TOXICOLOGICAL PROFILE FOR BROMOMETHANE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

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

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

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

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about bromomethane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Bromomethane has been found in at least 12 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for bromomethane. As EPA evaluates more sites, the number of sites at which bromomethane is found may change. This information is important for you to know because bromomethane may cause harmful health effects and because these sites are potential or actual sources of human exposure to bromomethane.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as bromomethane, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS BROMOMETHANE?

Bromomethane (also called methyl bromide) is a colorless gas without much smell. Some bromomethane is formed in the ocean, probably by algae or kelp. However, most is made by humans to kill various pests (rats, insects, fungus, etc.) that might be present in homes, foods, or soil. Some bromomethane is also used to make other chemicals.

Bromomethane is usually stored in sealed containers to keep it from evaporating. If leaking containers of bromomethane are put in a waste site, most of the bromomethane will probably escape into the air. Small amounts might leak into the soil or pass through the soil and dissolve in underground water. Bromomethane has been found in underground water at two hazardous waste sites on the NPL.

Bromomethane breaks down in the environment to other chemicals. In air, it usually takes about 11 months for half the bromomethane that was released to disappear. In underground water, it usually takes about 1 month for half the bromomethane to break down.

More information on the properties and use of bromomethane and how it behaves in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO BROMOMETHANE?

Because bromomethane is a gas, you are most likely to be exposed by breathing it in air. In most places around the world, levels in air are usually less than 0.025 parts of bromomethane per billion parts of air (ppb). Some cities have higher levels (up to about 1-2 ppb) because of releases from chemical factories and automobile exhausts. You will probably not be exposed to high levels unless you are near a place where bromomethane is being used for fumigation. Workers who fumigate homes or fields may be exposed to very high levels if proper safety precautions are not followed. Because bromomethane evaporates so quickly, it is usually not found in food, surface water, or soil.

More information on how you might be exposed to bromomethane is given in Chapter 5.

1.3 HOW CAN BROMOMETHANE ENTER AND LEAVE MY BODY?

If bromomethane is present at a waste site, you are most likely to be exposed to it by breathing the vapors in contaminated air. You might also be exposed by drinking water from contaminated wells, although this is less likely. If you breathe in bromomethane, about half of it will pass through your lungs and enter your blood. Studies in animals suggest that if you swallow bromomethane in water, nearly all of it will pass through your stomach or intestines and enter your body. Bromomethane that enters your body either from your lungs or stomach is quickly spread throughout your body by your blood. Most bromomethane in your body is broken down into other chemicals, and these chemicals leave your body in the urine or in the air you breathe out. This usually begins happening within minutes, and is usually nearly complete within several days. We do not know how much bromomethane can enter your body through the skin, but the amount is probably small.

More information on how bromomethane enters and leaves your body is given in Chapter 2.

1.4 HOW CAN BROMOMETHANE AFFECT MY HEALTH?

If you breathe bromomethane, you may develop a headache and begin to feel weak and nauseated several hours later. If you breathe a large amount, fluid may build up in your lungs and it may be hard to breathe. You may have muscle tremors, and sometimes even seizures. Your kidneys may also be injured, and urine production may slow or stop. In severe cases, these effects can lead to death. In less serious cases, most of these effects usually disappear after several weeks, but some of the effects may never go away.

Studies in animals suggest that if you swallow bromomethane, you might experience stomach irritation but would probably not experience lung, kidney, or brain injury. Bromomethane that gets on your skin can cause itching, redness, and blisters.

Studies in animals also suggest that bromomethane does not cause birth defects and does not interfere with normal reproduction except at high exposure levels. Animals that breathed bromomethane for 2 years did not develop cancer. Animals that swallowed bromomethane for 25 weeks had changes in their stomachs that could have been an early sign of cancer, but we do not know if swallowing bromomethane for a longer time would cause cancer. Both the International Agency for Research on Cancer and the EPA have determined that bromomethane is not classifiable as to its carcinogenicity in humans.

More information on the health effects of bromomethane in humans and animals can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO BROMOMETHANE?

Several tests are available to tell whether you have been exposed to bromomethane, but ‘each has limitations. The most direct test measures bromomethane in your blood or in the air you breathe out. However, this test is not usually used because most bromomethane does not stay in the body very long (see Section 1.3) and special measuring equipment is needed. More often, the main breakdown product of bromomethane (bromide) is measured in blood samples. Bromide is normally present in the blood of all people, but the levels of bromide increase when people are exposed to bromomethane. The amount of increase depends on the level of exposure. Tests for bromide are only useful if done within 1-2 days following exposure, and are not very helpful in predicting if exposed persons will have health effects or how serious the effects will be, because not all people respond to bromomethane the same way.

More information on how bromomethane can be measured in exposed humans is presented in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Concentrated bromomethane can be very dangerous, so the EPA allows only licensed professional fumigators to buy or use bromomethane. The government does not have any regulations at present about how much bromomethane can be present in outdoor air or water, but EPA requires water companies to test for this chemical in their water. The Food and Drug Administration (FDA) has set limits of 125-400 parts of bromide per million parts of food (ppm) for how much bromide may remain in food after the food is treated with bromomethane. The Occupational Safety and Health Agency (OSHA) limits the average level of bromomethane in workplace air to 5 ppm, and recommends that exposures be reduced to the lowest level feasible.

More information on government rules regarding bromomethane can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia '30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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

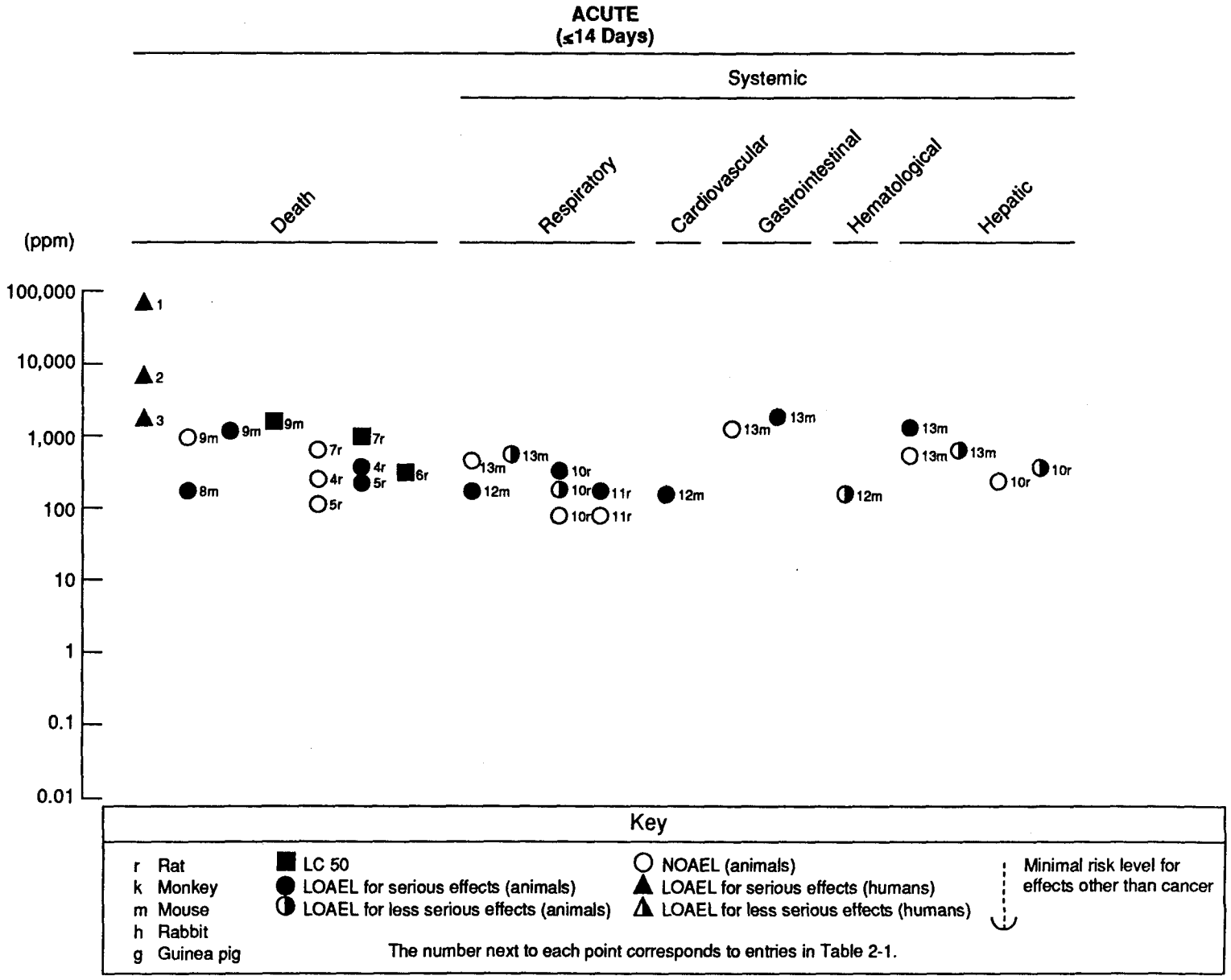


FIGURE 2-1 (Continued)

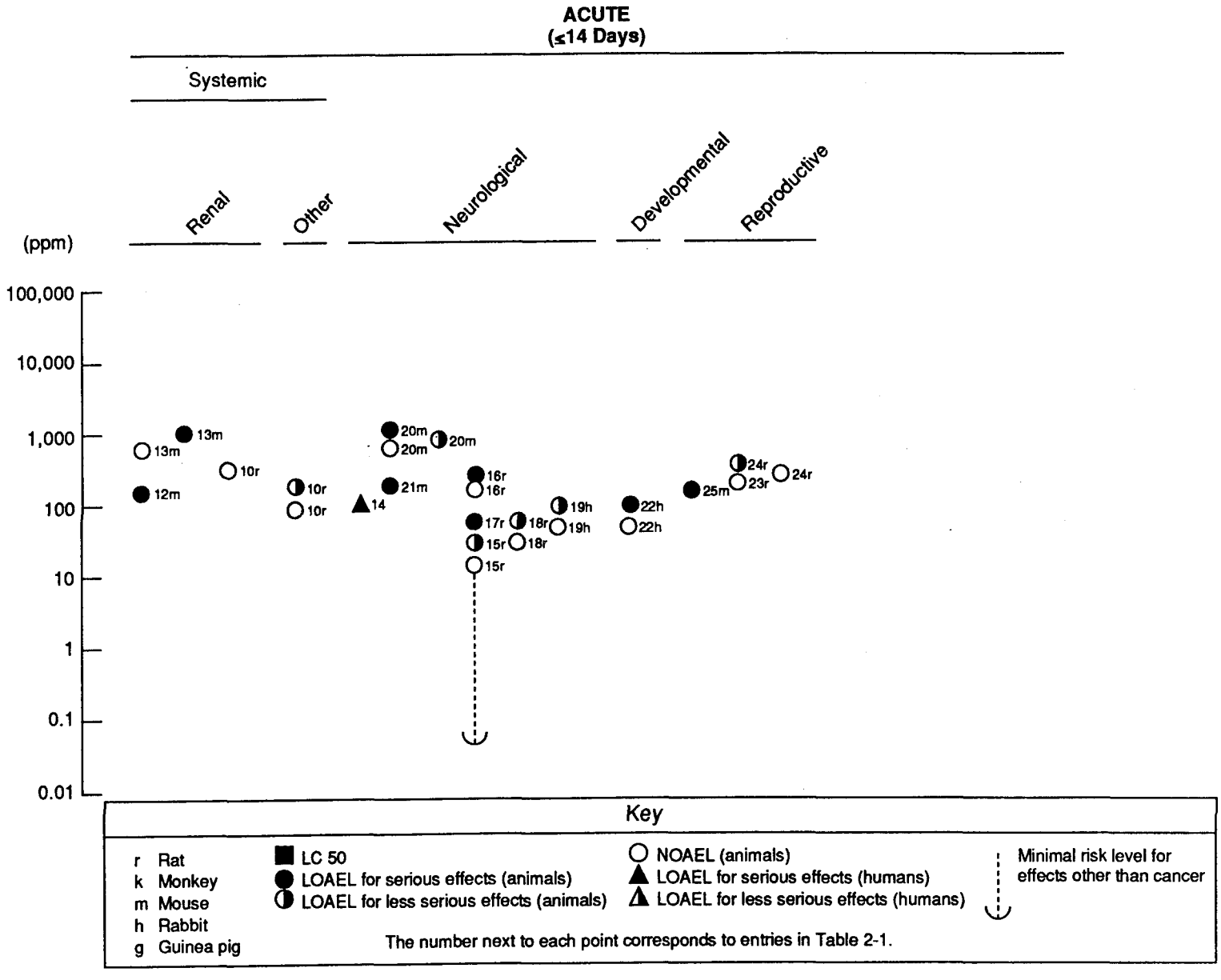


FIGURE 2-1 (Continued)

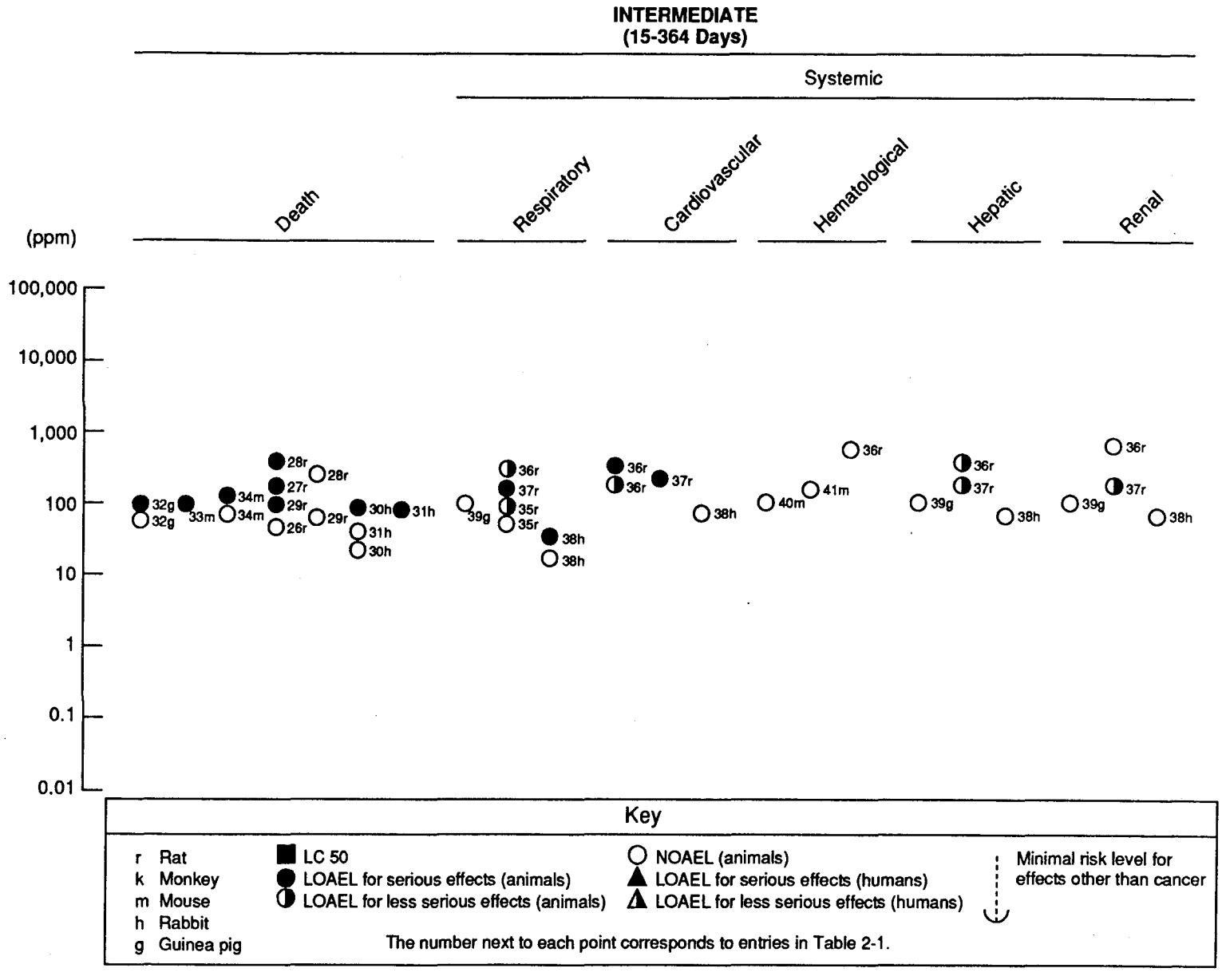


FIGURE 2-1 (Continued)

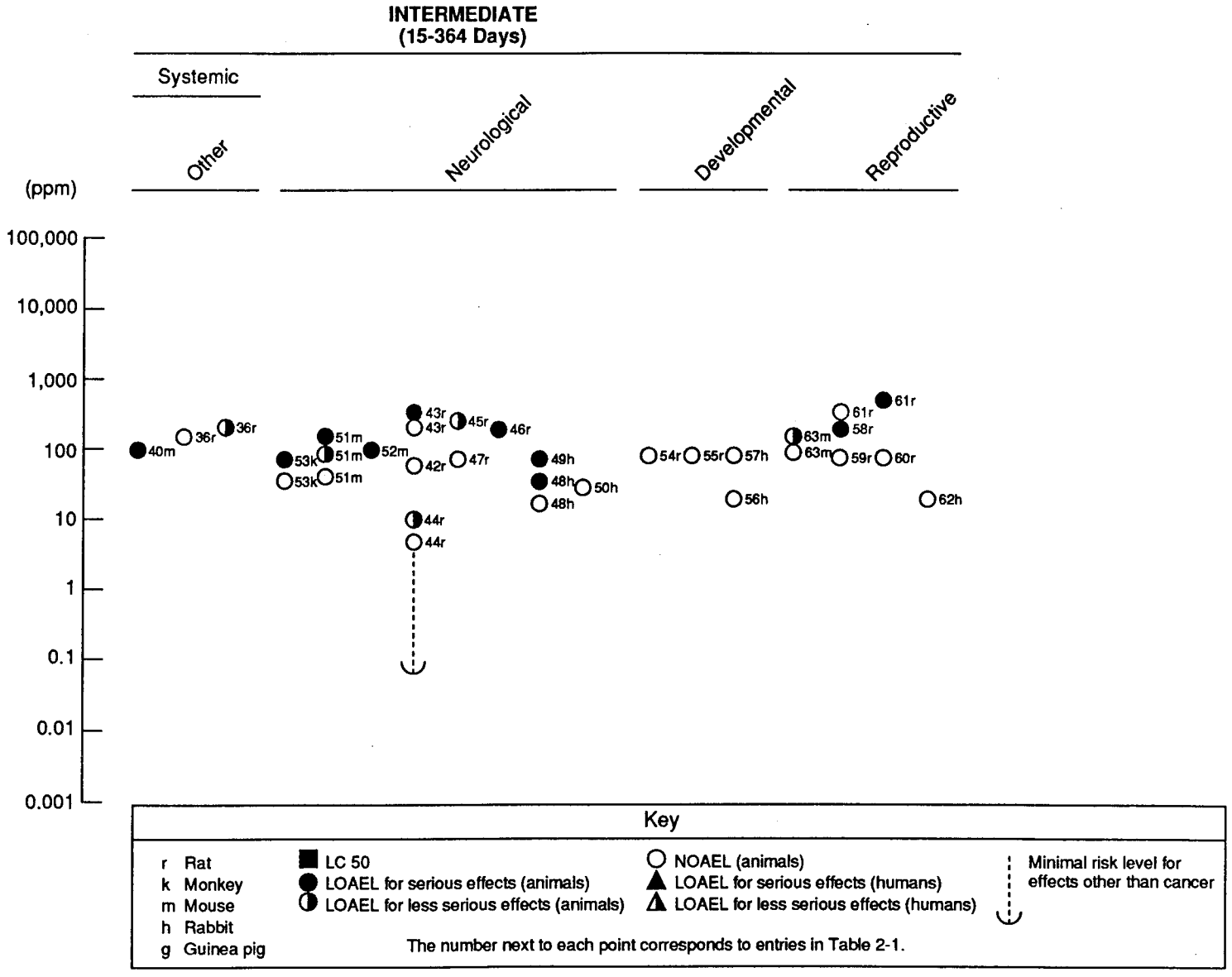
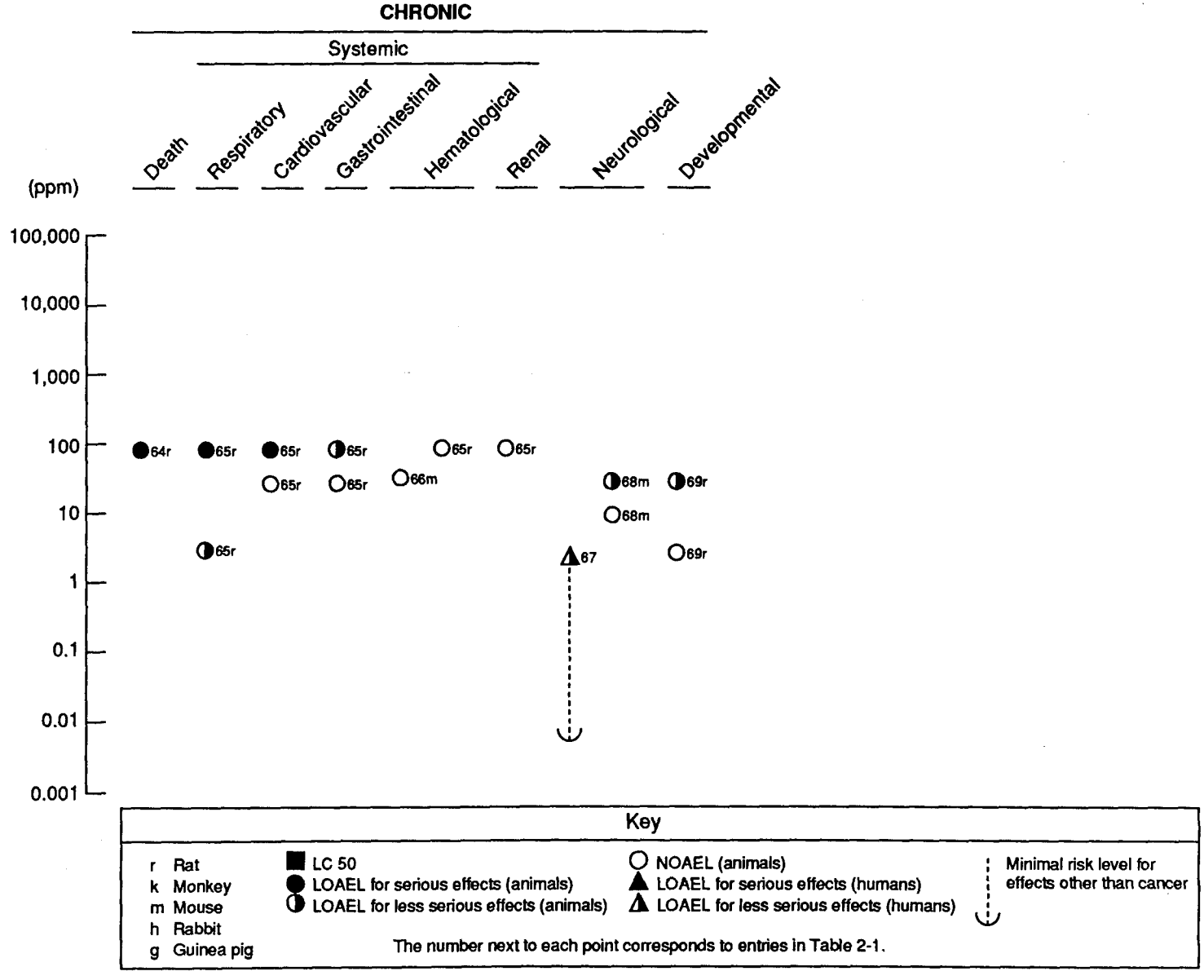


FIGURE 2-1 (Continued)



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.

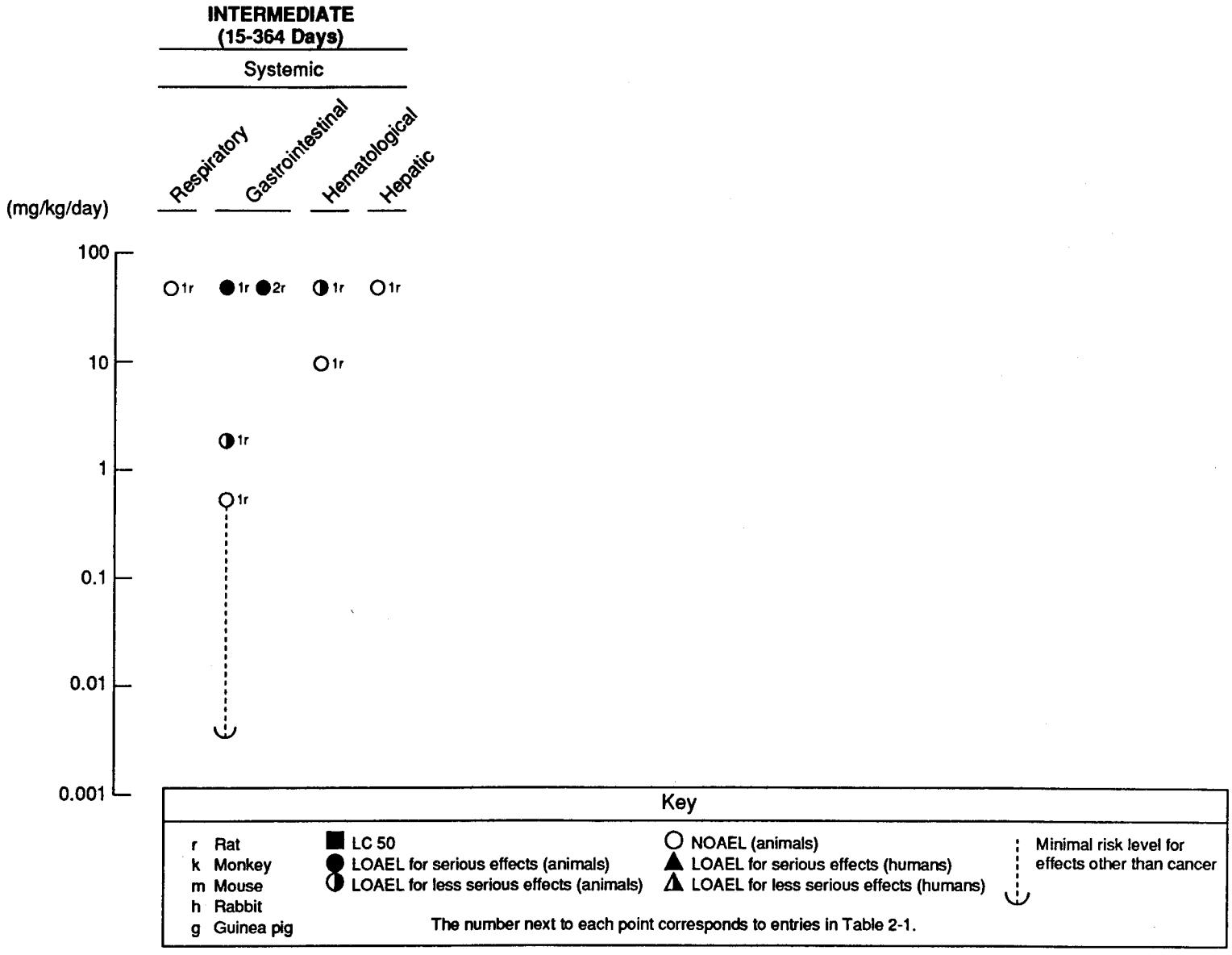
TABLE 2-2. Levels of Significant Exposure to Bromomethane - Oral

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.

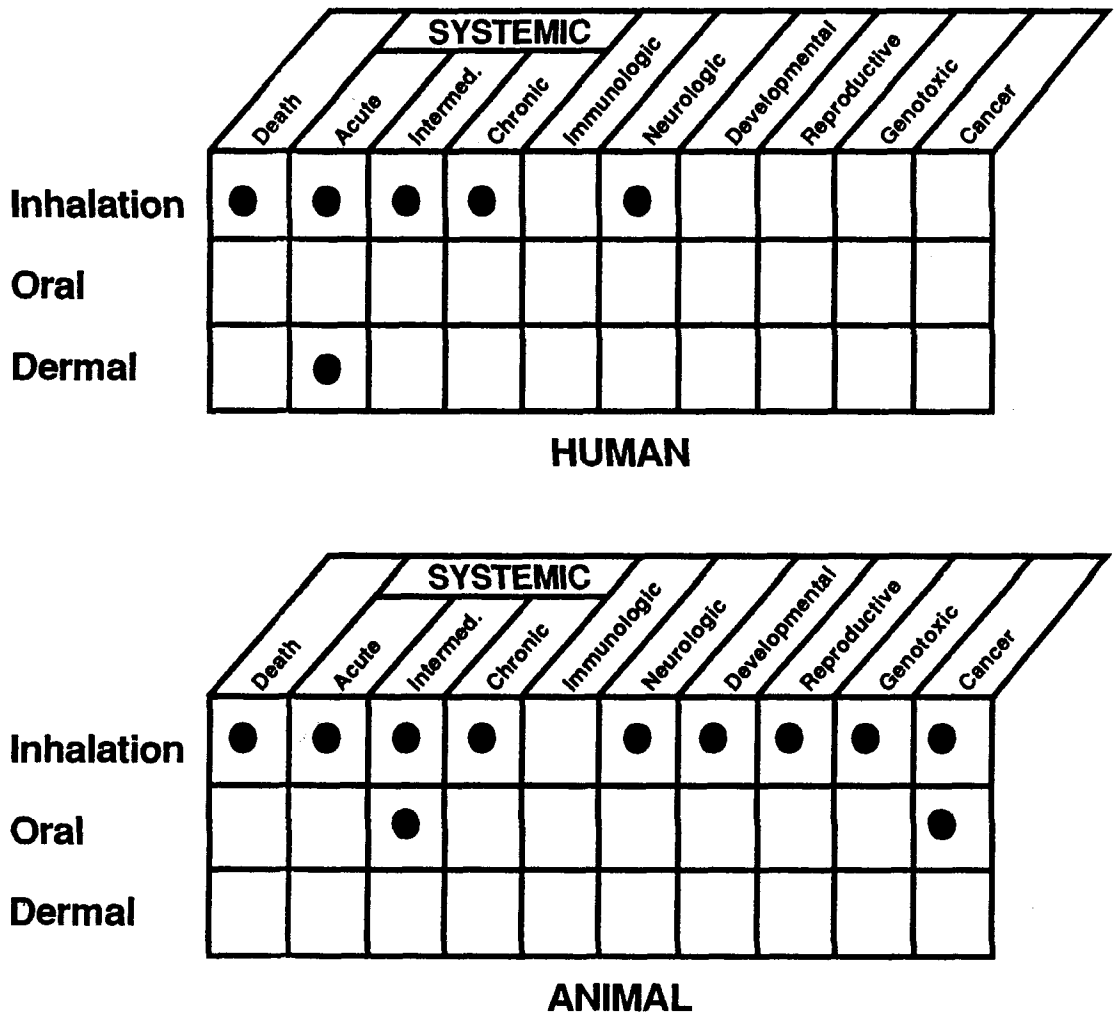
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data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

3. CHEMICAL AND PHYSICAL INFORMATION

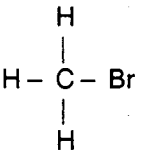
3.1 CHEMICAL IDENTITY

Table 3-1 lists common synonyms, trade names, and other pertinent identification information for bromomethane.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of bromomethane.

TABLE 3-1. Chemical Identity of Bromomethane

Characteristic	Information	Reference
Chemical name	Bromomethane	Windholz 1983
Synonyms	Methyl bromide; monobromomethane; methyl fume	IRIS 1989
Trade names	Embafume®; Terabol®	EPA 1986b
Chemical formula	CH_3Br	Windholz 1983
Chemical structure		Windholz 1983
Identification numbers:		
CAS registry	74-83-9	Sax and Lewis 1987
NIOSH RTECS	PA-900000	HSDB 1989
EPA hazardous waste	U029	NLM 1989
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN1062	NLM 1989
	IMCO 2.3	HSDB 1989
	NA1581	HSDB 1989
HSDB	799	NLM 1989
NCI	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Bromomethane

Property	Information	Reference
Molecular weight	94.95	Windholz 1983
Color	Colorless	Sax and Lewis 1987
Physical state	Gas	Windholz 1983
Melting point	-93.7°C	Windholz 1983
Boiling point	3.6°C	Windholz 1983
Density at 20°C[a]	3.97	Windholz 1983
Odor	Chloroform-like	Windholz 1983
Odor threshold:		
Water	No data	
Air	80 mg/m^3 (20 ppm)	Ruth 1986
Solubility:		
Water at 20°C	0.9 g/L	Verschueren 1983
	13.4-18.1 g/L	EPA 1986b
	13 g/L	Lyman et al. 1982
Organic solvents	Freely soluble	Windholz 1983
Partition coefficients:		
Log K_{ow}	1.1	Callahan et al. 1979
Log K_{oc}	0.77	Mabey et al. 1982
Vapor pressure at 20°C	1,420 mmHg	Mabey et al. 1982
Henry's law constant:		
(20°C)	0.013 atm•m^3/mole	Lyman et al. 1982
	0.197 atm·m^3/mole	Mabey et al. 1982
Autoignition temperature	Nonflammable	EPA 1986b
Flashpoint	Nonflammable	EPA 1986b
Flammability limits	Nonflammable	EPA 1986b
Conversion factors	1 ppm = 3.95 mg/m^3	Verschueren 1983
	1 mg/m^3 = 0.25 ppm	Verschueren 1983
Explosive limits	Nonflammable	EPA 1986b

[a]Density of vapor relative to air.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Bromomethane is produced by reaction of methanol with hydrobromic acid, followed by distillation of the product (HSDB 1989; IARC 1986; Windholz 1983). Table 4-1 summarizes information on U.S. companies that reported the manufacture or use of bromomethane in 1987 (TRI 1989). The quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting by these facilities. Not all facilities that should have reported have done so. Of the companies that did report, only two facilities produced bromomethane for sale and distribution: the Ethyl Corporation production facility in Magnolia, Arkansas, and the Great Lakes Chemical Corporation production facility in El Dorado, Arkansas (HSDB 1989; SRI 1987, 1988, 1989; TRI 1989). The current combined production volume of these two facilities is approximately 19,500 metric tons (43 million pounds) (HSDB 1989; IARC 1986). This is nearly a two-fold increase over the production volume of 11,200 metric tons (25 million pounds) reported for 1972 (IARC 1986).

4.2 IMPORT/EXPORT

Imports of bromomethane were 735 metric tons (1.6 million pounds) in 1982, while exports were 2,130 metric tons (4.7 million pounds) in 1984 and 4,135 metric tons (9 million pounds) in 1987 (HSDB 1989). More detailed data regarding the import and export of bromomethane were not located.

4.3 USE

The primary use of bromomethane is as a soil or space fumigant for the control of insects, fungi, and rodents (EPA 1986b; HSDB 1989; IARC 1986). Space fumigation is usually performed by enclosing the structure in a sealed tent and releasing bromomethane gas inside, while soil fumigation is usually done by injecting bromomethane into the soil underneath a nonporous covering. Bromomethane is also used as a methylating agent in various chemical reactions, and as a solvent to extract oils from nuts, seeds, and wool. Bromomethane was also used in fire extinguishers in Europe from the 1920s through the 1940s (IARC 1986), but never gained widespread use as a fire extinguishing agent in the United States (Alexeeff and Kilgore 1983).

4.4 DISPOSAL

Because bromomethane is a gas above 3.6°C (38°F), most disposal is by release to the atmosphere (see Section 5.2.1). Disposal of liquid or solid wastes that contain bromomethane is regulated by federal restrictions which apply to hazardous substances (see Chapter 7).

TABLE 4-1. Facilities That Manufacture or Process Bromomethane[a]

Facility	Location	Maximum Amount on site (lbs)	Use
Amoco Chemical Company	Decatur, AL	100-999	As an impurity
Great Lakes Chemical Co. El Dorado-Main Plant	El Dorado, AR	1,000,000-9,999,999	For sale/distribution
Gerber Products Company	Fort Smith, AR	1,000-9,999	In ancillary or other uses
Ethyl Corporation	Magnolia, AR	1,000,000-9,999,999	Produce; for sale/distribution; as a byproduct
	Hollister, CA	100,000-999,999	As a formulation component
Asgrow Florida Company	Belle Glade, FL	No Data	As a formulation component
Hms Chemicals Inc	Palmetto, FL	100,000-999,999	As a formulation component
Florida Fertilizer Co. Inc.	Wauchula, FL	100,000-999,999	For sale/distribution; in repackaging
Hercules-Brunswick Plant	Brunswick, GA	1,000-9,999	In ancillary or other uses
Borden, Inc. Grocery & Specialty Products	Lowell, MA	10,000-99,999	In ancillary or other uses
Borden, Inc. Gorcery & Specialty Prds.	Warren, MI	1,000-9,999	In ancillary or other uses
Mobay Corporation - Agricultural Chemicals Div.	Kansas City, MO	100,000-999,999	As a reactant
Comet Delta, Inc.	Greenville, MS	1,000-9,999	In ancillary or other uses
Coastal Chemical Corporation	Greenville, NC	100,000-999,999	In re-packaging
The Pillsbury Company	Buffalo, NY	No Data	In ancillary or other uses
Hershey Chocolate U.s.a. Hershey Plant	Hershey, PA	1,000-9,999	In ancillary or other uses
Consolidated Cigar Corp.	Cayey, PR	No Data	In ancillary or other uses
Amoco Chemical Company Cooper River	Wando, SC	100-999	Produce; as a byproduct
Cargill Flour Milling	Saginaw, TX	1,000-9,999	In ancillary or other uses

[a]Derived from TRI 1989.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Because bromomethane is a gas under ordinary conditions, humans are most likely to be exposed to bromomethane in air. Low levels can be detected in air around the globe, perhaps onginating from natural sources in the ocean. Somewhat higher levels occur in urban environments, due to release from industrial point sources and from use of leaded gasoline. Extremely high levels may be encountered in air where bromomethane is being used for fumigation. Trace levels have been detected in some groundwater samples, but levels in surface water and food are usually negligible. Bromomethane may also be generated in drinking water as the result of chlorination, but this has not yet been quantified.

Bromomethane in air is quite stable, undergoing breakdown by reaction with hydroxyl radicals with a half-life of about 11 months. Bromomethane in other media (water, soil) volatilizes sufficiently rapidly that breakdown in these media (via hydrolysis or reaction with organic components) is usually minor.

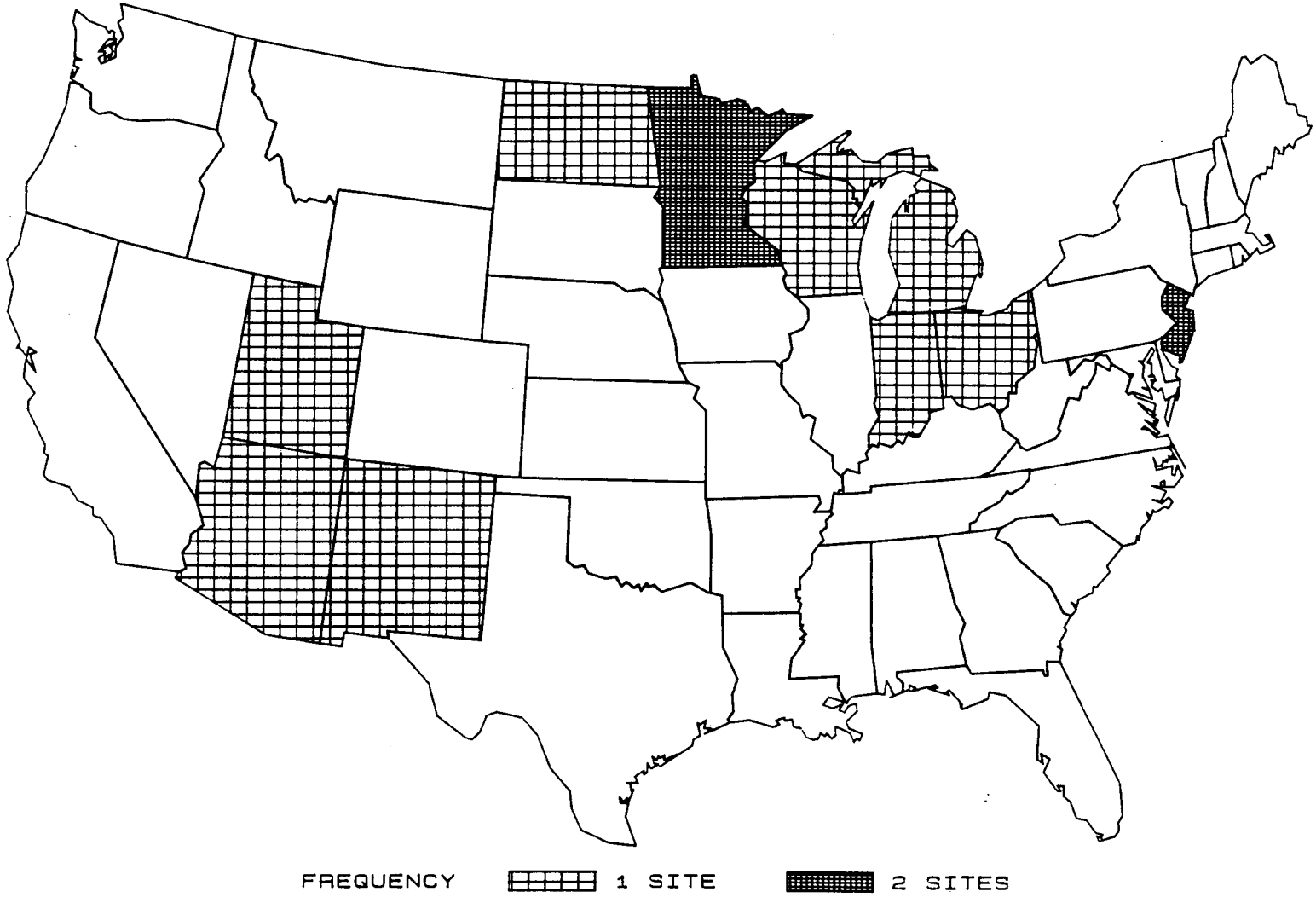
The EPA has identified 1,177 NPL sites. Bromomethane has been found at 12 of the sites evaluated for the presence of this chemical (View 1989). However, we do not know how many of the 1,177 sites have been evaluated for bromomethane. As more sites are evaluated by the EPA, the number may change. The frequency of sites where bromomethane has been found within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Since bromomethane is highly volatile, nearly all environmental releases of bromomethane are into the-air. The most important anthropogenic releases are from fumigation activities, since bromomethane is simply dispersed into the air after fumigation is completed. Based on current estimates that about 80% of bromomethane production is used for fumigation (65% for soil fumigation and 15% for space fumigation), and assuming that nearly all of this is ultimately released to air, approximately 34 million pounds/year may be released to air by this practice (HSDB 1989; IARC 1986). Air releases may also occur in association with industrial production and processing of bromomethane, as shown in Table 5-1 (TRI 1989). Based on the data reported, total releases to air from industrial activities in the United States were 1.3 million pounds in 1987. However, the quality of the TRI data must be viewed with caution since the 1987 data represent first-time, incomplete reporting of estimated releases by these facilities. Not all sources of chemical wastes are included, and not all facilities that should have reported have done so.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH BROMOMETHANE CONTAMINATION *



* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Bromomethane[a]

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Amoco Chemical Company	Decatur, AL	131,000	0	0	0	131,000	0	0
Great Lakes Chemical Co. El Dorado-Main Plant	El Dorado, AR	621,000	2,200	0	0	623,200	0	3,080
Gerber Products Company	Fort Smith, AR	20,000	No Data	No Data	0	20,000	0	0
Ethyl Corporation	Magnolia, AR	83,000	0	0	0	83,000	0	0
	Hollister, CA	250	0	0	0	250	0	0
Asgrow Florida Company	Belle Glade, FL	1,850	0	0	0	1,850	0	0
Hms Chemicals Inc	Palmetto, FL	250	0	0	0	250	0	0
Florida Fertilizer Co. Inc.	Wauchula, FL	357	0	0	0	357	0	0
Hercules-Brunswick Plant	Brunswick, GA	72,900	0	0	0	72,900	0	0
Borden, Inc. Grocery & Specialty Products	Lowell, MA	18,200	No Data	0	0	18,200	No Data	No Data
Borden, Inc. Gorcery & Specialty Prds.	Warren, MI	14,200	No Data	0	0	14,200	No Data	0
Mobay Corporation - Agricultural Chemicals Div.	Kansas City, MO	11,500	0	0	0	11,500	0	0
Comet Delta, Inc.	Greenville, MS	21,300	0	0	0	21,300	0	0
Coastal Chemical Corporation	Greenville, NC	29	0	0	0	29	0	0
The Pillsbury Company	Buffalo, NY	12,000	No Data	0	0	12,000	0	No Data
Hershey Chocolate U.s.a. Hershey Plant	Hershey, PA	40,879	0	0	0	40,879	0	No Data
Consolidated Cigar Corp.	Cayey, PR	7,140	0	0	0	7,140	0	0
Amoco Chemical Company Cooper River	Wando, SC	220,000	0	0	0	220,000	0	0
Cargill Flour Milling	Saginaw, TX	30,000	0	0	0	30,000	0	0
Totals		1,305,855	2,200	0	0	1,308,055	0	3,080

[a]Derived from TRI 1989.
[b]POTW -- publicly-owned treatment works.

The ocean is another important source of bromomethane release to air. It seems likely that this is the result of bromomethane production by marine organisms, but the exact source is not known (IARC 1986). Singh et al. (1983b) calculated that the amount released from the ocean was large enough to account for most bromomethane in the atmosphere, but Penkett et al. (1985) showed that anthropogenic releases were the most important source. This is supported by the observation that atmospheric levels are about 40% higher in the northern hemisphere (0.015-0.026 ppb) than the southern hemisphere (0.011-0.019 ppb) (Penkett et al. 1985; Singh et al. 1983b).

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

5.2.2 Water

Because of its volatility, very little bromomethane is released to water. As shown in Table 5-1, no surface water releases were reported in the United States from industrial producers or processors of bromomethane (TRI 1989), although in one case about 2,000 pounds of bromomethane was released to groundwater through underground injection. Some bromomethane may leach from fumigated soil into surface water (EPA 1986b; IARC 1986). Most of this would be expected to quickly volatilize into air (see Section 5.3.1.), although some could migrate downward into groundwater where evaporation is not significant.

Bromomethane has not been detected in surface waters near any of 405 waste sites (including 99 NPL sites) where it was investigated, but it was detected in six groundwater samples from two locations (both NPL sites) (CLPSD 1989). The geometric mean of six samples from these two sites was 17 $\mu g/L$.

5.2.3 Soil

Soil fumigation is the primary use of bromomethane in the United States, accounting for approximately 65% of total consumption (EPA 1989c; IARC 1986). Based on reported production for 1984 (43 million pounds), this would be about 28 million pounds/year. However, as discussed in Section 5.3.1, most bromomethane will tend to evaporate from the soil within 1-2 days, so soil contamination is normally not persistent. No industrial releases of bromomethane to soil were reported for 1987 (TRI 1989; see Table 5-1), and bromomethane has not been detected in soils or sediments at 455 hazardous waste sites, including 99 NPL sites (CLPSD 1989).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Bromomethane is a readily volatile compound, with a boiling point of 3.6°C (Windholz 1983) and a vapor pressure at 20°C of 1,420 mmHg (Mabey et al. 1982). Consequently, bromomethane has a strong tendency to volatilize into air from other media (soil, water).

Because bromomethane is quite soluble in water (approximately 13-18 g/L) (EPA 1986b), some bromomethane in air may partition into clouds, rain, or surface waters. This tendency is described by the Henry's law constant (H), which for bromomethane has a value of 0.2 atm·m^3/mole (Mabey et al. 1982). This value is sufficiently large to indicate that partitioning of bromomethane from air into water will be quite small. Conversely, the rate of bromomethane volatilization from water into air will be quite high, depending on mixing, temperature, and depth. The measured rate constant for volatilization is 22.5 cm/hr, which corresponds to a volatilization half-life of 3.1 hours for water 1 meter deep (Lyman et al. 1982). Half-lives of volatilization for lakes and deeper rivers range from 1 to 5 days (EPA 1986b). Rapid volatilization into indoor air would also be expected if contaminated water were used for showering, bathing, or cooking, but this has not been studied.

Bromomethane, either as a gas or dissolved in water, has relatively low affinity for soils. This has been established by direct observation (Brown and Rolston 1980; Chisholm and Koblitsky 1943; Fuhr et al. 1948), and is also expected on the basis of the relatively small K_{oc} (measured values range from 1 to 10) for this chemical (EPA 1986b; Roy and Griffin 1985). Volatilization of bromomethane from soil is also relatively rapid, with half-lives ranging from 0.2 to 0.5 days, depending on depth (Jury et al. 1984). Bromomethane is not expected to bioconcentrate in aquatic organisms because of its low octanol/water partition coefficient (K_{ow}) (estimated to be about 13) (Callahan et al. 1979). The bioconcentration factor (BCF) for bromomethane has not been measured experimentally. However, based on an empirical relation between the BCF and the K_{ow} (Neely et al. 1974), the estimated BCF for bromomethane is about 3. This low estimated BCF indicates that bromomethane should not significantly bioconcentrate (EPA 1986b).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The main degradation pathway for bromomethane in air is reaction with photochemically-generated hydroxyl radicals. The rate constant for this reaction has been measured to be 4.14×10^{-14} $cm^3 \cdot molecule^{-1} \cdot sec^{-1}$ at 25°C, and 2.7×10^{-14} $cm^3 \cdot molecule^{-1} \cdot sec^{-1}$ at -8°C (the average temperature of the troposphere) (Davis et al. 1976). Assuming a concentration of atmospheric hydroxyl radicals of 9×10^5 molecules/cm^3, this corresponds to a tropospheric half-life of about 11 months. Thus, breakdown is relatively slow, and

bromomethane will tend to become widely dispersed in the atmosphere. Molecules that diffuse upward and reach the stratosphere may undergo direct photolytic degradation by ultraviolet radiation (Robbins 1976), but this degradation pathway accounts for only a small fraction (about 3%) of atmospheric bromomethane degradation (EPA 1986b).

5.3.2.2 Water

Bromomethane tends to undergo slow hydrolysis in water, yielding methanol, bromide ion, and hydrogen ion. The rate constant of this reaction has been measured to be about $3x10^{-7}$/second at 25°C (Castro and Belser 1981), and hydrolytic half-lives may range between 20 and 38 days, depending on temperature and pH (Castro and Belser 1981; Ehrenberg et al. 1974; Mabey and Mill 1978). It should be noted that these hydrolysis half-lives are considerably longer than typical volatilization half-lives (see Section 5.3.1). Thus, most bromomethane will volatilize from water before extensive hydrolysis occurs.

5.3.2.3 Soil

The principal fate of bromomethane in soil is volatilization, but some may react with organic soil constituents to yield nonvolatile end products, including bromide ion (Brown and Rolston 1980; Goring et al. 1975; Shiroishi et al. 1964). There is little evidence that bromomethane in soil is degraded by microorganisms (EPA 1986b).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

As shown in Table 5-2, bromomethane has been detected in air samples from regions all around the globe. Concentrations over the oceans and in rural areas are typically less than 0.025 ppb (0.1 $\mu g/m^3$), while concentrations in suburban and urban areas may range up to 1.2 ppb (5 $\mu g/m^3$). These values are all much lower than may be encountered near places where bromomethane is being used for fumigation (25 ppm or 100,000 $\mu g/m^3$) (Bond and Durnas 1987).

5.4.2 Water

Bromomethane occurs in ocean waters at a concentration of about 1-2 ng/L (Lovelock 1975; Singh et al. 1983b), but is not a common contaminant in fresh waters in the United States. It was not detected in storm water runoff from 15 U.S. cities (Cole et al. 1984) or in influents to sewage treatment plants in four cities (Levins et al. 1979), and was detected in only 1.4% of over 900 surface water samples recorded in the STORET database (Staples et al. 1985). The median concentration in these positive samples was less than 10 µg/L.

TABLE 5-2. Summary of Bromomethane Levels in Air

Location	Concentration ($\mu g/m^3$)[a] Maximum	Mean	References
Northern Hemisphere	No data	0.02-0.08	Penkett et al. 1985; Singh et al. 1979b
Arctic	0.09	0.043	Berg et al. 1984
Oceanic	No data	0.09	Singh et al. 1983b
Rural/Suburban United States	No data	0.002-0.32[b]	Brodzinsky and Singh 1983; Harsch and Rasmussen 1977; Shah and Heyerdahl 1988
Urban United States	0.25-5.1	0.16-2.2	Brodzinsky and Singh 1983; Harsch and Rasmussen 1977; Shah and Heyerdahl 1988; Shikiya et al. 1984; Singh et al. 1981b, 1982
Source dominated[c]	$1.1x10^5$	No data	Bond and Dumas 1987
Hazardous waste sites	No data	-[d]	La Regina et al. 1986

[a]1 $\mu g/m^3$ = 0.25 ppb (0.00025 ppm).
[b]Median value.
[c]Data measured 25 m from a flour mill being fumigated with bromomethane.
[d]Detected, but not quantified; detection limit $\approx$0.4 $\mu g/m^3$.

5. POTENTIAL FOR HUMAN EXPOSURE

Bromomethane has been detected (but not quantified) in drinking water supplies of several U.S. cities (Coleman et al. 1976; EPA 1975; Kool et al. 1982; Kopfler et al. 1977; Shackelford and'Keith 1976). Bromomethane in drinking water is presumably generated as an inadvertent byproduct following chlorination.

Occurrence of bromomethane in groundwater is somewhat more likely than in surface water, since evaporation is restricted. Bromomethane has been detected in groundwater in New Jersey (Greenberg et al. 1982) but not in Wisconsin (Krill and Sonzogni 1986).

5.4.3 Soil

No data were found on bromomethane levels in soil. Bromomethane is not expected to be a stable constituent of soil, since it either .evaporates or reacts.with organic soil components (see Section 5.3.2.3). However, bromide ion may be retained in fumigated soil (IARC 1986). Bromomethane was not detected in 353 sediment samples from STORET stations in the United States (Staples et al. 1985).

5.4.4 Other Environmental Media

Although bromomethane is used extensively as a fumigant for grains and other food products, it is rarely detected unchanged as a residue in foods. Most of the fumigant is rapidly lost to the atmosphere, and the remaining portion reacts with the food components, producing residues of inorganic bromide (IARC 1986; NAS 1978). Daft (1987, 1988, 1989) and Cova et al. (1986) reported that bromomethane was not detected in hundreds of food products, and Duggan et al. (1983) found-bromomethane in only 3 of 5,631 samples of vegetables. The tolerances for residues on agricultural commodities and processed foods that have been set by EPA and FDA are for bromide ion, not bromomethane (21 CFR 193; 40 CFR 180).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Inhalation of bromomethane in ambient air is the predominant exposure route for most people in the United States. Singh et al. (1981b) calculated that average daily doses of bromomethane from air in 3 U.S. cities ranged from 4.5 to 24.5 μg/person, based on total air intake of 23 m^3/day by an adult. These estimates were based on 1979 monitoring data in urban areas. It is likely that urban bromomethane levels are currently lower than in the past, due to decreased emissions from automobiles using leaded gasoline (see Section 5.2.1). Based on the very low levels of bromomethane in water and the negligible levels in food, it appears that exposure of the general population to bromomethane from sources other than air is likely to be insignificant under normal circumstances.

Exposure of workers to bromomethane is highly variable, depending on conditions. Exposure levels inside factories are regulated by OSHA, and the 8-hour average concentration is not permitted to exceed 5 ppm (OSHA 1989).

Highest exposures are most likely to occur during fumigation activities, especially when bromomethane is first released to the environment after fumigation ends. Exposure levels under these conditions could reach from 25 to 2,500 ppm (IARC 1986; NIOSH 1984a; Van Den Oever et al. 1982), which would correspond to a dose of 100-10,000 mg/hour for an exposed worker. NIOSH estimated that about 105,000 workers in the United States were potentially exposed to bromomethane in the workplace in 1980 (NIOSH 1984a).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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

5.7 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 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.

5.7.1 Data Needs

Physical and Chemical Properties. The physical and chemical properties of bromomethane are sufficiently well known to allow estimation of environmental fate. Although there is some disparity in reported values for the solubility in water and Henry's law constant for bromomethane (see Table 3-1), further studies to define these parameters more precisely do not appear essential, since volatilization from water is so rapid.

5. POTENTIAL FOR HUMAN EXPOSURE

Production, Import/Export, Use, and Disposal. Large quantities of bromomethane are produced and used in this country (TRI 1989), and there is significant opportunity for humans to be exposed to both during production and use (IARC 1986). Information is available on current volumes, and available data suggest production is increasing (IARC 1986). The main use of bromomethane is as a fumigant for soil, agricultural produce, and structures (IARC 1986), but data on the amount of bromomethane used for each type of fumigation were not located. Due to its volatility, nearly all releases from fumigation are to air (TRI 1989), and this is the medium most likely to be contaminated. Currently there are no regulations which restrict this release.

According to the Emergency Planning and Community Nght-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The fate of bromomethane in the environment is dominated by rapid evaporation into air, where it is quite stable (EPA 1986b). The rates of volatilization from soil and water have been studied and are known with reasonable precision (although such rates are typically sitespecific) (Jury et al. 1984; Lyman et al. 1982). The rates of breakdown by hydrolysis, reaction with hydroxyl radical, and direct photolysis in the stratosphere have also been estimated (Castro and Belser 1981; Davis et al. 1976; Robbins 1976). Further studies to improve the accuracy of available rate constants for these processes would be helpful, but do not appear to be essential in understanding the basic behavior of bromomethane in the environment.

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

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

Exposure Levels in Environmental Media. Several studies are available documenting bromomethane concentrations in ambient air (Brodzinsky and Singh 1983; Harsch and Rasmussen 1977), but data for bromomethane in water are rare. Bromomethane has been analyzed for, but rarely detected, in foods (Daft 1987, 1988, 1989). Human exposure levels of bromomethane by inhalation of urban air have been calculated (Singh et al. 1981b). However, these levels are based on monitoring data more than 10 years old. Since urban air concentrations of bromomethane may have decreased due to reduced emissions from automobiles, exposure levels calculated from past data should be taken as an upper limit, and new levels calculated from current monitoring data would be useful. Additional monitoring data on levels in air near sites where bromomethane is being made or used would also be valuable in defining environmental levels.

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

Exposure Registries. No exposure registries for bromomethane were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No information was located on any on-going studies on the fate and transport of bromomethane. However, two studies related to human exposure to bromomethane are being supported by the U.S. Department of Agriculture and conducted at the University of California, Davis. One project will analyze bromomethane residues on foods, and the second will quantitate exposure levels of field workers to bromomethane and develop appropriate procedures to minimize exposure from this source. Remedial investigations and feasibility studies at NPL sites that contain bromomethane will provide further information on environmental concentrations and human exposure levels near waste sites.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring bromomethane in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify bromomethane. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect bromomethane in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

As a volatile material, bromomethane is readily determined by gas chromatographic analysis. The selectivity and sensitivity of detection are increased by the use of an electron capture detector or a halide-specific detector, both of which are very sensitive for organohalides such as bromomethane. Specificity in detection is achieved with mass spectrometric detectors.

6.1 BIOLOGICAL MATERIALS

Bromomethane may be isolated from biological materials either by extraction into an organic solvent, or simply by collecting headspace vapors. Table 6-1 summarizes several methods used by researchers for measuring parent bromomethane in blood or tissues. Detection limits are sufficiently low that levels in blood or tissue associated with health effects can easily be measured. However, as discussed in Section 2.3.4, parent bromomethane is cleared from blood and tissues quite rapidly, so detection of bromomethane exposure in humans is typically performed by measuring serum bromide levels instead. Several methods for measuring bromide ion in serum are also presented in Table 6-1. These methods are also sufficiently sensitive that detection limits (0.5-2.5 ppm) are lower than typical levels of bromide in serum of unexposed people (5-15 ppm), and increases due to bromomethane exposure can easily be measured (Alexeeff and Kilgore 1983).

6.2 ENVIRONMENTAL SAMPLES

Collection of bromomethane from environmental samples is nearly always achieved by trapping on a solid sorbent such as activated charcoal. For air samples, this is done simply by drawing the air through the sorbent. For water, soil, or solid wastes, bromomethane is purged from the sample by flushing with an inert gas, and this is then passed through the sorbent. Desorption may be achieved by extraction in a convenient solvent, or by heating. Table 6-2 summarizes a number of methods that have been developed for measuring bromomethane in various types of environmental media. In all cases, detection limits are much lower than levels of health concern.

TABLE 6-1. Analytical Methods for Determining Bromomethane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bromomethane					
Blood, tissue	Purge with inert gas, trap on Tenax® GC, desorb thermally[a]	GC/MS	3 ng/mL blood 6 ng/mL tissue	No data	Pellizzari et al. 1985
Blood, tissue, adipose	Homogenize in toluene, centrifuge, inject supernatant fluid	GC/ECD	1 ng/g	100	Honma et al. 1985
Food	Collect headspace vapor	HRGC	0.4 ppb	No data	DeVries et al. 1985
Grain	Extract with acetone, collect headspace vapor from acetone extract	GC	<1 mg/kg	91.3±3	Scudamore 1985
Bromide					
Blood plasma	Collect headspace vapor of HBr from plasma treated with dimethyl sulfate at 85°C	HRGC	<0.5 µg/mL bromide	97.3±6.3 at 5 µg/mL	Yamano et al. 1987
Tissues	Extract in 18% trichloroacetic acid; derivatize to 1,2-dibromo-cylcohexanone	GC/ECD	2.5 µg/g	17	Honma et al. 1985
Serum, urine	Digest in KOH. Convert to bromate, then to tetrabromorosaniline	Colorimetric (570 nm)	1 µg/mL	100±1	Hunter 1955

[a]Method for the determination of volatile halocarbons in blood and tissue adaptable to bromomethane determination.

ECD = electron capture detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

TABLE 6-2. Analytical Methods for Determining Bromomethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Sorption by activated carbon, desorption by carbon disulfide	GC/FID	<20 mg/m^3	No data	Mackenzie Peers 1985
Air	Sorption by HBr-treated activated carbon, desorption with carbon disulfide	GC/ECD	0.2 ppm	No data	LeFevre et al. 1989
Air	Retention by activated carbon, removal as headspace gas	GC/ECD	2 µg/m^3	37-91	Woodrow et al. 1988
Exhaust gas	Collect on Tenax® GC, desorb	GC/MWP	<90 µg/m^3	No data	Baumann and Heumann 1987
Water	Purge with inert gas, trap on sorbent trap, desorb thermally	GC/HSD	Approx. 0.5 µg/L	No data	APHA 1985a
Water	Purge with inert gas, trap on sorbent trap, desorb thermally	GC/MS	<1 µg/L	96±11	APHA 1985b
Water	Purge with inert gas, trap on sorbent trap, desorb thermally	GC/HSD	0.01 µg/L	90-110±10[a]	EPA 1988d
Water	Purge with inert gas, trap on sorbent trap, desorb thermally	HRGC/HSD	0.01-0.05 µg/L	97±4	EPA 1988e
Water	Purge with inert gas, trap on sorbent trap, desorb thermally	HRGC/MS	0.11 µg/L	95±8	EPA 1988g
Wastewater	Purge with inert gas, trap on sorbent trap, desorb thermally	GC/MS	No data	88±23	EPA 1982b
Solid waste	Purge by helium, collect on solid, thermally desorb	GC/MS	10 µg/kg	111±48 at 37.2 µg/L	EPA 1986c

[a]Value for similar volatile organohalide compounds in air, not determined directly for bromomethane.

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; HSD = haldie specific detector; MS = mass spectrometry; MWP = microwave plasma

6.3 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 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.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Exposure to bromomethane may be evaluated by measuring parent bromomethane, serum bromide, or methylated adducts. Existing methods can measure parent bromomethane in blood or expired air with excellent sensitivity (Honma et al. 1985; Pellizzari et al. 1985; Woodrow et al. 1988), but this is rarely done because bromomethane is cleared so quickly. Several sensitive methods exist for measuring serum bromide (Honma et al. 1985; Hunter 1955; Yamano et al. 1987), and this is the most common means for evaluating exposure. However, increased bromide is not specific for bromomethane exposure, and levels may vary widely between individuals. No routine methods have been established for measuring methyl adducts in DNA or protein (except those involving ^{14}C-labeled bromomethane). Efforts to develop sensitive and specific immunoassays for these adducts would be valuable, since levels of these adducts may be directly proportional to tissue damage. In addition, combination of a method for detecting methyl adducts with a test for increased serum bromide would increase specificity in bromomethane exposure estimates.

The characteristic markers of effect in people exposed to high levels of bromomethane are lung irritation, renal shut-down, and central nervous system injury (Clarke et al. 1945; O'Neal 1987; Prain and Smith 1952). In people exposed to low levels, only the neurological effects can be detected (Anger et al. 1986; Kishi et al. 1988; Verberk et al. 1979). Other than standard clinical neurological or neurobehavior tests, no specific biomarkers of bromomethane effects are known. Since parameters measured in these tests are highly variable among individuals, these tests are neither specific nor particularly sensitive. Efforts to identify and develop a more specific and objective biomarker of exposure would be valuable in evaluating the health significance of exposures that might occur in the environment or near waste sites.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The medium of main concern for human exposure to bromomethane is air. Trace levels may occur in water or soil, but human exposures from these sources are not expected to be large enough to be of concern except in rare situations. Existing analytical methods can measure bromomethane in air (LeFevre et al. 1989; Mackenzie Peers 1985; Woodrow et al. 1988) and other environmental media (APHA 1985a, 1985b; EPA 1982b, 1986c, 1988d, 1988e, 19883) at levels considerably below those of health concern. The accuracy and precision of the methods are established, and adequate specificity may be achieved by use of mass spectrophotometric detectors. Nevertheless, further efforts to improve accuracy and ease of sample isolation and transfer to the analytical instrument would be helpful.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of bromomethane and other volatile organic compounds in blood. These methods use purge and trap methodology and magnetic mass spectrometry which gives detection limits in the low parts per trillion range.

Research is underway at the Cooperative Institute for Research in Environmental Sciences (CIRES) at the University of Colorado, Boulder, to improve methods of analysis for bromomethane and related compounds in environmental samples.

Examination of the literature suggests that studies are in progress to improve means for determining bromomethane, its metabolites, and related compounds in biological samples and environmental media. For example, a "Master Analytical Scheme" is being developed for organic compounds in water (Michael et al. 1988), which includes bromomethane as an analyte. The overall goal is to detect and quantitatively measure organic compounds at 0.1 μg/L in drinking water, 1 μg/L in surface waters, and 10 μg/L in effluent waters. Improvements continue to be made in chromatographic separation and detection. Problems associated with the collection of bromomethane on a sorbent trap, followed by thermal desorption may be overcome with direct purging to a capillary column with whole column cryotrapping (Pankow and Rosen 1988). Current research activities in supercritical fluid extraction (King 1989) and supercritical fluid chromatography (Smith 1988) include organohalide analytes such as bromomethane in biological samples and environmental media.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for bromomethane by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Bromomethane

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA	5 ppm (20 mg/m^3), skin	OSHA 1989 (29 CFR 1910.1000) Table Z-1-A
b. Water:			
EPA ODW	Monitoring requirements for unregulated contaminants	Yes	EPA 1987b (40 CFR 142)
EPA OWRS	General permits under NPDES	Yes	40 CFR 122, Appendix D, Table II
	General Pretreatment Regulations for Existing and New Sources of Pollution	Yes	40 CFR 403
	Hazardous substance	Yes	40 CFR 116
	Reportable quantity	1,000 pounds	40 CFR 117.3
c. Food:			
EPA OPP	Tolerances for residues of inorganic bromides resulting from fumigation with methyl bromide in or on raw agricultural commodities	5-240 ppm	40 CFR 180.123
	Tolerances for residues of inorganic bromide resulting from soil treatment with combinations of chloropicrin, methyl bromide and propargyl bromide	25-300 ppm	40 CFR 180.199
FDA	Tolerances of inorganic bromide in processed food as a result of fumigation with methyl bromide	125-400 ppm	21 CFR 193.250
	Tolerances for residues of inorganic bromide from fumigation with methyl bromide on cereal grains and processed grains used in production of fermented malt beverages	125 ppm	21 CFR 193.225, 193.230
d. Other:			
EPA OERR	Reportable quantity	1,000 pounds	EPA 1989a,b 40 CFR 302.4)
	Extremely Hazardous Substance Threshold Planning Quantity	1,000 pounds	EPA 1987a (40 CFR 355)
EPA OPP	Restricted use pesticide	Yes	40 CFR 162.31

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980b (40 CFR 261)
	Groundwater monitoring list (Appendix IX)	Yes	EPA 1987c (40 CFR 264)
	Land disposal restrictions	Yes	EPA 1987d, 1988b (40 CFR 268)
EPA OTS	Toxic chemical release reporting rule	Yes	EPA 1988a (40 CFR 372)
	Health and safety data reporting rule	Yes	EPA 1988c (40 CFR 716.120)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	5 ppm (19 mg/m^3)	ACGIH 1991
NIOSH	IDLH	2,000 ppm	NIOSH 1990
	REL	carcinogen; lowest feasible concentration	
b. Water:			
EPA OWRS	Ambient Water Quality Criteria		EPA 1980a
	Ingesting water and organisms:	1.9×10^{-4} mg/L[b]	
	Ingesting organisms only:	1.57×10^{-2} mg/L[b]	
	For noncarcinogenic effects	1.4 mg/L	
c. Other:			
EPA	Carcinogenic Classification	Group D[c]	EPA 1989c,
	Oral RfD	1.4×10^{-3} mg/kg/day	IRIS 1989
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1989
Connecticut		400 $\mu g/m^3$ (8 hr)	
Kansas		47.6 $\mu g/m^3$ (annual)	
Massachusetts		2.6 $\mu g/m^3$ (24 hr)	
Nevada		0.476 mg/m^3 (8 hr)	
North Dakota		0.20 mg/m^3 (8 hr)	
Pennsylvania (Philadelphia)		480 $\mu g/m^3$ (1 yr)	
South Carolina		100 $\mu g/m^3$ (24 hr)	
Vermont		0.01 $\mu g/m^3$ (annual)	
Virginia		350 $\mu g/m^3$ (24 hr)	
b. Water:	Drinking water quality standards		FSTRAC 1988
Arizona		2.5 $\mu g/L$	
Kansas		0.19 $\mu g/L$	
Massachusetts		0.01 mg/L	ORS 1989

[a]Group 3: Not classifiable as to carcinogenic potential.
[b]Values for incremental lifetime cancer risk of 10^{-6} for halomethanes as a class based on carcinogenicity of chloroform.
[c]Group D: Not classifiable as to human carcinogenicity.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = recommended exposure limit; RfD = reference dose; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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API. 1989c. American Petroleum Institute Statistics Department. Latest API statistics: Week ending October 6, 1989. The Oil Daily, October 13, 1989.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

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

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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

In Vivo -- Occurring within the living organism.

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

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

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

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

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

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

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

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

9. GLOSSARY

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

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution. Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an g-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

9. GLOSSARY

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

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELS), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column.

(6) Exposure Freauencv/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompani.es the MAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

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

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-l

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

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

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

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

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

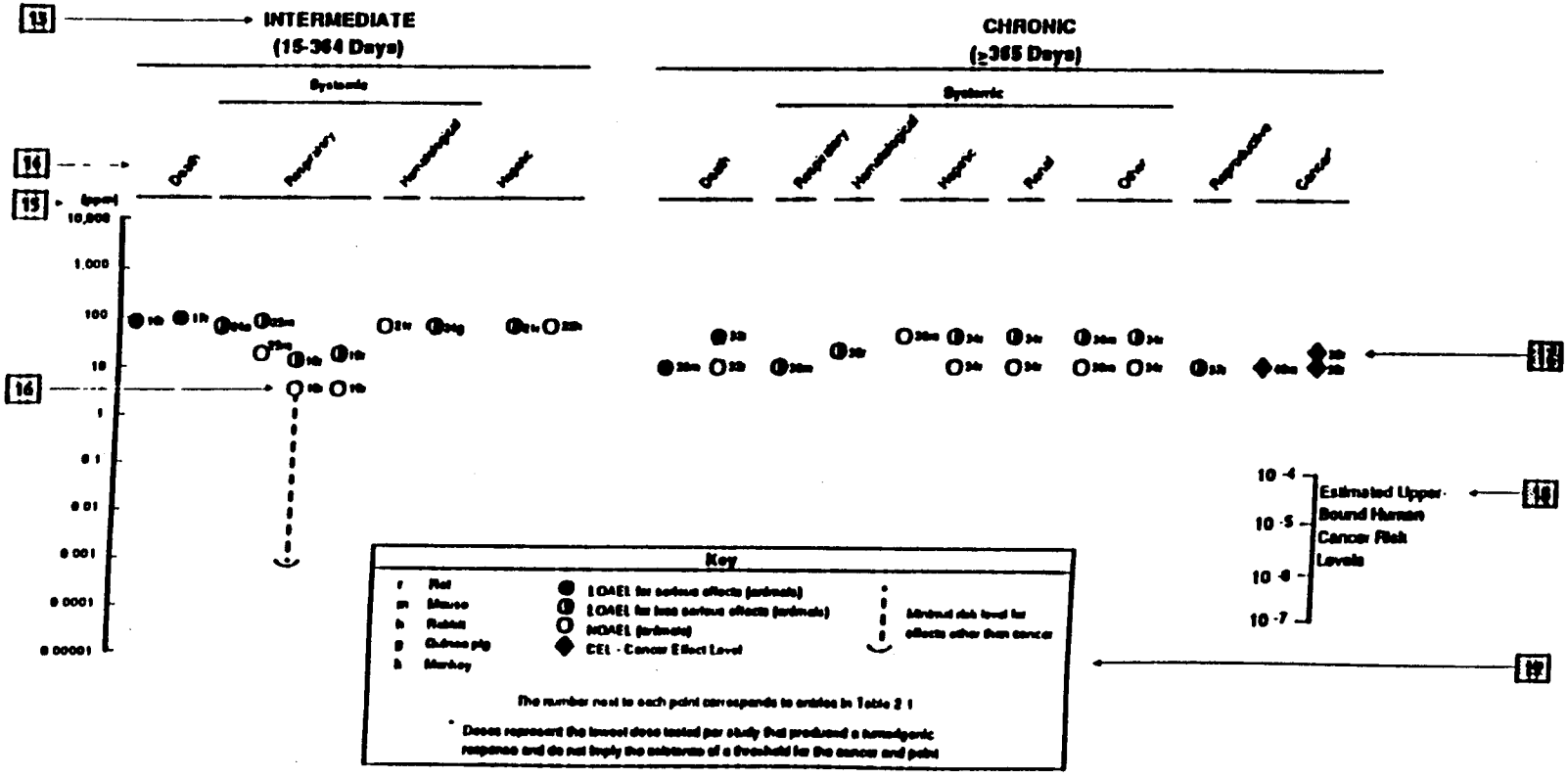

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

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

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

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existingtoxicokinetic, genotoxic, andcarcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans), In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter

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mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to

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=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for bromomethane. The panel consisted of the following members: Dr. Judith S. Bellin, Private Consultant, Washington, DC; Dr. Caroline Holsapple (formerly Caroline Kramer), Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, VA; Dr. Norman M. Trieff, Department of Preventive Medicine and Community Health, The University of Texas Medical Branch, Galveston, TX; and Dr. Nancy Reiches, Private Consultant, Columbus, Ohio. These experts collectively have knowledge of bromomethane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.