subjective symptoms in workers within 2 weeks of 1-bromopropane introduction into the workplace. Adverse effects included respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). Acute animal inhalation studies are limited to two single-exposure studies evaluating lethality (Elf AtoChem S.A. 1997; Kim et al. 1999) and one evaluating sperm motility (Garner et al. 2007), a 1-week study evaluating neurogenesis and endocrine end points (Zhang et al. 2013), and a 1-week study evaluating morphological and biochemical changes in the brain (Wang et al. 2002); all of these studies were conducted in rats.

The lowest LOAEL identified in these studies may have been lower than 800 ppm because in the Garner et al. (2007) study, sperm motility was significantly decreased in mice following a single 6-hour exposure to an initial concentration of 800 ppm 1-bromopropane, which decreased steadily during the exposure period. Wang et al. (2002) reported for morphological changes in the medulla oblongata and posterior tibial nerve in rats exposed to 800 ppm 1-bromopropane, but not ≤400 ppm, for 1 week (Wang et al. 2002). However, it should be noted that only 1 rat/group was assessed for morphological alterations. Wang et al. (2002) also reported several biochemical changes in the central nervous system following exposure to 1-bromopropane at ≥200 ppm. The adversity of these changes is unclear because there were no clear associations between biochemical and morphological changes. Other reported neurological effects included decreased activity and ataxia after single exposures to ≥1,800 ppm, but not 300 ppm (Kim et al. 1999). No exposure-related changes in hippocampal neurogenesis, adrenal weight, or plasma corticosterone levels were reported in male rats intermittently exposed to 1,000 ppm 1-bromopropane for 1 week (Zhang et al. 2013). A study that reported decreased grip strength in male rats exposed for 8 hours/day to 1,000 ppm 1-bromopropane for 14 days was used to derive an acute-duration inhalation MRL for 1-bromopropane (Honma et al. 2003). Yet, the acute database would benefit from studies examining a comprehensive set of neurotoxicological end points as well as developmental studies to adequately characterize the most sensitive adverse effects following acute exposure. Additionally, a morphological study with larger animal groups and/or a comprehensive neurological battery in animals would be useful.

Acute oral studies are limited to a single-dose lethality study in rats (Elf Atochem S.A. 1993), a single-exposure study evaluating hepatotoxicity and immunotoxicity in mice (Lee et al. 2007), a 10-day study

evaluating male reproductive end points in rats (Yu et al. 2008), and two 12-day studies evaluating neurobehavioral end points (learning and memory) in rats (Guo et al. 2015; Zhong et al. 2013). The lowest LOAELs identified in these studies were 200 mg 1-bromopropane/kg/day for impaired spatial learning and memory during the Morris water maze test in rats (Guo et al. 2015; Zhong et al. 2013) and 200 mg/kg/day for reduced antibody responses to the T-dependent SRBC antigen (Lee et al. 2007). A NOAEL of 100 mg 1-bromopropane/kg/day was identified in the Guo et al. (2015) study. Other effects reported at higher doses in other studies include congestion, hemorrhage, cellular swelling, and vacuolization of hepatocytes in mouse liver at ≥500 mg 1-bromopropane/kg/day, but not 200 mg 1-bromopropane/kg/day (Lee et al. 2007); degeneration of spermatocytes in mouse testes at 600 mg 1-bromopropane/kg/day (only dose tested) (Yu et al. 2008); and a 13% decrease in body weight at 800 mg 1-bromopropane/kg/day, but not ≤400 mg 1-bromopropane/kg/day (Zhong et al. 2013). While the acute oral database is limited, observed neurological effects are consistent with neurological effects observed in the more comprehensive inhalation database. Therefore, the LOAEL of 200 mg 1-bromopropane/kg/day for impaired spatial learning and memory was selected as the basis for the acute-duration oral MRL (Zhong et al. 2013); the results of Guo et al. (2015) support the oral MRL. Additional studies examining a comprehensive set of systemic and neurological end points, as well as developmental studies, would be useful to reduce uncertainty in the identification of the most sensitive outcome following acute oral exposure.

The available data for dermal exposure are limited to a single dermal study that reported a lack of cutaneous effects and lethality at 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1995); however, this is not a primary route by which humans are exposed to 1-bromopropane.

Intermediate-Duration Exposure. The only intermediate-duration inhalation studies in humans are case studies, most of them reporting neurological signs and symptoms in workers following exposure to >100 ppm 1-bromopropane for a few weeks or months, including marked ataxia, impaired balance and coordination, sensory deficits, inability to walk, and damage to peripheral nerves (Ichihara et al. 2002; Majersick et al. 2007; MMWR 2008; Raymond and Ford 2007; Sclar 1999). Several intermediate-duration inhalation studies in animals are available. Similar to the human case studies, animal studies reported neurological effects following intermediate-duration inhalation exposure at concentrations ranging from 50 to 1,500 ppm (Banu et al. 2007; Fueta et al. 2002, 2004, 2007; Honma et al. 2003; Ichihara et al. 2000b; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2003; Yu et al. 1998, 2001; Zhang et al. 2013); all these studies were conducted in rats. Other effects observed at similar exposure levels include altered sperm parameters and liver effects at ≥50 ppm in rats

and mice (Kim et al. 1999; Liu et al. 2009). The study by Honma et al. (2003) identified a NOAEL and LOAEL of 10 ppm and 50 ppm, respectively, for neurological effects in rats and was used to derive an intermediate-duration inhalation MRL for 1-bromopropane.

No intermediate-duration oral or dermal studies were located for 1-bromopropane; however, these are not primary routes by which humans are exposed to 1-bromopropane.

Chronic-Duration Exposure and Cancer. An epidemiological study of 1-bromopropane production workers from three plants in China reported neurological effects in females exposed to median 1-bromopropane concentrations ≥1.28 ppm for ~40 months, including decreased vibration sense, electrophysiological changes, and impaired visual perception and memory (Li et al. 2010). Limitations of the study acknowledged by the investigators include: (1) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (2) clinical assessment of vibration threshold using a tuning fork is inherently inaccurate due to examiner bias and subject characteristics (age, weight, height); and (3) uncertainty in the assessment of cumulative exposure (1–3-day measurements, presumed to be the same level for entire duration of employment). Criticisms from others (Smith et al. 2011) include lack of monitoring data for the controls and possible underestimation of exposure since masks were not used. However, findings from this study were determined to be adequate as the basis for a chronic inhalation MRL, although confidence in this MRL is low due to the acknowledged limitations. Further discussion regarding the rationale for selecting the human study to derive the chronic inhalation MRL of 0.02 ppm, as well as data from a supporting animal study that yielded a virtually identical MRL of 0.03 ppm, can be found in Appendix A. Additional epidemiological studies of neurological end points in workers with better study designs (preferably prospective, longitudinal studies), longer durations of employment, more diligent measurement and reporting of exposure levels, and standardized measurement methods (particularly a quantitative measure of vibration sense) would be useful to better characterize the neurotoxicity of 1-bromopropane and increase the confidence in the MRL.

A limited number of studies have assessed carcinogenic effects of 1-bromopropane in rodents. In rats exposed by inhalation to 1-bromopropane for 2 years, significantly increased incidences of tumors were found in multiple sites: large intestine adenomas in females and skin keratoacanthoma, basal cell adenoma or squamous cell carcinoma, malignant mesothelioma, and pancreatic islet adenoma in males (Morgan et al. 2011; NTP 2011). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females (Morgan et al. 2011; NTP

2011). No studies have evaluated cancer mortality or morbidity in groups of 1-bromopropane-exposed humans. The chronic or carcinogenic effects of 1-bromopropane have not been investigated in humans or animals following oral or dermal exposures; however, these are not considered major routes of 1-bromopropane exposure. Studies of cancer mortality or morbidity in cohorts of 1-bromopropane-exposed workers and mechanistic studies of interspecies differences in 1-bromopropane carcinogenicity may help to better determine the potential carcinogenicity of 1-bromopropane in humans.

Genotoxicity. Available studies do not clearly identify 1-bromopropane as a genotoxic agent, and only a limited number of end points have been evaluated. The only study located regarding genotoxic effects in humans exposed to 1-bromopropane reported a weak association between 1-bromopropane exposure and DNA damage in peripheral lymphocytes (Toraason et al. 2006). *In vivo* animal studies did not show micronuclei induction or dominant lethality (Chung et al. 2006; NTP 2011; Saito-Zuzuki et al. 1982; Yu et al. 2008). *In vitro* studies have reported mixed findings for reverse mutation and DNA damage (Barber et al. 1980, 1981; Hasspieler et al. 2006; NTP 2011; Torasson et al. 2006). Additional studies for various genotoxic end points, including clastogenicity, could be useful to determine the genotoxicity of 1-bromopropane. Due to the volatility of 1-bromopropane, *in vitro* studies utilizing closed test systems would be preferential.

Reproductive Toxicity. Limited information regarding reproductive effects of 1-bromopropane in humans is available from two NIOSH Health Hazard Evaluation reports and two preliminary health surveys in workers exposed to 1-bromopropane (Ichihara et al. 2004a, 2004b; NIOSH 2002, 2003a). In these studies, no self-reported effects on fertility or menstrual cycles were observed in 1-bromopropane exposed workers and there was no evidence of exposure-related changes in sperm count, motility, or morphology in a limited number of individuals (three exposed males, nine unexposed males). However, several studies in rats and mice suggest that repeated inhalation exposure to 1-bromopropane may adversely affect both the male (sperm effects, decreased testosterone) and female reproductive systems (altered estrous cycles) at concentrations as low as 50 and 250 ppm, respectively (Banu et al. 2007; Ichihara et al. 2000a; Liu et al. 2009; NTP 2011; Yamada et al. 2003). Results from a comprehensive 2-generation study in rats showed that exposure of males and females to 750 ppm 1-bromopropane for at least 70 days before mating resulted in complete infertility and exposure to 500 ppm reduced fertility by 48% (BSOC 2001a). Exposure to lower concentrations (250 ppm) reduced prostate weight in F0 males and increased estrous cycle length in F1 females. Alterations in sperm parameters were reported in rats at ≥500 ppm and in mice at ≥250 ppm in the 14-week NTP (2011) study. Because Liu et al. (2009) reported significant sperm alterations in three strains of mice exposed to 50 ppm 1-bromopropane for 4 weeks,

studies trying to replicate the findings of Liu et al. (2009) may be warranted. In addition, measurements of hepatic levels of CYP2E1 and GST activities in the B6C3F1 strain of mice used in the NTP (2011) study would be useful to possibly explain the significantly lower sensitivity of that strain for sperm effects compared to the mice strains studied by Liu et al. (2009). Epidemiology studies with fewer limitations (greater number of subjects, longer exposure durations, and better control for confounding factors) would help characterize the reproductive toxicity of 1-bromopropane in humans. Additional studies in animals do not seem necessary at this time.

Developmental Toxicity. No studies were located for developmental effects in humans after exposure to 1-bromopropane, and available studies in animals are inadequate to determine if developmental toxicity is a concern following 1-bromopropane exposure in humans. Two studies in rats showed that maternal exposure to 1-bromopropane during gestation can induce reductions in fetal or neonate body weight (BSOC 2001b; Fueta et al. 2015). Data from a 2-generation reproductive study in rats showed that exposure to 500 ppm 1-bromopropane can affect growth in rat pups (Albemarle Corporation 2002). An additional study in rats showed that perinatal exposure to 800 ppm can drastically reduce viability during the first weeks of life (Furuhashi et al. 2006). No teratogenic effects were reported in developmental studies. Based on the fact that 1-bromopropane did not have significant effects on endocrine organs in animals, and the chemical structure of 1-bromopropane, it seems unlikely that 1-bromopropane could affect development by disrupting endocrine processes. Therefore, studies focused on this issue do not seem warranted at this time.

Immunotoxicity. No studies were located that evaluated immunological effects in humans after inhalation exposure to 1-bromopropane, and available studies in animals are insufficient to assess the immunotoxic potential of 1-bromopropane exposure in humans. In animals exposed to 1-bromopropane via inhalation for 4–10 weeks, suppression of the IgM plaque forming response to immunization with SRBCs was observed in splenocytes harvested from female rats and mice exposed to 1,000 and ≥125 ppm, respectively (Anderson et al. 2010). Other exposure-related changes observed included reduced spleen weight and cellularity and significant changes in spleen cell subpopulations. Immune responses to SRBC and ConA were also reduced in mice dosed once by gavage with ≥200 mg 1-bromopropane/kg (Lee et al. 2007). No other animal studies examining immune function were located. Epidemiology studies evaluating immune end points and immunotoxicity batteries in animals would be useful to better characterize the immunotoxicity of 1-bromopropane.

Neurotoxicity. The main target of concern following 1-bromopropane exposure in humans is the nervous system because the available data clearly indicate that the nervous system is a target for 1-bromopropane toxicity in humans and animals. Observed effects in humans range from subtle neurological deficits at exposure levels as low as 1.28 ppm 1-bromopropane, such as decreased vibration sense and paresthesia, to frank neurotoxic effects at exposures to concentrations ≥100 ppm, including ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002, 2004b; Li et al. 2010; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015). Evidence from animal studies supports the 1-bromopropane neurotoxicity findings in humans. Observed effects in acute and intermediate-duration inhalation studies in rats showed that concentrations as low as 50 ppm can induce changes in neurobehavior, muscle strength, electrophysiology, and morphology and biochemistry of neural tissues (Banu et al. 2007; Fueta et al. 2002; Guo et al. 2015; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 1998, 2001). Impaired learning and memory, sedation, and biochemical changes were also reported at doses as low as 200 mg 1-bromopropane/kg/day in the only available oral studies in rats examining neurological end points (Elf Atochem S.A. 1993; Zhong et al. 2013). Additional studies may be conducted to try to identify an acute-duration oral NOAEL for neurotoxicity, but consideration should be given to the fact that the oral route of exposure is not a route of concern for the general public or for occupational exposure. Research aimed at identifying the moiety(s) responsible for 1-bromopropane-induced neurotoxicity would be valuable. Studies could be conducted to examine the influence of CYP or GSH inducers or inhibitors or null strains of rodents on neurotoxic potency. Additional epidemiological studies in workers, particularly prospective, longitudinal studies, would be useful to lend support to the findings reported in the cross-sectional study by Li et al. (2010), which included minor neurological impairments in female workers exposed to median 1-bromopropane concentrations reported to be as low as 1.28 ppm. The critical effect identified in this study was increased vibration sense threshold; however, the methods employed relied heavily on the neurologist administering the test. Therefore, studies including quantitative measures of vibration sense as well as other neurophysiological and neurobehavioral parameters would be of particular interest. Improved procedures for more reliable exposure assessment are also necessary.

Epidemiological and Human Dosimetry Studies. Epidemiological studies are limited to a cross-sectional study in Chinese 1-bromopropane production workers from three factories (Li et al. 2010), two preliminary health surveys in Chinese 1-bromopropane production workers from a single factory (Ichihara et al. 2004a, 2004b), and two NIOSH health surveys in 1-bromopropane glue sprayers (NIOSH 2002, 2003a). As discussed above in the Chronic Studies section, the Li et al. (2010) study was selected

as the basis of the chronic-duration inhalation MRL. Additional epidemiological studies in 1-bromopropane-exposed workers, particularly prospective, longitudinal studies, may help to better characterize the potential neurotoxicity and carcinogenicity of 1-bromopropane in humans.

Biomarkers of Exposure and Effect.

Exposure. Proposed biomarkers of exposure to 1-bromopropane include urinary levels of N-acetyl-S-(n-propyl)-L-cysteine, bromide, and 1-bromopropane itself (Hanley et al. 2006, 2009, 2010; Ichihara et al. 2004a; Kawai et al. 2001; Mathias et al. 2012; Valentine et al. 2007), as well as globin S-propylcysteine adducts in blood (Valentine et al. 2007). Use of N-acetyl-S-(n-propyl)-L-cysteine is expected to be more specific to 1-bromopropane than bromide due to the presence of the bromide ion in foods, although in a study of workers involved in 1-bromopropane manufacture, urinary 1-bromopropane concentrations were significantly correlated with TWA concentrations of 1-bromopropane in workplace air (Ichihara et al. 2004a). Other compounds considered as potential biomarkers were determined to be uncorrelated with exposure (3-bromopropionic acid) or were excluded from analysis due to low concentrations in urine (N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine) (Mathias et al. 2012). Additional occupational studies may better determine the reliability of proposed biomarkers of exposure.

N-Acetyl-S-(n-propyl)-L-cysteine has been measured in the urine of children and adult members of the U.S. general population participants in NHANES 2011–2012 (Jain 2015a, 2015b). The results showed no significant differences between geometric means in males and females and significantly lower levels in children (3.4 ng/mL) than in adults (5.7 ng/mL). Differences between race/ethnicities were reported. N-Acetyl-S-(n-propyl)-L-cysteine also was measured in urine collected from pregnant women during the third trimester of pregnancy (median, 2.61 ng/mL) (Boyle et al. 2016). These studies suggest that urinary N-acetyl-S-(n-propyl)-L-cysteine is found ubiquitously in the general population. However, it is unclear how the general public was exposed to 1-bromopropane, as most exposure is expected to be occupational (NTP 2011; see Section 6.5 for more details). This suggests that exposure to other chemicals and/or endogenous metabolism may be additional sources of urinary N-acetyl-S-(n-propyl)-L-cysteine. Studies designed to identify other environmental or endogenous sources of N-acetyl-S-(n-propyl)-L-cysteine would help to clarify the specificity of N-acetyl-S-(n-propyl)-L-cysteine as a biomarker of 1-bromopropane exposure in non-occupational settings. If the specificity of N-acetyl-S-(n-propyl)-L-cysteine is quantified (or another more specific biomarker is identified), research could potentially be aimed at estimating biomonitoring equivalents for 1-bromopropane would be useful. Biomonitoring

equivalents are defined as the concentration or range of concentrations of a chemical or its metabolites in a biological matrix (i.e., urine for N-acetyl-S-(n-propyl)-L-cysteine) that is consistent with an existing noncancer health-based exposure guidance value (i.e., reference dose [RfD] or reference concentration [RfC]) (Aylward et al. 2013). Comparing biomonitoring equivalents with guidance values helps determine whether exposure to a chemical is excessive. Biomonitoring equivalents have been derived for a number of chemicals (Aylward et al. 2013).

Effect. There are no specific biomarkers to characterize effects caused by 1-bromopropane. Additional information on the mechanism of neurotoxicity may suggest a useful biomarker of either exposure or effect. However, at this time, there is little to suggest that such biomarkers exist.

Absorption, Distribution, Metabolism, and Excretion. The detection of urinary metabolites in humans and animal exposed to 1-bromopropane provides qualitative evidence for absorption by the gastrointestinal tract and the respiratory tract, but quantitative data on the extent of absorption are not available (Garner and Yu 2014; Garner et al. 2006, 2007; Hanley et al. 2006, 2009, 2010; Ishidao et al. 2002; Jones and Walsh 1979; Valentine et al. 2007). *In vitro* dermal absorption characteristics have been measured in studies with human skin samples (Frasch et al. 2011). 1-Bromopropane is not expected to accumulate in tissues due to efficient processes leading to exhalation of parent material or metabolically produced CO_2 and urinary excretion of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. Most urinary and exhaled metabolic products are debrominated leading to elevated levels of bromide ion in blood and urine (Hanley et al. 2006, 2009, 2010; Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Valentine et al. 2007). Oxidation steps are mediated by CYP2E1 and other, as yet unspecified, CYP oxygenases; reduced glutathione is the principal conjugating molecule for the parent compound, as well as for proposed oxygenated brominated intermediate metabolites (Garner et al. 2006, 2007; Jones and Walsh 1979).

Comparative Toxicokinetics. Metabolic disposition and toxicokinetic studies have found differences between mice and rats that reflect higher capacity for oxidative metabolism of 1-bromo-propane in mice than rats (Garner and Yu 2014; Garner et al. 2006, 2007). In rats given nominal single intravenous doses of 5, 20, or 100 mg 1-bromopropane/kg, the percentage dose exhaled as metabolized CO_2 or excreted as oxygenated metabolites in urine decreased with increasing dose, whereas the percentage dose excreted in urine as metabolites from the glutathione conjugation pathway and the

percentage dose exhaled as parent material increased with increasing dose (Garner et al. 2006). In mice, the percentage dose exhaled as metabolized CO_2 did not decrease with increasing dose to the same degree as in rats, and the percentage dose exhaled as parent material did not significantly change with increasing dose (Garner et al. 2006, 2007). Additional research may increase understanding of how these species differences in metabolism and toxicokinetics may be related to species differences in the sensitivity to 1-bromopropane-induced toxicity. A PBPK model for 1-bromopropane in F-344 rats was developed (Garner et al. 2015). The model examined two metabolic assumptions for gas uptake in inhalation studies. Experiments are being conducted to further develop the model by including the compartments of the metabolites of 1-bromopropane in order to help with quantitative extrapolation of animal studies to humans (Garner et al. 2015).

Methods for Reducing Toxic Effects. Oxygen therapy and positive-pressure ventilation may be useful following inhalation exposure to 1-bromopropane to promote the loss of unmetabolized 1-bromopropane from the lungs (Currance et al. 2007; HSBD 2014). Washing of 1-bromopropane from exposed body surfaces is beneficial. In cases of ingestion of isolated hydrocarbons, the use of activated charcoal to reduce gastrointestinal absorption is generally not recommended (Gummin 2015; Thompson 2014); however, its use may be justified in patients with mixed overdoses (Gummin 2015). Other than these general guidelines, there is very little information available on methods of mitigating the toxic effects of 1-bromopropane. Additional data on the outcome of emergency response procedures would be beneficial. Further research assessing the efficacy of antioxidants and compounds that increase glutathione levels, thus preventing the formation of hepatotoxic intermediates or metabolites that affect sperm parameters, would be valuable. Studies of the benefit of diet, ethanol absence, and controlled exposure to prescription or nonprescription drugs on blood levels of 1-bromopropane and its metabolites could provide information that would be helpful in understanding the impact of these factors on the risks from occupational exposure.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

The health effects of 1-bromopropane exposure in children are unknown; however, the nervous system is expected to be a target based on findings in adults. Because the nervous system is still developing in children, they might be more susceptible to 1-bromopropane toxicity than adults if exposure to 1-bromo-

propane were to occur. However, since exposure to 1-bromopropane occurs mainly in occupational settings, children are not expected to experience exposures to 1-bromopropane.

Fetuses and infants may potentially be exposed to 1-bromopropane through their mothers; however, there are no human studies that evaluated effects in offspring of mothers exposed to 1-bromopropane during pregnancy and/or lactation. Studies evaluating placental or lactation transfer of 1-bromopropane would be useful for determining the potential risk to developing offspring. Limited information from a 1-generation study in rats indicates that there is a potential for alterations in growth and maturity of offspring following gestational and lactation exposure to 1-bromopropane vapors (Furuhashi et al. 2006). Guideline developmental toxicity studies would be useful to better characterize the potential developmental toxicity of 1-bromopropane.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies pertaining to 1-bromopropane have been identified (RePORTER 2014).