2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of bromomethane and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for bromomethane based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers 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 (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989d), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Bromomethane exists as a gas under ordinary temperature and pressure, so most studies of bromomethane toxicity have focused on the inhalation route of exposure. Studies with reliable quantitative exposure-response information are summarized in Table 2-1 and Figure 2-1, and the adverse effects of inhalation exposure are discussed below.

2.2.1.1 Death

There are many reports of humans who have died following acute inhalation exposure to bromomethane. Most cases have involved accidental exposures associated with manufacturing or packaging operations, use of fire extinguishers containing bromomethane, or fumigation activities (Alexeeff and Kilgore 1983). Death is not immediate, but usually occurs within 1-2 days of exposure (Marraccini et al. 1983; Prain and Smith 1952). The cause of death is not certain, but is probably due to neurological and lung injury. Fatal exposure levels in humans are usually not known, but limited data suggest the value depends in part on exposure duration. For example, lethality has been reported in humans following exposure to 60,000 ppm for 2 hours (Wyers 1945) and 1,600-8,000 ppm for 4-6 hours (Holling and Clarke 1944; Miller 1943).

Studies in animals indicate that acute exposures to levels of 160-980 ppm may be lethal (Alexeeff et al. 1985; Eustis et al. 1988; Honma et al. 1985; Hurtt et al. 1987a; Irish et al. 1940; Kato et al. 1986). Several studies reveal there is an extremely narrow margin between lethal and nonlethal exposures. For example, Kato et al. (1986) found no deaths in rats exposed to 700 ppm for 4 hours, but 100% lethality in animals exposed to 800 ppm. Similarly, Irish et al. (1940) found 100% survival in rats exposed to 100 ppm for 24 hours, and 100% lethality at 220 ppm. Longer-term exposures of animals can lead to death after exposure to levels as low as 66-120 ppm (Drew 1984; Haber 1987; Hardin et al. 1981; Irish et al. 1940; Reuzel et al. 1987).

The highest NOAEL values and all reliable LOAEL values for lethality in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Bromomethane - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Human	2 hr				60000 (death in 1 hour)	Wyers 1945
2	Human	6 hr				8200 (death from pulmonary edema)	Miller 1943
3	Human	4 hr				1600 (3 men died)	Holling and Clarke 1944
4	Rat	5 d 6hr/d		250		325 (3/5 died)	Hurtt et al. 1987a
5	Rat	22 hr (1 exp)		110		260 (LC100)	Irish et al. 1940
6	Rat	8 hr (1 exp)				302 (LC50 -- 8 hours)	Honma et al. 1985
7	Rat	4 hr		700		780 (LC50)	Kato et al. 1986
8	Mouse	2 wk 5d/wk 6hr/d				160 (50% lethality in 8-10 days)	Eustis et al. 1988
9	Mouse	1 hr (1 exp)		900		980 (1/6 died) 1160 (LC50)	Alexeeff et al. 1985
Systemic							
10	Rat	5 d 6hr/d	Resp	90	175 (mild injury to nasal epithelium)	325 (severe injury to nasal epithelium)	Hurtt et al. 1987a
			Hepatic	250	325 (focal necrosis)		
			Renal	325			
			Other	90	175 (vacuolization, lipid accumulation in renal cortex)		
11	Rat	1-5 d 6hr/d	Resp	90		200 (loss of olfactory epithelium)	Hurtt et al. 1988a

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
12	Mouse	2 wk 5d/wk 6hr/d	Resp			160 (degeneration of nasal epithelium)	Eustis et al. 1988
			Cardio			160 (cardiomyopathy)	
			Hemato		160 (decreased RBC, increased WBC)		
			Renal			160 (nephrosis)	
13	Mouse	1 hr (1 exp)	Resp	440	560 (decreased lung weight)		Alexeeff et al. 1985
			Gastro	1200		1490 (colon hemorrhage)	
			Hepatic	440	560 (decreased liver weight)	1200 (congestion, hemorrhage)	
			Renal	700		900 (enlarged, pale kidney)	
Neurological							
14	Human	1-2 wk (occup)				100 (impaired vision, ataxia, numbness)	Johnstone 1945
15	Rat	8 hr (1 exp)		16[b]	31 (decreased brain neurotrans-mitters)		Honma 1987
16	Rat	5 d 6hr/d		175		250 (ataxia, CNS necrosis)	Hurtt et al. 1987a
17	Rat	8 hr (1 exp)				63 (impaired reflexes)	Honma et al. 1985
18	Rat	8 hr (1 exp)		31	63 (altered neuro-transmitter levels)		Honma et al.1987
19	Rabbit	13 d Gd 7-19 6hr/d		40	80 (ataxia, lethargy)		Breslin et al. 1990
20	Mouse	1 hr (1 exp)		560	700 (hyperactivity)	980 (cerebral hemorrhage, ataxia, tremors)	Alexeeff et al. 1985
21	Mouse	2 wk 5d/wk 6hr/d				160 (necrosis in CNS)	Eustis et al. 1988

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Developmental							
22	Rabbit	13 d Gd 7-19 6hr/d		40		80 (increased anomalies and malformations)	Breslin et al. 1990
Reproductive							
23	Rat	5 d 6hr/d		200			Hurtt and Working 1988
24	Rat	5 d 6hr/d		250	325 (delayed spermiation)		Hurtt et al. 1987a
25	Mouse	2 wk 5d/wk 6hr/d				160 (testicular degeneration)	Eustis et al. 1988
INTERMEDIATE EXPOSURE							
Death							
26	Rat	36 wk 5d/wk 6hr/d		55			Anger et al. 1981
27	Rat	3-6 wk 5d/wk 6hr/d				160 (50% lethality after 3 weeks)	Eustis et al. 1988
28	Rat	3 wk 5d/wk 4hr/d		200		300 (3/12 died)	Ikeda et al. 1980
29	Rat	6 mo 5d/wk 8hr/d		66		100	Irish et al. 1940
30	Rabbit	15 d Gd1-15 6hr/d		20		70 (24/25 died)	Hardin et al. 1981
31	Rabbit	6 mo 5d/wk 8hr/d		33		66 (14/42 died)	Irish et al. 1940

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
32	Gn Pig	6 mo 5d/wk 8hr/d		66		100 (4/11 died)	Irish et al. 1940
33	Mouse	20 wk 5d/wk 6hr/d				100 (48% of males died)	Haber 1987
34	Mouse	13 wk 5d/wk 6hr/d		80		120 (increased mortality)	Drew 1984
Systemic							
35	Rat	6 mo 5d/wk 8hr/d	Resp	66	100 (mild congestion)		Irish et al. 1940
36	Rat	6 wk 5d/wk 4hr/d	Resp		300 (minor lesions)		Kato et al. 1986
			Cardio		150 (focal fibrosis)	300 (increased serum level of cardiac enzymes)	
			Hemato	400			
			Hepatic		300 (fatty degeneration)		
			Renal	400			
			Other	150	200 (decreased body weight)		
37	Rat	3-6 wk 5d/wk 6hr/d	Resp			160 (degeneration of nasal epithelium)	Eustis et al. 1988
			Cardio			160 (cardiomyopathy)	
			Hepatic		160 (minimal necrosis)		
			Renal		160 (minimal nephrosis)		
38	Rabbit	6 mo 5d/wk 8hr/d	Resp	17		33 (congestion, pneumonia)	Irish et al. 1940
			Cardio	66			
			Hepatic	66			
			Renal	66			

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
39	Gn Pig	6 mo 5d/wk 8hr/d	Resp Hepatic Renal	100 100 100			Irish et al. 1940
40	Mouse	20 wk 5d/wk 6hr/d	Hemato Other	100		100 (severe body weight loss)	Haber 1987
41	Mouse	13 wk 5d/wk 6hr/d	Hemato	120			Drew 1984
Neurological							
42	Rat	36 wk 5d/wk 6hr/d		55			Anger et al. 1981
43	Rat	6 wk 5d/wk 4hr/d		200		300 (paralysis)	Kato et al. 1986
44	Rat	3 wk (cont)		5[c]	10 (decreased neuro-transmitters)		Honma et al.1982
45	Rat	3 wk 5d/wk 4hr/d			200 (altered behavior)		Ikeda et al. 1980
46	Rat	3-6 wk 5d/wk 6hr/d				160 (CNS necrosis)	Eustis et al. 1988
47	Rat	4 wks 4d/wk 7.5hr/d		65			Anger et al. 1981
48	Rabbit	6 mo 5d/wk 8hr/d		17		33 (paralysis)	Irish et al. 1940
49	Rabbit	4 wks 4d/wk 7.5hr/d				65 (impaired nerve function)	Anger et al. 1981
50	Rabbit	8 mo 4d/wk 7.5hr/d		27			Russo et al. 1984

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
51	Mouse	13 wk 5d/wk 6hr/d		40	80 (mild limb crossing and twitching)	120 (severe limb crossing and twitching)	Drew 1984
52	Mouse	20 wk 5d/wk 6hr/d				100 (tremors, paralysis)	Haber 1987
53	Monkey	6 mo 5d/wk 8hr/d		33		66 (convulsions)	Irish et al. 1940
Developmental							
54	Rat	6 wk 5d/wk 7hr/d		70			Sikov et al. 1980
55	Rat	19 d Gd1-19 6hr/d		70			Hardin et al. 1981
56	Rabbit	24 d 7hr/d		20			Sikov et al. 1980
57	Rabbit	15 d Gd1-15 6hr/d		70			Hardin et al. 1981
Reproductive							
58	Rat	3-6 wk 5d/wk 6hr/d				160 (testicular degeneration)	Eustis et al. 1988
59	Rat	6 wk 5d/wk 7hr/d		70			Sikov et al. 1980
60	Rat	19 d Gd1-19 6hr/d		70			Hardin et al. 1981
61	Rat	6 wk 5d/wk 4hr/d		300		400 (testicular atrophy)	Kato et al. 1986

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
62	Rabbit	24 d 7hr/d		20			Sikov et al. 1980
63	Mouse	13 wk 5d/wk 6hr/d		80	120 (decreased sperm density)		Drew 1984
CHRONIC EXPOSURE							
Death							
64	Rat	128 wk 5d/wk 6hr/d				90 (early mortality)	Reuzel et al. 1987
Systemic							
65	Rat	128 wk 5d/wk 6hr/d	Resp		3 (irritation of nasal epithelium)	90 (hemothorax)	Reuzel et al. 1987
			Cardio	30		90 (thrombi in heart, myocardial degeneration)	
			Gastro	30	90 (hyperkeratosis of esophagus)		
			Hemato	90			
			Renal	90			
66	Mouse	103 wk 5d/wk 6hr/d	Hemato	33			Haber 1987
Neurological							
67	Human	8 yr (occup)			2.3[d] (increased prevalence of muscle ache, fatigue, ataxia)		Anger et al. 1986
68	Mouse	103 wk 5d/wk 6hr/d		10	33 (abnormal posture)		Haber 1987

Table 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Developmental							
69	Rat	2 gen. 5d/wk 6hr/d		3	30 (reduced pup weights)		Enloe et al. 1986

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive acute inhalation Minimal Risk Level (MRL) of 0.05 ppm (50 ppb); animal dose extrapolated to human dose according to method of EPA (1989d); values of blood/air partition coefficients assumed to be equal for animals and humans; dose adjusted for less-than-continuous exposure (8 hours/24 hours), and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive intermediate MRL of 0.05 ppm (50 ppb); animal dose extrapolated to human dose according to method of EPA (1989d); values of blood/air partition coefficients assumed to be equal for animals and humans; dose value divided by an uncertainty factor of 100 (10 for extrapolation from humans to animals, and 10 for human variability).
[d]Used to derive chronic MRL of 0.005 ppm (5 ppb); dose adjusted for intermittant exposure (8 hours/day, 5 days/wk), and divided by an uncertainty factor of 100 (10 for use of a LOAEL, and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; cont = continuous; d = day(s); exp = exposure; Gastro = gastrointestinal; Gd = gestation day; gen. = generation; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month; NOAEL = no-observed-adverse-effect level; occup = occupational; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = week(s); yr = year(s)

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

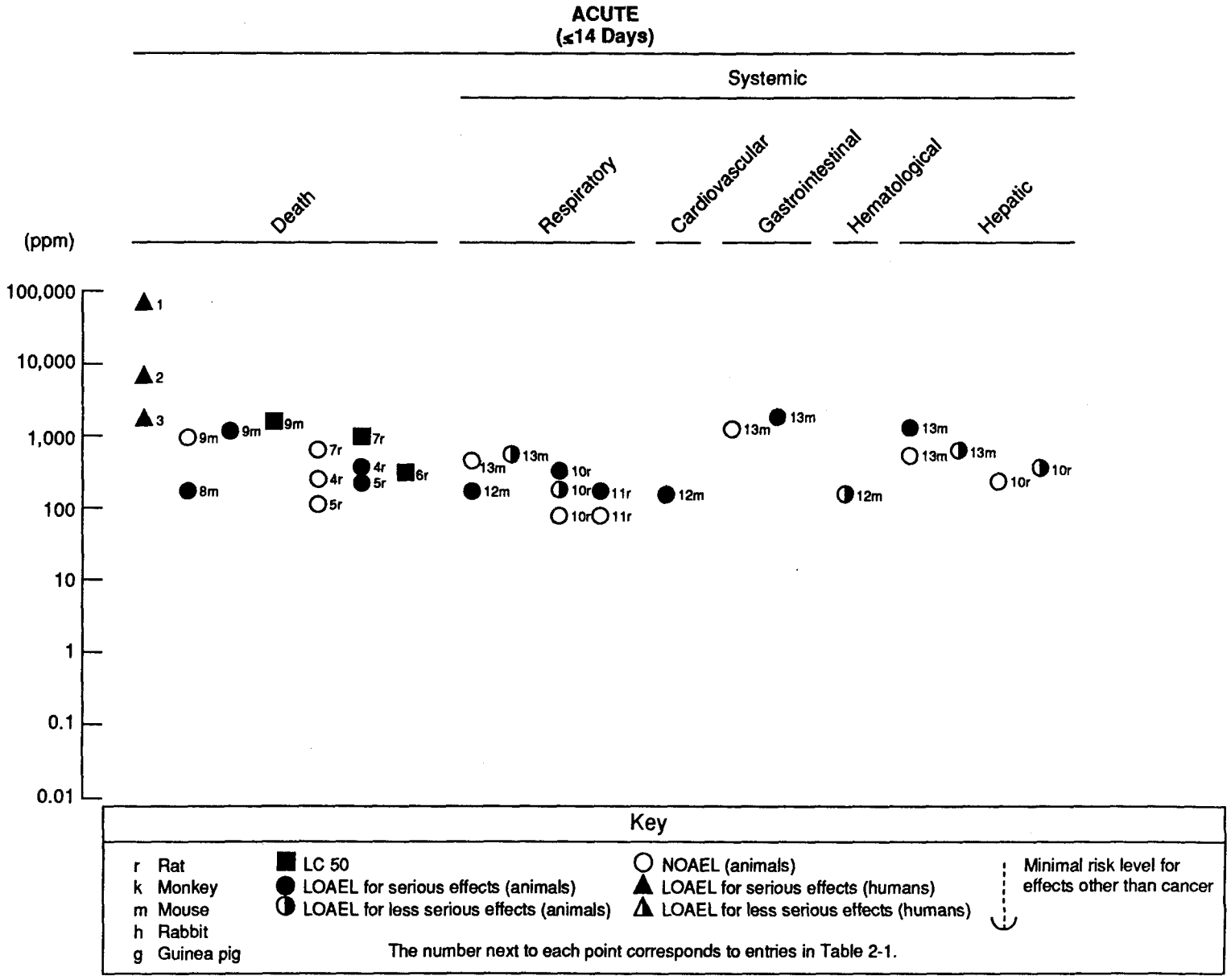


FIGURE 2-1 (Continued)

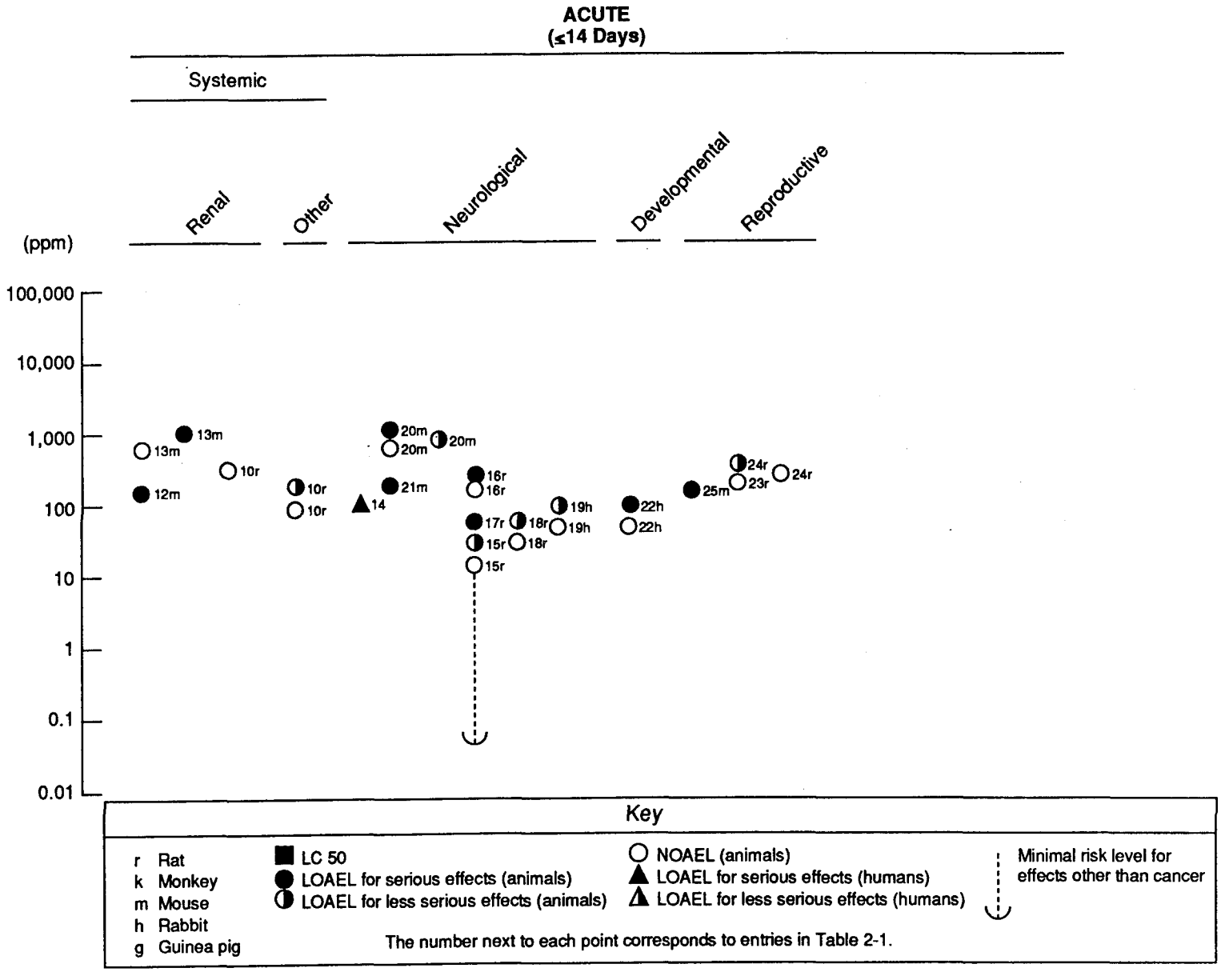


FIGURE 2-1 (Continued)

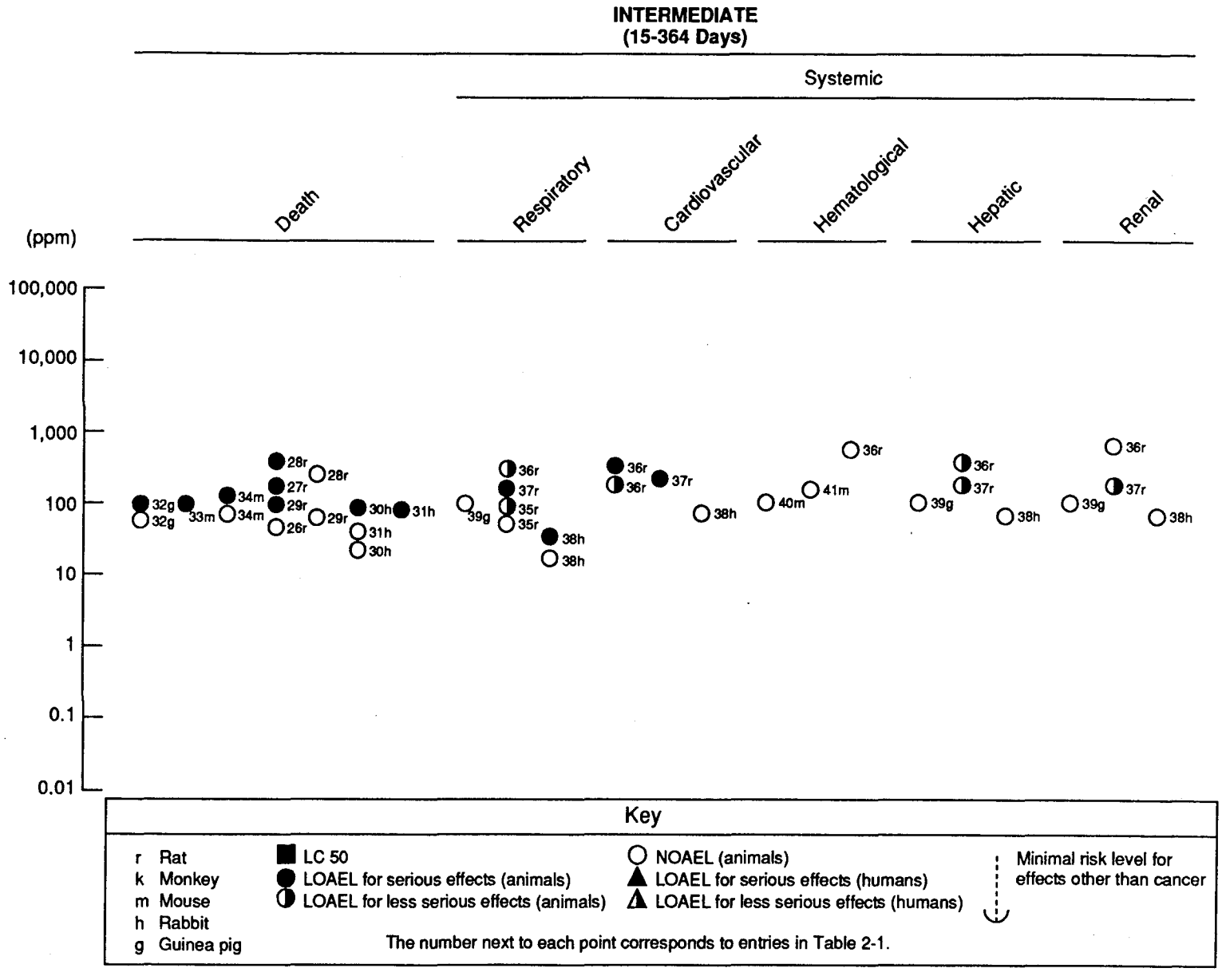


FIGURE 2-1 (Continued)

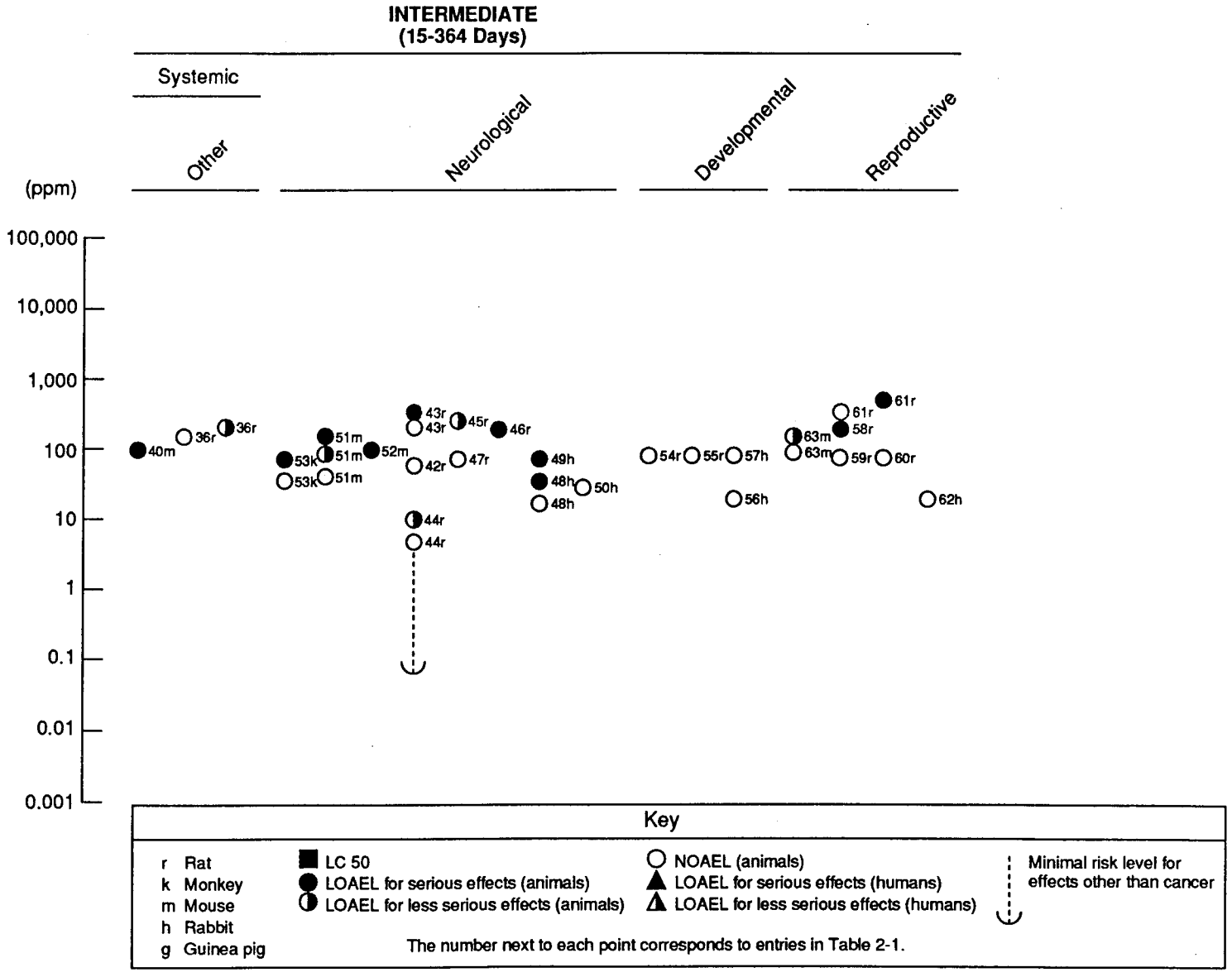
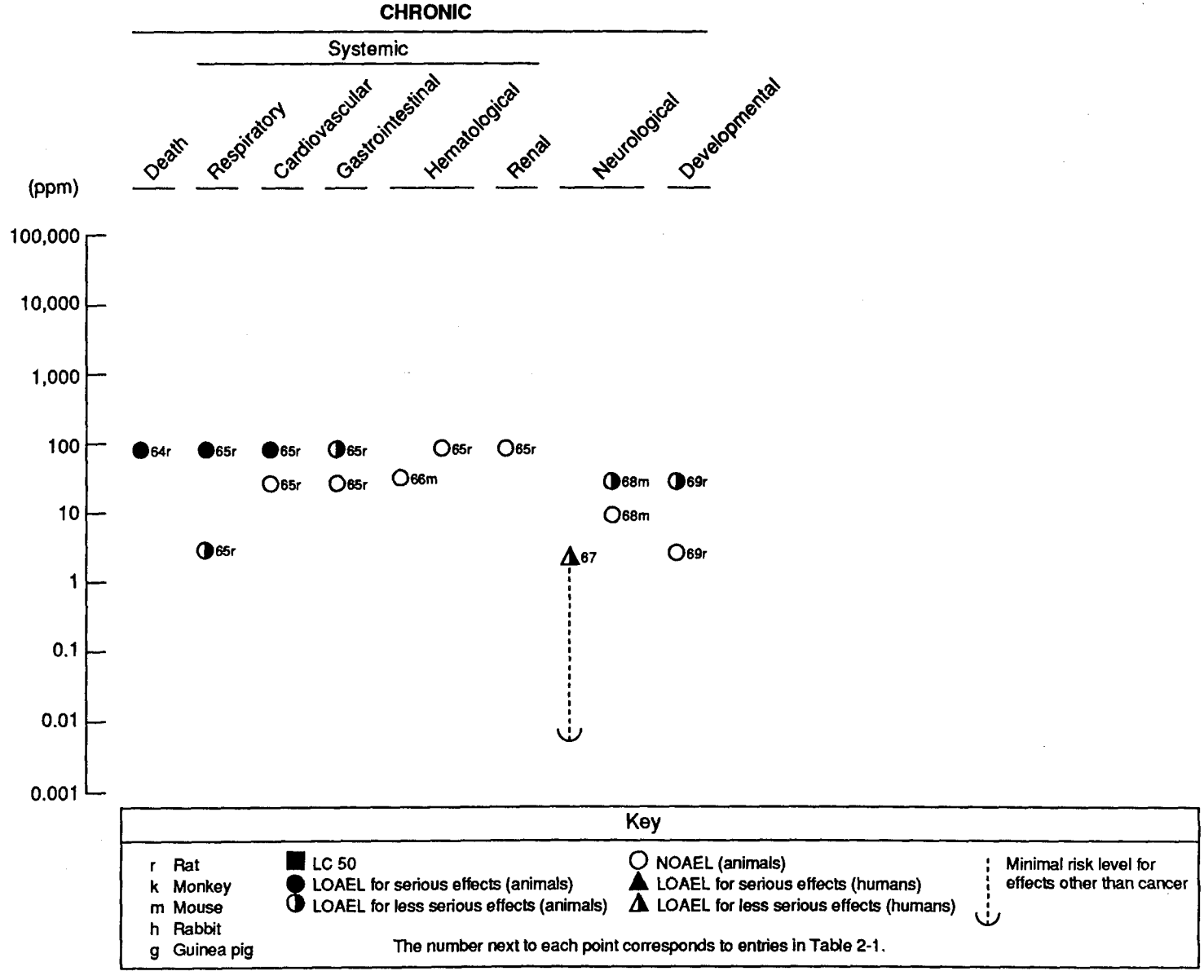


FIGURE 2-1 (Continued)



2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects on humans or animals after inhalation exposure to bromomethane. Information on other systemic effects is presented below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. Studies in humans indicate that the lung may be severely injured by inhalation exposure to bromomethane. Edema is the most common effect, and is often accompanied by focal hemorrhagic lesions (Greenberg 1971; Marraccini et al. 1983; Miller 1943; Prain and Smith 1952; Wyers 1945). This injury can severely impair respiratory function and lead to hypoxia, cyanosis, and complete respiratory failure (Greenberg 1971; Hine 1969; O'Neal 1987). Similar edematous and hemorrhagic lesions are seen in lungs of several rodent species exposed to bromomethane (Irish et al. 1940; Kato et al. 1986; Reuzel et al. 1987; Sato et al. 1985) and severe damage can also occur to the nasal epithelium (Eustis et al. 1988; Hurtt et al. 1987a, 1988a). As shown in Table 2-l and Figure 2-1, these effects occur mainly at acute exposure levels of 100 ppm or higher, but may occur at levels of 3-10 ppm if exposure duration is extended (Reuzel et al. 1987; Sato et al. 1985).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to bromomethane, but several studies in mice and rats indicate that the heart is susceptible to injury. Effects which have been repor.ted at exposure levels of 90-160 ppm include cardiomyopathy (Eustis et al. 1988), myocardial degeneration and cardiac thrombi (Reuzel et al. 1987) and fibrosis (Kato et al. 1988).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to bromomethane. Gastrointestinal effects have not been noted in most animal studies, but Alexeeff et al. (1985) reported an unusual increase in hemorrhagic lesions of the colon in mice exposed to high concentrations (1,490 ppm) of bromomethane, and Reuzel et al. (1987) noted an increased incidence of hyperkeratosis of the esophagus and stomach in rats exposed to 90 ppm. This effect is probably mediated by transport of bromomethane from the lungs to the throat by mucociliary clearance (Reuzel et al. 1987).

Hematological Effects. Hematological effects have not been observed in humans exposed to bromomethane (Johnstone 1945; Kantarjian and Shasheen 1963; Longley and Jones 1965; O'Neal 1987; Viner 1945; Wyers 1945). In animals, decreased red and white blood cell counts were noted in one study of rats exposed to 160 ppm (Eustis et al. 1988), but hematological effects were not detected by others (Drew 1984; Haber 1987; Kato et al. 1986; Reuzel et al. 1987). These studies indicate that blood and blood-forming cells are not important target tissues for bromomethane.

Hepatic Effects. Case reports of humans exposed to bromomethane vapors indicate the liver may become swollen and tender in some cases (Hine 1969; O'Neal 1987; Miller 1943; Prain and Smith 1952), but often no significant liver injury is detected (Greenberg 1971; Hine 1969; Marraccini et al. 1983). Similar results have been reported in animals, with mild signs of liver injury (edema, focal hemorrhages, minimal necrosis) being noted in some studies at levels of 150-600 ppm (Alexeeff et al. 1985; Eustis et al. 1988; Hurtt et al. 1987a; Kato et al. 1986), with no significant injury at levels of 66 ppm (Irish et al. 1940).

Renal Effects. Adverse renal effects are often reported in humans exposed to high levels of bromomethane vapor. Common effects include congestion, anuria or oliguria, and proteinuria (Hine 1969; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Viner 1945; Wyers 1945). However, there are many cases where renal effects are minimal or absent (Hine 1969; Johnstone 1945; Longley and Jones 1965). Similar signs of renal injury have been reported in several animal studies, including swelling, edema, nephrosis, and tubular necrosis (Alexeeff et al. 1985; Eustis et al. 1988).

Dermal/Ocular Effects. Bromomethane vapor is irritating to the skin and eyes, and humans who are exposed to bromomethane in air may experience conjunctivitis, erythema, rashes, or even blisters (Marraccini et al. 1983; O'Neal 1987; Wyers 1945). The effects of direct dermal or ocular contact with bromomethane vapors are discussed more fully in Section 2.2.3.2. No studies were located regarding dermal or ocular effects following systemic absorption of bromomethane in animals or humans.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to bromomethane.

2.2.1.4 Neurological Effects

Inhalation exposure to bromomethane frequently leads to a spectrum of neurological effects in humans. Initial symptoms typically include headache, nausea, confusion, weakness, numbness, and visual disturbances (Anger et al. 1986; Hine 1969; Kantarjian and Shasheen 1963; Marraccini et al. 1983; O'Neal 1987; Rathus and Landy 1961; Watrous 1942). In severe cases, these effects may progress to ataxia, tremor, seizures, paralysis, and coma (Behrens and Dukes 1986; Greenberg 1971; Longley and Jones 1965; Marraccini et al, 1983; O'Neal 1987; Prain and Smith 1952; Prockop and Smith 1986; Rathus and Landy 1961; Viner 1945; Wyers 1945). In most cases of acute exposure, the effects do not occur immediately, but develop after a lag of several hours (Clarke et al. 1945). If death does not ensue, symptoms usually decrease in severity over the course of several weeks to several months, although frequently they do not disappear completely (Chavez et al. 1985; Greenberg 1971; Hine 1969; Johnstone 1945; Kantarjian and Shasheen 1963; Longley and Jones 1965; Prockop and Smith 1986).

Quantitative data on the exposure levels leading to neurological effects in humans are limited. Early studies indicated that workplace exposure to concentrations of 100 ppm or even less for 1-2 weeks could lead to headache, nausea, numbness, and ataxia (Johnstone 1945; Watrous 1942). Longer-term exposure (8 years) to average levels of 2.3 ppm are suspected to be the cause of an increased incidence of neurological symptoms (muscle ache, .fatigue, ataxia) in a group of fumigators who used bromomethane (Anger et al. 1986). Based on this value, a chronic inhalation MRL of 0.005 ppm was calculated, as described in footnote "d" of Table 2-1.

Inhalation studies in animals confirm that the central nervous system is injured by inhalation exposure to bromomethane. Clinical effects that have been detected include tremors, ataxia, paralysis, and seizures (Alexeeff et al. 1985; Anger et al. 1981; Breslin et al. 1990; Drew 1984; Haber 1987; Hurtt et al. 1987a; Irish et al. 1940; Kato et al. 1986). Histological lesions in the brain (focal necrosis and hemorrhage) have also been detected (Alexeeff et al. 1985; Eustis et al. 1988; Hurtt et al. 1987a). As shown in Table 2-l and Figure 2-1, neurological effects are typically observed at exposure levels ranging between 80 and 1,000 ppm, although longer-term (6 month to 2 year) exposure of rabbits, monkeys, or mice has led to functional neurological impairment at concentrations of 33-66 ppm (Haber 1987; Irish et al. 1940). As in humans, these effects tend to be at least partly reversible when exposure ceases (Irish et al. 1940).

The most sensitive indicator of neurological effects in animals appears to be alterations in the levels of neurotransmitters in the brain. In rats exposed to bromomethane for 8 hours, there was a significant decrease in the hypothalamic concentration of norepinephrine and a decrease in the activity of tyrosine hydroxylase at an exposure level of 31 ppm, but not at 16 ppm (Honma 1987). Based on this value (16 ppm), an acute inhalation MRL value of 0.05 ppm was calculated as described in footnote "b" of Table 2-1. When exposure duration was extended to 3 weeks (24 hours/day), dramatic decreases in norepinephrine and 5-hydroxytryptamine were detected at exposure levels of 10 ppm but not at 5 ppm (Honma et al. 1982). Based on this value (5 ppm), an intermediate inhalation MRL of 0.05 ppm was calculated as described in footnote "c" of Table 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to bromomethane. Several studies in rats and rabbits indicate that inhalation exposure to levels up to 70 ppm during gestation does not result in any significant developmental effects, even when there is severe maternal toxicity (Hardin et al. 1981; Sikov et al. 1980). However, an increased incidence of anomalies.and malformations was observed in offspring from rabbits exposed to 80 ppm during gestation (Breslin et al. 1990), and decreased pup weights were noted in a multigeneration study in rats exposed to 30 ppm (Enloe et al. 1986). The NOAEL and LOAEL values are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to bromomethane. In male animals, effects on the testes (delayed spermiation, tubular degeneration, atrophy) have been observed in rats and mice exposed to 160-405 ppm for 1-6 weeks (Eustis et al. 1988; Hurtt et al. 1987a; Kato et al. 1988) or 120 ppm for 13 weeks (Drew 1984). However, exposure of male rats to 70 ppm for 5 days did not interfere with normal reproductive function and impregnation success (McGregor 1981). No effects on* reproductive function in females have been observed in rats or rabbits exposed to levels up to 70 ppm before and during gestation (Sikov et al. 1980), even though these levels produce maternal toxicity. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to bromomethane. In animals, the frequency of bone marrow cells with chromosomal aberrations was not increased in rats exposed to 70 ppm for 5 days (McGregor 1981), but was increased several-fold in rats exposed to 140 ppm for 14 days (Ikawa et al. 1986). Djalali-Behzad et al. (1981) found that inhalation exposure of mice to bromomethane for 4 hours led to alkylation of DNA in liver and spleen, although the levels were quite low. In contrast to these positive findings, no genotoxic effects could be detected in sperm from rats or mice exposed to 70 ppm bromomethane for 5 days, using either the dominant lethal or recessive lethal tests, or by direct examination of the sperm (McGregor 1981). These studies indicate that bromomethane does have genotoxic potential, but that effects may be minimal and difficult to measure following brief or low dose exposure. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

The carcinogenic potential of bromomethane has not been formally investigated in epidemiological studies of occupationally-exposed workers. Wong et al. (1984) studied the incidence of cancer in a cohort of workers exposed to a wide variety of brominated chemicals, and noted that two men who died of testicular cancer had both been exposed to bromomethane. However, since there are numerous risk factors for testicular cancer, and since the workers may have been exposed to other chemicals, this observation is not sufficient to indicate that bromomethane is carcinogenic. No evidence of carcinogenic effects was detected in mice exposed to 33 ppm for 2 years (Yang 1990), or in rats exposed to 90 ppm for 29 months (Reuzel et al. 1987).

2.2.2 Oral Exposure

Because bromomethane is a gas under ordinary conditions, the oral toxicity of this compound has not been thoroughly studied. No information was located regarding health effects in humans after oral exposure to

bromomethane. Available data from oral studies in animals are summarized in Table 2-2 and Figure 2-2, and this information is discussed below.

2.2.2.1 Death

No studies were located regarding lethality in humans or animals after oral exposure to bromomethane.

2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, musculoskeletal, renal, or dermal/ocular effects in humans or animals after oral exposure to bromomethane. Information on other systemic effects is presented below. The highest NOAEL values and all reliable LOAEL values for these systemic effects are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to bromomethane. In animals, no histological evidence of lung injury was detected in rats exposed to oral doses of 50 mg/kg/day for 13 weeks (Danse et al. 1984). Slight atelectasis was observed in some animals exposed to oral doses of 10 or 50 mg/kg/day, but this was judged to be due to inadvertent inhalation exposure that occurred during oral dosing (Danse et al. 1984).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to bromomethane. Several studies in animals have shown that repeated (90-day) administration of concentrated solutions of bromomethane (40-5,000 mg/L, dissolved in oil) by gavage to rats can result in irritation and hyperplasia of the epithelium in the forestomach (Boorman et al. 1986; Danse et al. 1984). No effects were observed in animals administered 0.4 mg/kg/day (Danse et al. 1984). Mild focal hyperemia was detected at concentrations of 200 mg/L (equivalent to a dose of 2 mg/kg/day), with hyperplasia, hyperkeratosis, and fibrosis developing after repeated administration of 1,000 mg/L (equivalent to a dose of 10 mg/kg/day) or higher. Repeated doses of 5,000 mg/L (50 mg/kg/day) caused frank ulcerations of the forestomach. These lesions appear to be the result of a direct irritant effect of bromomethane on the epithelium. The epithelial hyperplasia regresses when exposure is stopped, although fibrotic lesions or adhesions which developed during exposure remain (Boorman et al. 1986). The possible relationship between this hyperplastic response and cancer of the forestomach is discussed below in Section 2.2.2.8.

Based on the data of Danse et al. (1984), it is judged that doses up to 0.4 mg/kg/day do not produce significant adverse effects on the stomach, and this dose has been used to derive an intermediate oral MRL of 0.003 mg/kg/day as described in footnote "b" of Table 2-2.

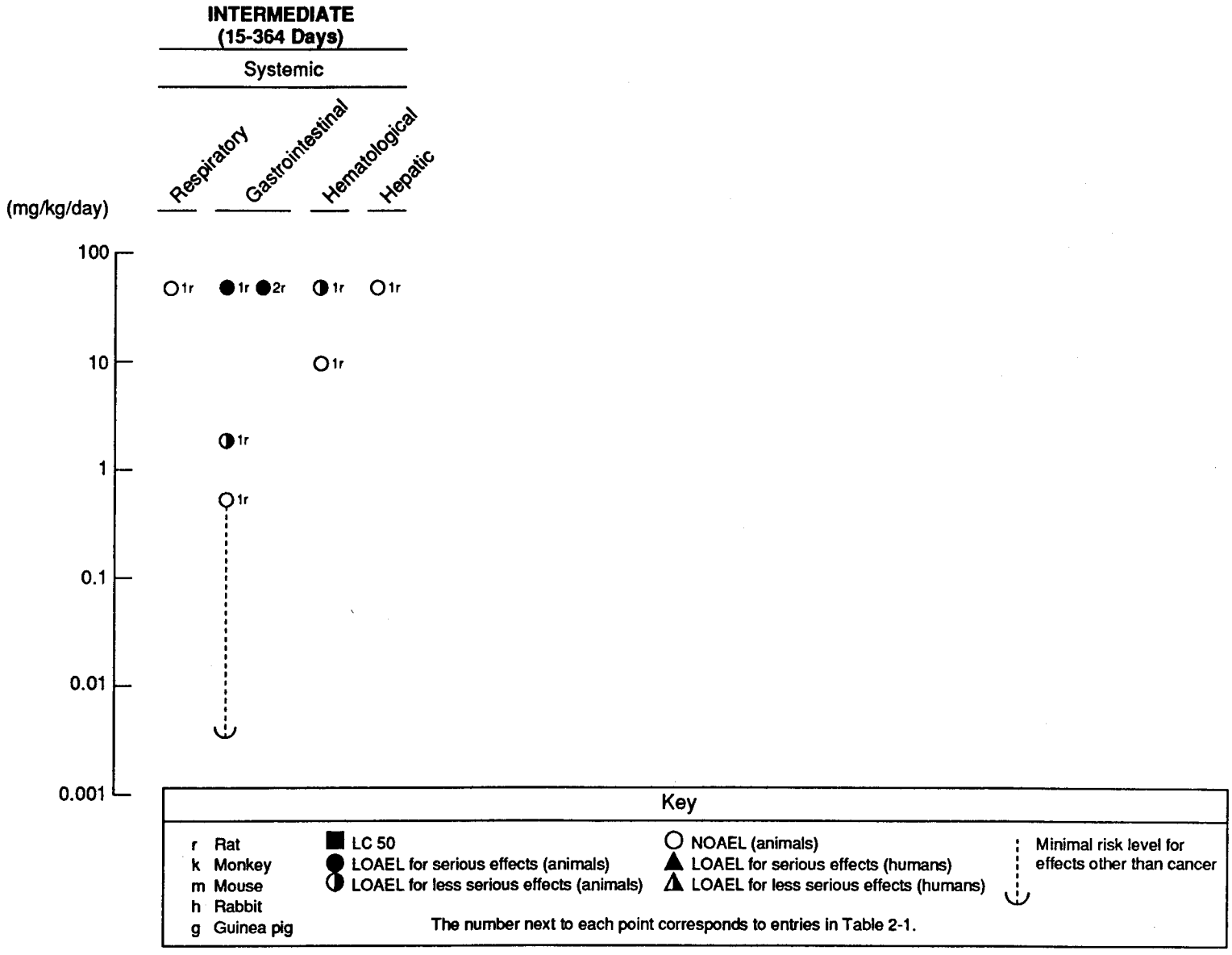
TABLE 2-2. Levels of Significant Exposure to Bromomethane - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Systemic								
1	Rat	(G)	13 wk 5d/wk	Resp	50			Danse et al. 1984
				Gastro	0.4[b]	2 (hyperplasia, focal hyperemia)	50 (ulcers)	
				Hemato	10	50 (slight anemia)		
				Hepatic	50			
2	Rat	(G)	13-25 wk 5d/wk	Gastro			50 (fibrosis, inflammation, hyperplasia)	Boorman et al. 1986

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate duration oral Minimal Risk Level (MRL) of 0.003 mg/kg/day; dose adjusted for intermittent exposure (5d/wk) and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

d = day(s); (G) = gavage - not specified; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

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



Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to bromomethane. Slight anemia was observed in rats exposed to doses of 50 mg/kg/day for 13 weeks, but this was judged to be secondary to the pronounced lesions of the forestomach (Danse et al. 1984). No evidence of other hematological effects was detected at doses up to 10 mg/kg/day.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to bromomethane. In animals, histological signs of liver damage were not detected in rats given doses up to 50 mg/kg/day for 90 days (Danse et al. 1984).

Other Systemic Effects. Rats exposed to oral doses of 50 mg/kg/day for 90 days did not gain weight normally (Boorman et al. 1986; Danse et al. 1984). This effect was probably secondary to decreased food intake, and was not observed at doses up to 10 mg/kg/day (Danse et al. 1984).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to bromomethane.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after oral exposure to bromomethane.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to bromomethane.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to bromomethane.

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to bromomethane. Danse et al. (1984) exposed rats by gavage to bromomethane (in oil) for 90 days, and observed a dose-dependent increase in the incidence of forestomach lesions which were interpreted as squamous cell carcinomas. However, histological diagnosis of epithelial carcinomas in the presence of marked hyperplasia is difficult (Wester and Kroes 1988). After reevaluation of the histological slides, a panel of scientists from the

National Toxicology Program (NTP) concluded that there was no evidence of a neoplastic response in this study, but rather only hyperplasia and inflammation (IRIS 1989). This is consistent with the observation that the hyperplasia of the forestomach produced by 13 weeks of exposure to bromomethane regresses when exposure is ended (Boorman et al. 1986). However, longer-term (25 week) oral exposure of rats to 50 mg/kg/day of bromomethane led to a forestomach lesion in one rat (out of 15 exposed) that was judged to be a very early carcinoma. Although this observation is not adequate to draw firm conclusions, these data suggest that the initial hyperplasia produced by bromomethane may occasionally lead to neoplasia after sufficient time.

2.2.3 Dermal Exposure

The effects of dermal contact with bromomethane have been described in numerous case reports of humans who were exposed either to liquid bromomethane (mainly from fire extinguishers) or bromomethane vapors (mainly during fumigation activities). These studies are discussed below. No studies were located regarding dermal exposure of animals to bromomethane.

2.2.3.1 Death

No cases were located in which dermal exposure to bromomethane led to death in humans.

2.2.3.2 Systemic Effects

Adverse effects on the respiratory system, cardiovascular system, gastrointestinal tract, blood, musculoskeletal system, liver, or kidneys have not been observed in humans exposed to bromomethane by the dermal route (e.g., Butler et al. 1945; Hine 1969; Wyers 1945; Zwaveling et al. 1987).

Dermal/Ocular Effects. Direct dermal contact with bromomethane can lead to severe injury to the skin. Symptoms usually do not appear immediately, but develop a few hours after exposure. Early signs typically include a burning or itching sensation, with erythema, edema, and large blisters that resemble second-degree burns developing somewhat later (Butler et al. 1945; Hezemans-Boer et al. 1988; Watrous 1942; Wyers 1945). Injury is usually mild on exposed skin areas where rapid evaporation can occur and is more severe in moist or covered regions where evaporation is retarded (Watrous 1942; Zwaveling et al. 1987). Effects generally begin to subside within 5-10 days after exposure (Watrous 1942), and recovery is usually complete within about 1 month (Butler et al. 1945; Zwaveling et al. 1987).

The exposure levels leading to dermal effects of this sort are rarely known. Most cases involve people doused with liquid bromomethane (Longley and Jones 1965; Watrous 1942) or exposed to very high vapor levels (Hezemans-Boer et al. 1988; Zwaveling et al. 1987) (see Table 2-3). Numerous case reports of humans exposed to lower levels of bromomethane fumes did not include

TABLE 2-3. Levels of Significant Exposure to Bromomethane Vapor - Dermal

Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE						
Systemic						
Human	40 min (1 exp)	Derm/oc			10000 (blisters)	Hezemans-Boer et al. 1988

Derm/oc = dermal/ocular; exp = exposure; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level

descriptions of dermal effects, even though the level of inhalation exposure caused profound or even fatal neurological or respiratory effects (e.g., Greenberg 1971; Hine 1989; Marraccini et al. 1983).

No studies were located regarding the following effects in humans or animals after dermal exposure to bromomethane:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to bromomethane.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the amount of bromomethane absorbed by humans during inhalation exposure. Several studies in rats indicate that the rate of bromomethane uptake across the lung is directly proportional to the concentration in air, 1.6 $(kg\ hr)^{-1}$ with estimated rate constants ranging from 0.32 to (Gargas and Andersen 1982; Medinsky et al. 1985). Fractional absorption appears to be about 50% at exposure levels up to around 180 ppm (Medinsky et al. 1985). At high levels (310 ppm), the total amount absorbed appears to reach a maximum (62 mg/kg), suggesting that some aspect of uptake (perhaps glutathione availability) becomes limiting (see Section 2.3.3).

2.3.1.2 Oral Exposure

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

2.3.1.3 Dermal Exposure

No quantitative studies were located regarding bromomethane absorption across the skin of humans or animals.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding bromomethane distribution in humans after inhalation exposure. In rats exposed to ^{14}C-bromomethane in air, radioactive label was widely distributed throughout the body (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Levels were somewhat higher in lung, adrenal, liver, and kidney than in other tissues (Bond et al. 1985; Jaskot et al. 1988). The form of the label was not studied by these researchers, but is probably mostly metabolites. However, Honma et al. (1985) showed that low levels of parent bromomethane can be detected for up to 24 hours after exposure.

2.3.2.2 Oral Exposure

No studies were located regarding bromomethane distribution in humans after oral exposure. In rats given oral doses of ^{14}C-bromomethane, label was distributed widely throughout the body, with highest levels in liver and kidney (Medinsky et al. 1984).

2.3.2.3 Dermal Exposure

No studies were located on bromomethane distribution in humans or animals after dermal exposure.

2.3.3 Metabolism

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

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

The amount of bromomethane broken down by this reaction in the body is not known, but increased levels of both methanol and bromide have been detected in exposed animals (Gargas and Andersen 1982; Honma et al. 1985). Bromomethane may also react with organic thiols (R-SH) to yield S-methyl derivatives:

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

This has been shown to result in formation of S-methylcysteine derivatives in hemoglobin of mice exposed to bromomethane (Iwasaki 1988b), and by analogy with methyl chloride (Kornburst and Bus 1983), is likely to result in formation of S-methyl glutathione (Medinsky et al. 1985). Further metabolism of methanol or S-methyl derivatives such as those mentioned above then leads to the formation of carbon dioxide (generally accounting for 40%-50% of the administered dose) and other unidentified nonvolatile metabolites (generally accounting for about 20%-25% of the dose) (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion of bromomethane in humans after inhalation exposure. In animals exposed to bromomethane vapors, excretion occurs mainly by expiration of carbon dioxide or by urinary excretion of nonvolatile metabolites (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Only small amounts are excreted in the feces. Very little parent bromomethane is exhaled (Jaskot et al. 1988; Medinsky et al. 1985), and tissue levels of parent bromomethane decrease with a half-life of only about 15-30 minutes (Honma et al. 1985; Jaskot et al. 1988). Half-lives for clearance of metabolites from the body and most tissues range from 2 to 10 hours (Honma et al. 1985; Jaskot et al. 1988).

A significant fraction (about 25%-30%) of ^{14}C-label remains in tissues after 24-72 hours and is excreted more slowly (Jaskot et al. 1988; Medinsky et al. 1985). This slow excretion of label presumably represents turnover of various intracellular metabolites or adducts, although this has not been established.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of bromomethane by humans after oral exposure. One study in animals indicates that the rate and pattern of excretion of ^{14}C-label following oral exposure to ^{14}C-bromomethane is similar to that following inhalation exposure: 32% was exhaled as carbon dioxide, 43% was excreted in the urine, 4% of unmetabolized parent compound was exhaled, 2% was excreted in the feces, and 14% remained in the body after 72 hours (Medinsky et al. 1984).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of bromomethane by humans or animals after dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

Bromomethane exists as a gas at ordinary temperatures, so the most likely route of human exposure is by inhalation. The hazard of this compound is increased by the fact that it has very little odor at potentially toxic levels (Alexeeff and Kilgore 1983), and effects on the body are generally delayed. Thus, people may be exposed to hazardous levels without being aware that the exposure is occurring.

There are a number of studies that provide good quantitative doseresponse data by the inhalation route, and inhalation MRLs have been derived for acute, intermediate and chronic inhalation exposure. The acute value is based on a study in rats in which exposure to 31 ppm for 8 hours caused altered levels of brain neurotransmitters, while 16 ppm had no effect (Honma

1987). The MRL of 0.05 ppm was obtained by adjusting the NOAEL (16 ppm) for less than continuous exposure (8 hour/day) and dividing by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). The intermediate-duration inhalation MRL is based on a 3-week study in rats in which exposure to 10 ppm resulted in decreased brain neurotransmitters, while 5 ppm did not (Honma et al. 1982). The intermediate MRL of 0.05 ppm was derived from the NOAEL (5 ppm) by dividing by an uncertainty factor of 100, as described above. The chronic inhalation MRL is based on an epidemiological study of workers who had an increased prevalence of muscle ache, fatigue, and ataxia following chronic exposure to average levels of 2.3 ppm (Anger et al. 1986). The MRL was derived by adjusting this LOAEL (2.3 ppm) to account for noncontinuous exposure (8 hr/day, 5 days/week), and by dividing by an uncertainty factor of 100 (10 for use of a LOAEL, and 10 for human variability).

Because bromomethane tends to volatilize and exists mainly as a gas at room temperature, only two oral toxicity studies have been performed (Boorman et al. 1986; Danse et al. 1984). Both studies were performed by administering bromomethane dissolved in oil to rats and both studies reported that irritation of the stomach was the chief effect. The 13-week study by Danse et al. (1984) identified a NOAEL of 0.4 mg/kg/day and a LOAEL of 2 mg/kg/day. An intermediate-duration oral MRL of 0.003 mg/kg/day was derived from the NOAEL (0.4 mg/kg/day) by adjusting for intermittent exposure (5 days/week) and dividing by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

No dermal MRLs have been derived for bromomethane due to the lack of an appropriate methodology for development of dermal MRLs.

More detailed information on the adverse effects associated with exposure to bromomethane is presented below.

Death. Many people have died following accidental inhalation exposure to high levels of bromomethane (Alexeeff and Kilgore 1983). The exposure levels leading to death in humans are not precisely defined, with estimates ranging from 1,600 to 60,000 ppm, depending on duration of exposure (Holling and Clarke 1944; Miller 1943; Wyers 1945). Lethal exposure levels in animals also depend on duration of exposure, with mortality occurring in rats and rabbits after 24 hours exposure to 220 ppm (Irish et al. 1940), or after 2 weeks to 2 years exposure to 66-100 ppm (Drew 1984; Haber 1987; Hardin et al. 1981; Ikeda et al. 1980; Irish et al. 1940; Reuzel et al. 1987). Exposure to a lethal concentration of bromomethane is only likely to occur in the immediate vicinity of fumigation activities or a major spill, and is not of concern under normal circumstances.

Systemic Effects.

Respiratory Effects. Acute inhalation exposure of humans and animals to bromomethane can result in marked lung irritation (edema, hemorrhagic lesions), and this may lead to moderate to severe impairment of respiratory

function (Greenberg 1971; O'Neal 1987; Prain and Smith 1952). Dose-response data are limited for humans, but the effect range in animals is usually lo-1,000 ppm (see Figure 2-l). Exposures to concentrations of bromomethane this high are not likely near waste sites unless a major spill or accident occurs. Oral exposure does not appear to result in lung injury (Danse et al. 1984).

Renal Effects. The kidney also is sensitive to bromomethane. Anuria and proteinuria are common signs of renal injury in acutely exposed humans (O'Neal 1987; Prain and Smith 1952; Viner 1945), but dose-response data are not available. In animals, nephrosis has been noted in rats and mice exposed to 160 ppm for 2-6 weeks (Eustis et al. 1988).

Hepatic Effects. Mild effects (congestion, focal hemorrhages) are sometimes observed in liver and other tissues (O'Neal 1987; Prain and Smith 1952; Wyers 1945), but these effects do not appear to be as significant as the respiratory and renal injury.

Gastrointestinal Effects. Although data are limited, the only systemic tissue that has been found to be affected following oral exposure is the epithelium of the stomach (Boorman et al. 1986; Danse et al. 1984). This is presumably a result of direct contact between bromomethane and the gastrointestinal epi,thelium. Based on this effect, an intermediate-duration oral MRL of 0.003 mg/kg/day has been derived. It is likely that this effect (which has only been observed in animals dosed with concentrated solutions of bromomethane dissolved in oil) would be much less pronounced if exposure occurred via ingestion of more dilute solutions of bromomethane in water. However, this has not been studied.

Dermal/Ocular Effects. Direct dermal contact with bromomethane can cause mild to severe skin lesions such as erythema, itching, and blisters (Butler et al. 1945; Hezemans-Boer et al. 1988; Watrous 1942). These lesions, which normally heal within 2-4 weeks after exposure, have only been noted after exposure to liquid bromomethane or very high concentrations of vapor, and are unlikely to occur in persons exposed to bromomethane in the environment.

Immunological Effects. No studies were located regarding immunological effects in humans or animals after exposure to bromomethane. In the absence of any data, it is not possible to predict whether this is an effect of concern in exposed humans.

Neurological Effects. Humans acutely exposed to high concentrations of bromomethane vapor nearly always experience injury to the central nervous system. Initial effects, which usually occur within a few hours of exposure, include headache, weakness, and nausea (Marraccini et al. 1983; Wyers 1945), and may also include blurred or double vision (Chavez et al. 1985; Johnstone 1945). Depending on exposure level, these symptoms may progress into ataxia, tremors, and clonic seizures (Prain and Smith 1952; Prockop and Smith 1986). These effects typically begin to wane after several days, but recovery may not

be complete even after many months (Longley and Jones 1965; Rathus and Landy 1961). In rats, brain neurotransmitter levels were decreased following an acute exposure to 31 ppm (Honma 1987). Based on the NOAEL of 16 ppm identified by this study, an acute inhalation MRL of 0.05 ppm has been derived.

Only limited information is available on the effects of long-term inhalation exposure of humans to low levels of bromomethane. Headache, weakness, and increased prevalence of neurological signs such as muscle ache, fatigue, dizziness, and ataxia have been noted in workers exposed for extended periods in the workplace (Anger et al. 1986; Hine 1989; Kantarjian and Shasheen 1963; Kishi et al. 1988). No cases of severe neurological effects from long-term exposure to low levels have been noted in humans, but intermediate or chronic inhalation exposure of animals to bromomethane vapor is known to result in moderate to severe neurological injury. Rabbits and monkeys appear to be the most sensitive species, with convulsions and paralysis occurring at exposure levels of 33-66 ppm for 6 months (Irish et al. 1940). Continuous exposure to concentrations of 10 ppm decreased neurotransmitter levels in rats (Honma et al. 1982). Based on the NOAEL of 5 ppm identified by this study, an intermediate inhalation MRL of 0.05 ppm has been derived. The chronic exposure level leading to neurological effects in humans is not known precisely, but Anger et al. (1986) reported mild effects in workers exposed to an average of about 2.3 ppm. Based on this, a chronic inhalation MRL of 0.005 ppm has been derived.

No studies were located regarding neurological effects in humans or animals following oral exposure to bromomethane. Based on the clear neurological effects produced by inhalation exposure, it seems likely such effects would also be of concern following acute or repeated oral intake of adequate doses.

The mechanism of bromomethane-induced neurotoxicity is not known. It is generally agreed that effects are not the result of metabolic breakdown products such as methanol or bromide, since neither the characteristic effects nor the dose dependency correspond to those of the metabolites (Clarke et al. 1945; Honma et al. 1985). Rather, it is more likely that bromomethane acts by alkylating key cellular components such as enzymes (Lewis 1948; Rathus and Landy 1961).

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to bromomethane. Several studies of animals exposed to bromomethane vapors up to 70 ppm did not detect developmental effects, even though these concentration levels resulted in maternal toxicity (Hardin et al. 1981; Sikov et al. 1980). However, exposure of rabbits to 80 ppm during gestation resulted in increased incidence of several developmental anomalies in the off-spring (Breslin et al. 1990). These data suggest bromomethane may cause developmental effects, but only at high doses where other effects would also be of concern.

Reproductive Effects. No studies were located regarding reproductive effects in humans after exposure to bromomethane. Inhalation exposure of male rats to high levels of bromomethane (120-400 ppm) has resulted in decreased sperm production along with testicular degeneration and atrophy (Drew 1984; Eustis et al. 1988; Kato et al. 1986). However, exposures up to 70 ppm do not appear to interfere with reproductive functions in male (McGregor 1981) or female rats (Hardin et al. 1981; McGregor 1981; Sikov et al. 1980). It is difficult to judge from these data whether adverse reproductive effects are likely to occur in exposed humans, but it seems probable that the respiratory, neurological, and renal effects will normally be of greatest clinical concern.

Genotoxic Effects. Bromomethane has produced positive results in a number of mutagenicity test systems, both in vitro (Table 2-4) and in vivo (Table 2-5). This effect does not appear to require metabolic activation, which is consistent with the fact the bromomethane is a direct-acting alkylating agent which can methylate DNA (Ikawa et al. 1986; Starratt and Bond 1988). This property suggests that bromomethane might be carcinogenic, but this has not been established (see below).

Carcinogenic Effects. No epidemiological studies were located on cancer incidence in humans exposed specifically to bromomethane. One study of workers exposed to a variety of brominated chemicals noted that bromomethane was the only common exposure of two men who died of testicular cancer (Wong et al. 1984). However, this does not establish that bromomethane was the causative agent. Chronic inhalation studies performed in mice and rats revealed no evidence of carcinogenic effects at exposure levels of 33-90 ppm (Reuzel et al. 1987; Yang 1990). Rats given daily oral doses of 50 mg/kg/day for 90 days developed inflammation and keratosis of the forestomach, along with lesions that were onginally interpreted as squamous carcinomas (Danse et al. 1984). However, reevaluation of the histological specimens by NTP scientists indicated that the forestomach lesions in this study were hyperplastic but not neoplastic. A subsequent study also found hyperplasia but no neoplasia in rat forestomach (Boorman et al. 1986) after 13 weeks of exposure. After 25 weeks, one animal developed a lesion that was judged to be a very early carcinoma. These results are too limited (both in number of animals and exposure duration) to draw firm conclusions, but in view of the alkylating ability and positive mutagenicity finding for this chemical, it seems possible that longer-term exposure might lead to measurable increases in tumor frequency, EPA considers that the data currently available are inadequate to evaluate the carcinogenic potential of bromomethane, and has assigned this chemical to Group D (not classifiable as to human carcinogenicity) (IRIS 1989).

Similarly, the International Agency for Research on Cancer has placed bromomethane in Group 3 (not classifiable as to carcinogenic potential).

TABLE 2-4. Genotoxicity of Bromomethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Escherichia coli Sd-4 (forward mutation)	Gene mutation	No data	+	Djalali-Behzad et al. 1981
E. Coli WP2 hcr (gene reversion)	Gene mutation	+	+	Moriya et al. 1983
Salmonella typhimurium (TA100, TA1535) (gene reversion)	Gene mutation	+	+	Moriya et al. 1983
S. typhimurium (TA98, TA1537, TA1538) (gene reversion)	Gene mutation	-	-	Moriya et al. 1983
S. typhimurium (TA100) (dessicator system)	Gene mutation	No data	-	Simmon and Tardiff 1978
S. typhimurium (TA98) (plate test)	Gene mutation	-	-	Kramers et al. 1985
S. typhimurium (TA100) (plate test)	Gene mutation	+	+	Kramers et al. 1985
Klebsiella pneumoniae (ur^- pro^-) (fluctuation test)	Gene mutation	No data	+	Kramers et al. 1985
Eukaryotic organisms:				
Mouse lymphoma cells (L5178YTK+/-) (forward mutation)	Gene mutation	No data	+	Kramers et al. 1985
Syrian hamster embryo cells	Enhanced transformation by SA7 adenovires	No data	-	Hatch et al. 1983
Human peripheral lymphocytes	Sister chromatid exchanges	No data	+	Tucker et al. 1986
Rat liver cells	Unscheduled DNA synthesis	No data	-	Kramers et al. 1985
Human embryonic intestinal cells	Unscheduled DNA synthesis	-	-	McGregor 1981

+ = positive result; - = negative result; (+) = weakly positive result

TABLE 2-5. Genotoxicity of Bromomethane *In Vivo*

Species (test system)	End point	Results	Reference
Nonmammalian systems:			
Drosophila melanogaster Berlin-K wild type (sex-linked recessive lethal test)	Gene mutation	+	Kramers et al. 1985
D. melanogaster (somatic wing spot assay)	Recombinogenic activity	+	Katz 1987
D. melanogaster Oregon-K wild type (sex-linked recessive lethal test)	Gene mutation	-	McGregor 1981
Mammialian systems:			
Rat (bone marrow cells) CD Sprague-Dawley	Chromosome aberrations	-	McGregor 1981
Rat CD Sprague-Dawley	Dominant lethal	-	McGregor 1981
Mouse B6C3F1	Sperm abnormality	-	McGregor 1981
Mouse (liver and spleen cells) CBA	DNA alklyation	+	Djalali-Behzad et al. 1981
Rat (bone marrow cells) F344	Micronuclei inductions	+	Ikawa et al. 1986
Mouse (bone marrow cells) BDF_1	Micronuclei inductions	+	Ikawa et al. 1986

+ = positive result; - = negative result

2.5 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 or 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 biologic 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 bromomethane are discussed in Section 2.5.1.

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 often not substance specific. They also may not be directly adverse, but can'indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by bromomethane are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Bromomethane

The most convenient biomarker of bromomethane exposure is the concentration of bromide ion in the blood or serum. The relationship between bromide ion concentrations and the severity of effects in exposed people was

investigated by Alexeeff and Kilgore (1983), who assembled and evaluated data from a large number of case reports. Serum bromide levels are usually below 15 ppm in unexposed people. In bromomethane-exposed people, levels up to 80 ppm may occur without any obvious clinical signs, while levels of 150-400 ppm are observed in people with moderate to severe symptoms. Bromide is cleared from blood with a half-life of about 12 days in healthy people, and half-lives of 3-15 days have been observed in bromomethane-exposed people (Alexeeff and Kilgore 1983). Consequently, the correlation between serum bromide levels and severity of effects is most apparent within the first 1-2 days of exposure, and there may be little correlation later. Bromide ion is cleared mainly by excretion in the urine, but no studies were located on the use of urinary bromide levels as a biomarker of bromomethane exposure.

Measurement of parent bromomethane (e.g., in expired air, blood, or urine) has not been investigated as a possible biomarker of exposure in humans, mainly because studies in animals suggest that bromomethane is cleared so rapidly (half-lives of 15-30 min) that this is unlikely to be useful for monitoring environmental exposures. Similarly, methanol and other organic metabolites are also cleared with short half-lives (Honma et al. 1985; Jaskot et al. 1988), so they are also unlikely to be useful in biomonitoring. Formation of stable methylated adducts such as S-methylcysteine in hemoglobin is known to occur in animals following inhalation exposure to bromomethane (Iwasaki 1988a, 1988b), but this has not been developed as a biomonitoring method for humans.

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

2.5.2 Biomarkers Used to Characterize Effects Caused by Bromomethane

As discussed in Section 2.2, the effects that are most often observed in humans exposed to bromomethane vapor are central nervous system injury (disturbed vision, tremor, convulsions, coma), lung irritation (edema, impaired respiration), and renal injury (oliguria or anuria). Of these, neurological or neurobehavioral signs appear to be the most sensitive indication of effect, since preclinical symptoms can be observed in humans exposed to low levels of bromomethane in the workplace (Anger et al. 1986; Kishi et al. 1988; Verberk et al. 1979). Of course, positive findings for end points of this sort (headache, weakness, ataxia, nausea, double vision, abnormal electroencephalogram) are not specific indicators of bromomethane exposure, since other chemicals or diseases may produce similar neurological changes. Biomarkers that are useful in evaluating neurological effects have been discussed by Johnson (1987).

2.6 INTERACTIONS WITH OTHER CHEMICALS

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

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No studies were located to suggest that any specific human subpopulation may be more susceptible to bromomethane than average, although it may be expected that the young, the elderly, and people with lung, kidney, or neurological disease might be more readily affected than healthy adults. Studies in animals reveal that there are differences in sensitivity between species (e.g., Irish et al. 1940), and some studies have noted small differences in sensitivity between males and females (Eustis et al. 1988). It is not known if these differences apply to humans.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to bromomethane. However, 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 bromomethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to bromomethane is most likely to occur by inhalation or dermal contact (see Chapter 5). Inhalation exposure may cause neurological, respiratory and renal damage. Dermal contact may cause skin lesions while oral exposure leads to digestive tract mucosal membrane irritation (see Section 2.2).

Procedures that have been used to reduce absorption of bromomethane include the following. If dermal exposure to concentrated bromomethane occurs, contaminated clothing is removed and the skin thoroughly washed with soap or mild detergent and water (Bradford 1990; Ellenhorn and Barceloux 1988; Morgan 1982). General burn care may also be necessary in severe cases. If inhalation exposure is sufficient to cause lung damage, administration of oxygen, mechanical ventilatory support, and administration of diuretics and bronchodilators may be required to reduce the effects of pulmonary edema (Bradford 1990; Morgan 1982). If seizures occur, treatment with standard anticonvulsants may be required. It is unlikely that exposures near waste sites would be large enough to require interventions of this sort.

Intramuscular administration of sulfhydryl agents such as dimercaprol has been recommended to improve elimination of bromomethane, since bromomethane reacts with sulfhydryl groups (Bradford 1990). However, this treatment may cause troublesome side effects, and there is no evidence that such agents are effective when administered after exposure has occurred (Alexeeff and Kilgore 1983; Ellenhorn and Barceloux 1988; Rathus and Landy 1961). Treatment with N-acetylcysteine has been suggested, since this compound is a precursor to glutathione, and elevated glutathione levels may be protective against bromomethane toxicity (Bradford 1990). It is not expected that treatments of this sort would normally be required for low dose exposures that occur near waste sites. Additional details regarding treatment following bromomethane intoxication may be found in the cited references.

2.9 ADEQUACY OF THE DATABASE

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

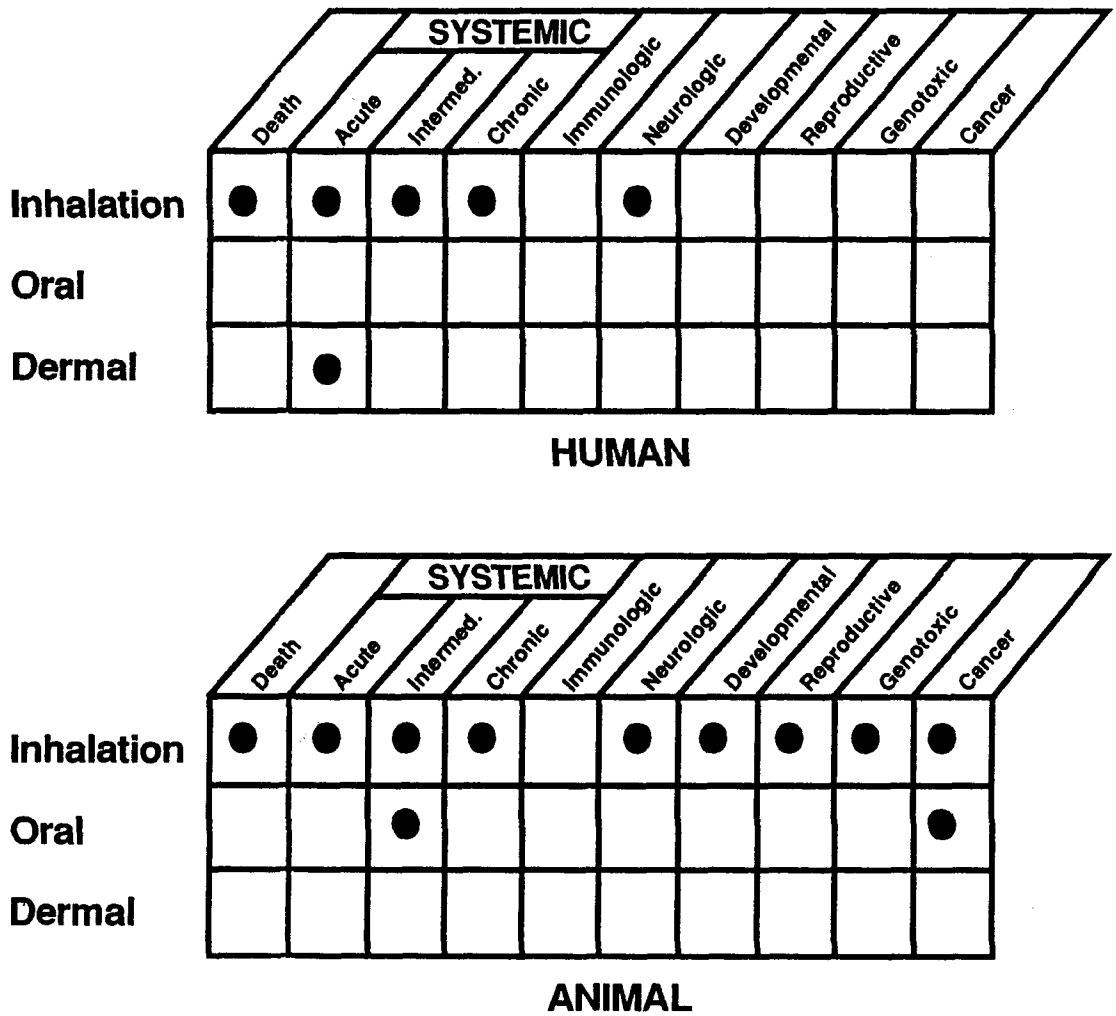
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Bromomethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to bromomethane are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of bromomethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

As shown in the upper portion of Figure 2-3, there are numerous studies of humans exposed to bromomethane by the inhalation route. These have focused mainly on the systemic and neurological effects of exposure, and other endpoints (immunological, developmental, reproductive, genotoxic, cancer) have not been investigated. There are also numerous case reports on the direct effects of bromomethane vapor or liquid on skin, but other effects have not been studied.

FIGURE 2-3. Existing Information on Health Effects of Bromomethane



● Existing Studies

Studies in animals (shown in the lower half of Figure 2-3) have also focused on inhalation exposure, and most endpoints (except immunotoxicity) have been investigated. In contrast, the effects of oral exposure have received only limited attention, focusing mainly on the inflammatory and possible carcinogenic effects in the stomach. No information was located on dermal exposure of animals.

2.9.2 Data Needs

Acute-Duration Exposure. There is sufficient information from studies of humans (Holling and Clarke 1944; Johnstone 1945; Miller 1943; Wyers 1945) to identify the principal target tissues of bromomethane following acute inhalation exposure (lung, kidney, nervous system). Studies in animals (Alexeeff et al. 1985; Eustis et al. 1988; Honma 1987; Honma et al. 1985, 1987; Hurtt et al. 1987a, 1988a; Hurtt and Working 1988) support and confirm these observations. These data are sufficient to derive an acute inhalation MRL (Honma 1987). Information is available on dermal effects following exposure of humans (but not animals) both to the vapor (Hezemans-Boer et al. 1988; Zwaveling et al. 1987) and the liquid (Longley and Jones 1965; Watrous 1942). While the dose-response curve for dermal effects is not well-defined, it is apparent that this is of concern mainly at high levels, and is unlikely to be of concern at exposure levels likely to be encountered in the environment or near waste sites.

No information is available on acute oral exposure of humans or animals to bromomethane. Extrapolation from acute inhalation data is probably not appropriate, since some of the effects (both inhalation and oral) are due to point-of-contact irritation. However, acute oral toxicity studies are probably not essential, since oral exposure of humans to acutely toxic levels of bromomethane is not likely to occur due to the high volatility of the compound.

Intermediate-Duration Exposure. Limited information is available on the effects of intermediate-duration inhalation exposure of humans to bromomethane (Kantarjian and Shasheen 1963; Viner 1945). It appears clear that the target tissues are the same as for acute-duration exposure, but dose-response data from intermediate-duration human studies are not available. However, there are a number of studies in animals that do provide quantitative data (Anger et al. 1981; Eustis et al. 1988; Haber 1987; Honma et al. 1982; Ikeda et al. 1980; Irish et al. 1940; Kato et al. 1986), and are sufficient to derive an intermediate-duration inhalation MRL (Honma et al. 1982). Further data from an intermediate-duration (90-day) study in animals recently completed by the NTP will help strengthen this data set, and additional intermediate-duration inhalation studies may not be required.

No information is available on the effects of intermediate-duration oral exposure in humans, but two animal studies (Boorman et al. 1986; Danse et al. 1984) provide sufficient data to identify the main target tissue (the stomach epithelium) and to define the dose-response relationship for this effect. These studies are suitable for derivation of an intermediate oral MKL, but

further studies would still be helpful to search more specifically for possible subclinical neurological effects. This is important since neurological effects appear to be the most sensitive effect by the inhalation route, and people may be exposed to low levels of bromomethane in drinking water drawn from contaminated groundwater sources. No information is available on intermediate-duration dermal exposure to bromomethane. However, humans are not likely to experience significant dermal exposures to bromomethane near waste sites, so research in this area does not appear to be essential.

Chronic-Duration Exposure and Cancer. There are several studies of humans chronically exposed to bromomethane in air (Anger et al. 1986; Chavez et al. 1985; Hine 1969; Kishi et al. 1988). These studies indicate neurological effects are the most sensitive effect following chronic exposure. Quantitative exposure data are limited, but are sufficient for derivation of a chronic inhalation MRL. The human data are supported by chronic inhalation studies in animals (Anger et al. 1986; Haber 1987). Nevertheless, further studies of humans exposed to low levels of bromomethane in the workplace would be helpful in order to increase the confidence in the chronic MRL. This is important since humans could be exposed to low levels of bromomethane in air near some waste sites. No information is available on effects in humans or animals after chronic oral exposure. Extrapolation from the inhalation route may not be appropriate, since two intermediate-duration studies in animals (Boorman et al. 1986; Danse et al. 1984) indicate that the stomach and not the nervous system is the main target following oral exposure. Chronic oral studies in animals would be helpful in evaluating human health risk by this route. This is important since humans might be exposed to low levels of bromomethane in drinking water drawn from contaminated groundwater sources.

No information is available from studies of humans on the carcinogenic effects of inhalation exposure to bromomethane, but chronic inhalation studies in mice and rats (Reuzel et al. 1987; Yang 1990)yielded no evidence of carcinogenic effect. Nevertheless, epidemiological investigations of the incidence of cancer in workers who use bromomethane would be helpful in assessing the cancer risk to humans who could be exposed to low levels of bromomethane in air near some waste sites.

The carcinogenic effects of oral exposure to bromomethane have been studied in two intermediate-duration studies (Boorman et al. 1986; Danse et al. 1984), but not in any chronic studies. The results suggest that bromomethane might be carcinogenic, but the data are difficult to interpret with certainty. Extrapolation from inhalation studies would not be appropriate, since the response observed is at the portal of entry (the forestomach). This is consistent with the concept that bromomethane is a direct-acting alkylating agent. Chronic oral exposure studies in animals would be valuable for clarifying the cancer risk of ingested bromomethane. This is needed since some people could be exposed to low levels of bromomethane in drinking water drawn from contaminated groundwater sources.

Genotoxicity. Bromomethane is a direct-acting alkylating agent, and there are studies both in vivo (Djalali-Behzad et al. 1981) and in vitro (Starratt and Bond 1988) which establish that it can methylate DNA. Studies of mutagenic potential in bacterial test systems have been mostly positive (Djalali-Behzad et al. 1981; Kramers et al. 1985; Moriya et al. 1983), as have several in vitro tests using eukaryotic cell types (Kramers et al. 1985; Tucker et al. 1986) and several in vivo tests in animals (Ikawa et al. 1986; Katz 1987; Kramers et al. 1985). Investigation of possible sister chromatid exchange or chromosome aberrations in peripheral lymphocytes of humans exposed in the workplace would be helpful in confirming the genotoxic potential of bromomethane, although studies in animals suggest that this effect may only be measurable at high exposure levels.

Reproductive Toxicity. No information was located regarding reproductive effects in humans. Intermediate-duration inhalation studies in animals (Eustis et al. 1988; Kato et al. 1986) indicate that the testes may undergo degeneration and atrophy at high exposure levels, but the doseresponse curve is not well defined. Further studies in animals to identify the threshold for this end point would be helpful in confirming that neurological effects are the most sensitive endpoint of toxicity. Two studies in female animals (Hardin et al. 1981; Sikov et al. 1980) have not detected reproductive effects even at doses that produced maternal toxicity. Additional studies to confirm this in several different animal species would be helpful.

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

Developmental Toxicity. There is no information on developmental effects in humans exposed to bromomethane, but two inhalation exposure studies in animals (rats and rabbits) indicate that developmental or teratogenic effects do not occur even at doses that are toxic to the dam (Hardin et al. 1981; Sikov et al. 1980). No information is available on developmental effects after oral exposure of animals to bromomethane, but the inhalation data suggest that is not likely to be of concern.

Immunotoxicity. No information was located on the immunological effects of bromomethane in humans or animals exposed by any route. A battery of immune function tests in several animal species exposed to bromomethane by the inhalation and the oral routes would be valuable in determining if the immune system is adversely affected, and if so, in determining species and route specificity, as well as the threshold for those effects.

Neurotoxicity. There is clear evidence from studies in humans and animals that the nervous system is adversely affected by inhalation exposure to bromomethane. This includes evidence of clinical neurological signs and

behavioral changes (Anger et al. 1986; Behrens and Dukes 1986; Clarke et al. 1945; Greenberg 1971; Hine 1969; Kantarjian and Shasheen 1963; Longley and Jones 1965; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Prockop and Smith 1986; Rathus and Landy 1961; Viner 1945; Wyers 1945), as well as biochemical changes and histological lesions in the brain (Alexeeff et al. 1985; Eustis et al. 1988; Honma 1987; Honma et al. 1982; Hurtt et al. 1987a). Although quantitative exposure information from humans is limited, the thresholds for acute, intermediate, and chronic inhalation exposures are known with reasonable precision. No information is available on humans exposed by the oral route, but two oral studies in rats (Boorman et al. 1986; Danse et al. 1984) did not produce any visible neurological signs. It is not known if this apparent route specificity is due simply to differences in dose, or to differences in absorption, distribution, or metabolism between routes. For this reason, additional oral dose-response studies in animals that focus specifically on histological, biochemical, or functional tests of nervous system injury would be valuable. If these tests indicate that the nervous system is not injured following oral exposure, additional toxicokinetic studies would be helpful in understanding the basis for the distinction between inhalation and oral effects.

Epidemiological and Human Dosimetry Studies. As noted previously, there are many reports on the adverse effects of bromomethane in humans. Most studies involve people with accidental acute high-level exposures in air, but there are also several studies of workers with repeated low-level exposures (Anger et al. 1986; Kishi et al. 1988; Verberk et al. 1979). These studies are sufficient to identify the main health effects of concern and to estimate the exposure levels that lead to effects. However, further studies of workers who are exposed to low levels during manufacture or use of bromomethane would be helpful, if reliable current and past exposure data are available. These additional quantitative human data would be valuable in increasing the confidence in the estimated safe exposure levels in the workplace and the environment. This would improve the ability to evaluate potential risk to humans exposed to low levels of bromomethane in air near waste sites.

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

animals would be helpful in determining the sensitivity of these biomarkers and evaluating their usefulness in monitoring people exposed to low levels of bromomethane near waste sites.

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

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

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

Mitigation of Effects. Recommended methods for the mitigation of acute effects of inhalation exposure to bromomethane include mechanical ventilatory support, administration of oxygen and supportive therapy for pulmonary edema (Bradford 1990; Morgan 1982). Administration of thiol compounds to react with absorbed bromomethane has also been suggested (Bradford 1990). Further studies on the efficacy of post-exposure treatment with agents of this type would be valuable. No information was located concerning mitigation of effects of lower-level or longer-term exposure to bromomethane. Further information on techniques to mitigate such effects would be useful in

determining the safety and effectiveness of possible methods for treating bromomethane-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

The NTP has recently completed a series of inhalation studies in rats and mice, including both noncancer and cancer evaluations. The results of these studies will provide valuable new data on the toxicity of this compound in animals. Dr. W. Kilgore (University of California, Davis) is studying methods for detecting exposure of field workers to bromomethane, and is obtaining data on health effects in these workers.