Toxicological Profile for

CHLOROMETHANE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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TOXICOLOGICAL PROFILE FOR CHLOROMETHANE

Prepared by:

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FOREWORD

The Superfund Amendments and Reauthorization Act 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 (also known as SARA) 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 list of the 200 most significant hazardous substances was published in the Federal Register on April 17, 1987 and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. 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, or chronic health effects, and
>
> (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, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is 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.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that

presents 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 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 front 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. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

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, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Acting Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about chloromethane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). Chloromethane has been found at 18 of these sites. However, we do not know how many of the 1177 NPL sites have been evaluated for chloromethane. As EPA evaluates more sites, the number of sites at which chloromethane is found may change. The information is important for you because chloromethane may cause harmful health effects and because these sites are potential or actual sources of human exposure to chloromethane.

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 substance such as chloromethane, 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 CHLOROMETHANE?

Chloromethane is a clear, colorless gas (vapor) that is difficult to smell. It has a faintly sweet, nonirritating odor at high levels in the air. It is a naturally occurring chemical that is made in large amounts in the oceans and is produced by some plants and rotting wood and when such materials as grass, wood, charcoal, and coal burn. Chloromethane is also produced industrially, but most of it is destroyed during use. It is used mainly in the production of other chemicals such as silicones, agricultural chemicals, and butyl rubber. Producers of the chemical supply the chemical to their customers as a liquified gas in metal containers. Chloromethane was used widely in refrigerators in the past, but generally this use has been taken over by newer chemicals such as Freon. Some functioning refrigerators more than about 30 years old may contain chloromethane. Since chloromethane is continuously released into the atmosphere from oceans and biomass, a very low concentration will always be present. When present in water, chloromethane will evaporate rapidly. Chloromethane will evaporate from the soil surface, but if present in a landfill or waste site, it may move downward and get into well water. For more information, please read Chapters 3, 4, and 5.

1. PUBLIC HEALTH STATEMENT

1.2 HOW MIGHT I BE EXPOSED TO CHLOROMETHANE?

Because chloromethane is made in the oceans by natural processes, it is present in air all over the world. In most areas, the outside air contains less than 0.001 part of chloromethane in a million parts of air (ppm). In cities, however, the air may contain up to 0.003 ppb. It is also present in some lakes and streams and has been found in drinking water (including well water) at very low levels in the ppb range. Chloromethane is also found in tap water that has been chlorinated. If chloromethane is present at waste sites, it may get into underground water as it passes downward through the soil. Very low levels may be present naturally in the soil. There have been no reports that chloromethane is found in food. You could be exposed to levels somewhat higher than the background levels, although probably still very low levels, if you live near a hazardous waste site or a source of industrial release. The people most likely to be exposed to increased levels of chloromethane in the air are those who work where it is made. Other occupations or industries that present a higher risk of exposure to chloromethane include building contracting, metal industries, transportation, car dealers, and service-station attendants. In the past (more than 30 years ago), chloromethane was widely used in refrigerators, and people may still be exposed to it if these old refrigerators leak the gas into their homes. Other consumer sources of chloromethane include cigarette smoke; polystyrene insulation; aerosol propellents; home burning of wood, grass, coal, or certain plastics; and the use of chlorinated swimming pools. For more information, please read Chapter 5.

1.3 HOW CAN CHLOROMETHANE ENTER AND LEAVE MY BODY?

Chloromethane can enter your body through the lungs if you breathe it in or through the digestive tract if you drink water containing it. Almost all of the chloromethane that you breathe in or drink rapidly enters the bloodstream from the lungs or the digestive tract. Chloromethane can also enter your body through the skin if you come into contact with it, but the amount that enters this way is not known. Breathing air that contains chloromethane vapor is the most likely way you could be exposed if you live near a hazardous waste site. Chloromethane goes rapidly from the lungs into the bloodstream, and then it or its breakdown products go to organs such as the liver, kidneys, and brain. The portion of the chloromethane that does not get changed in your body leaves in the air you breathe out, and the breakdown products of chloromethane formed in the body leave in the urine. These processes take anywhere from a few hours to a couple of days. For more information, please read Chapter 2.

1.4 HOW CAN CHLOROMETHANE AFFECT MY HEALTH?

If the levels are high enough (over a million times the natural level in outside air), brief exposures to chloromethane can have serious effects on the nervous system, including convulsions, coma, and death. Some people have died from breathing chloromethane that leaked from refrigerators in

rooms with little or no ventilation in their homes. Most of these cases occurred more than 30 years ago, but exposure could still happen if you have an old refrigerator that contains chloromethane as the refrigerant. Others exposed to high levels this way or to leaks while they were repairing refrigerators did not die but had effects such as staggering, blurred and double vision, dizziness, fatigue, personality changes, confusion, tremors, uncoordinated movements, nausea, and vomiting. These symptoms can last for several months or more, but complete recovery is possible. Exposure to chloromethane has also had harmful effects on the liver, kidney, heart rate, and blood pressure. If you work in an industry that uses chloromethane to make other products, you might be exposed to chloromethane levels that cause some symptoms that resemble drunkenness and impaired ability to perform simple tasks.

Harmful liver, kidney, and nervous system effects have developed after animals breathed air containing high levels of chloromethane (100,000 times higher than natural levels) for a few hours each day for 1 or more days. Animals have also died from exposure to high levels of chloromethane. When mice breathed the vapors for only several hours per day, they could be exposed to higher levels of chloromethane before developing effects than if they breathed the vapors all day for several days. The same effects occurred in animals when they were exposed to lower levels of chloromethane for longer periods. In long-term exposure experiments, animals that breathed air containing chloromethane grew more slowly than animals that were not exposed. Male rats that breathed air containing chloromethane developed effects in their reproductive organs that made them less fertile or even sterile. They also produced sperm that were damaged, causing female rats that became pregnant by these exposed male rats to lose their fetuses. Female rats that were exposed to chloromethane during pregnancy had smaller than normal fetuses with underdeveloped bones. Female mice that are exposed during pregnancy may produce fetuses with abnormal hearts, but this issue is controversial. Male mice that breathed air containing chloromethane for 2 years developed tumors in their kidneys, but female mice and male and female rats did not develop tumors. It is not known whether chloromethane could cause sterility, miscarriages, birth defects, or cancer in humans. For more information, please read Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the relationship between exposure to chloromethane and known health effects. Minimal Risk Levels (MRLs) are also included in Table 1-1. These MRLs were derived from animal data for both short-term and long-term exposure, as described in Chapter 2 and in Table 2-1. The MRLs provide a basis for comparison with levels that people might encounter in air. If a person is exposed to chloromethane at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because these levels are based on information currently available, some uncertainty is always asssociated with them. Also, because the method for deriving MRLs does not use any information about cancer, an

TABLE 1-1. Human Health Effects from Breathing Chloromethane*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
0.46		Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).
200	3 hours	Impaired ability to perform simple tasks.
29,000	4 hours	Serious nervous system effects, nausea, vomiting.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
0.40		Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).
265	2-3 weeks	Nervous system effects, blurry vision, dizziness, staggering, confusion.

*See Section 1.2 for a discussion of exposures encountered in daily life.

**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-2. Animal Health Effects from Breathing Chloromethane

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
100	11 days	Damage to brain cells in mice.
150	11 days	Death, muscle incoordination, liver damage, decreased growth rate in mice.
500	2-3 days	Damage to testes of rats.
1000	5 days	Decreased fertility of rats.
1500	13 days	Underdeveloped bones in fetuses of pregnant rats.
3000	5 days	Damaged sperm that cause abortion in rats.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
375	3 months	Decreased body weight in rats.
475	5 months	Decreased fertility in rats.
1000	6 months	Liver and nervous system effects (tremors, paralysis) in mice, damage to testes of rats.
1000	12 months	Decreased survival and kidney changes in mice.
1500	5 months	Sterility in rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Chloromethane*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects The health effects resulting from short-term exposure of humans to food containing specific levels of chloromethane are not known.
Levels in Water		The health effects resulting from short-term exposure of humans to water containing specific levels of chloromethane are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects The health effects resulting from long-term exposure of humans to food containing specific levels of chloromethane are not known.
Levels in Water		The health effects resulting from long-term exposure of humans to water containing specific levels of chloromethane are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Chloromethane

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of animals to food containing specific levels of chloromethane are not known.
Levels in Water		The health effects resulting from short-term exposure of animals to water containing specific levels of chloromethane are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to food containing specific levels of chloromethane are not known.
Levels in Water		The health effects resulting from long-term exposure of animals to water containing specific levels of chloromethane are not known.

MRL does not imply anything about the presence, absence, or levels of risk for cancer. The exposure levels of chloromethane in air that resulted from refrigerator leaks and caused coma and death are likely to be relatively high but are not known exactly, so they could not be listed in Table 1-1. People who have died in this way did not know that chloromethane was leaking because it is difficult to smell.

The mice referred to in Table 1-2 that died at 150 ppm were exposed almost all day for 11 days. Mice that were exposed for only 6 hours per day for 11 days died following exposure to much higher levels of chloromethane. As seen in Tables 1-3 and 1-4, the effects of eating food or drinking water containing chloromethane are not known. Furthermore, the effects of skin contact with chloromethane are not known. For further information, please read Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHLOROMETHANE?

There is no known reliable medical test to determine whether you have been exposed to chloromethane. Symptoms resembling drunkenness and food poisoning, along with a sweet odor of the breath, may alert doctors that a person has been exposed to chloromethane. For further information, please read Chapters 2, 3, and 6.

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

The Occupational Safety and Health Administration (OSHA) has set an average permissible exposure limit of 50 parts of chloromethane per million parts of workroom air (50 ppm) to protect workers during each 8-hour work shift in a 40-hour workweek. The exposure limit recommended by the National Institute for Occupational Safety and Health (NIOSH) is 100 ppm for each 8-hour workshift in a 40-hour workweek. Further information on governmental recommendations can be found in Chapter 7.

1.8 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 give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in the recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 *INTRODUCTION*

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to chloromethane. Its purpose is to present levels of significant exposure for chloromethane based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of chloromethane and (2) a depiction of significant exposure levels associated with various adverse health effects.

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 data in this section are 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, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) 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, determine whether or not the intensity of the effects varies 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 on 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 or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund 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) are 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 end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of

extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these 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

2.2.1.1 Death

Before its use as a refrigerant declined about 30 or more years ago, many human deaths were reported as a result of exposure to chloromethane vapors from leaks from home refrigerators and industrial cooling and refrigeration systems (Baird 1954; Borovska et al. 1976; Kegel et al. 1929; McNally 1946; Thordarson et al. 1965). In some cases, the individuals were found comatose or dead in their homes. In other cases, patients admitted to hospitals with typical neurological signs and symptoms of chloromethane poisoning (confusion, staggering, slurred speech) eventually became comatose, developed convulsions, and died. The concentrations and durations of exposure in these situations were not known. Exposure to high concentrations of chloromethane can result in moderate to severe neurological effects (see Section 2.2.1.4) but need not result in death if exposure is discontinued and/or medical attention is received in time. For example, workers exposed to concentrations as high as 600,000 ppm while repairing refrigeration leaks developed neurological symptoms, but did not die (Morgan Jones 1942).

In acute exposure situations, animals also died after developing severe signs of neurotoxicity. In an extensive investigation, a variety of species including rats, mice, guinea pigs, rabbits, dogs, cats, and monkeys were exposed to chloromethane until death (Dunn and Smith 1947; Smith 1947; Smith and von Oettingen 1947a,b). Severe neurological effects, such as paralysis, convulsions, and opisthotonos, developed before death. Although limitations of these studies, such as unknown purity of chloromethane, unconventional reporting of lethality data, and generally poor reporting of details, preclude precise determination of concentration-duration-response relationships, these studies demonstrate the universal response of animals to the neurotoxic and lethal effects of chloromethane. As seen in Table 2-1 and Figure 2-1, death of rats and mice from continuous exposure occurred at lower concentrations than from intermittent exposure, and mice appear to be more susceptible than rats. The greater susceptibility of mice has also been demonstrated in intermediate duration and chronic exposure studies (CIIT 1981). No effect on mortality was seen in rats exposed intermittently to 1000 ppm for up to 2 years; however, the same exposure of mice resulted

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	2 wk 4-5 d/wk 6 hr/d				3500 (killed in extremis)	Morgan et al. 1982
2	Rat	2 or 3 d 24 hr/d		500		1000	Burek et al. 1981
3	Rat	2 d 6 hr/d				7500 (8/12 deaths)	Chellman et al. 1986a
4	Mouse	11 d 5.5 hr/d				2400 (killed in extremis)	Landry et al. 1985
5	Mouse	12 d 6 hr/d		500		1000	Morgan et al. 1982
6	Mouse	1 d 6 hr/d				2200 (LC_{50}) 1500	Chellman et al. 1986b
7	Mouse	11 d 22 hr/d		100		150[a] (killed in extremis)	Landry et al. 1985
8	Mouse	2 wk 5 d/wk 6 hr/d				1500 (2/10 deaths)	Jiang et al. 1985
Systemic							
9	Human	1-2 wk 2-5 d/wk 1, 3 or 7.5 hr/d	Resp Cardio Hemato	150 150 150			Stewart et al. 1980
10	Human	1 d	Gastro		39,000 (nausea, vomiting)		Morgan Jones 1942

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
11	Human	1 d 4 hr/d	Gastro		29,000[b] (nausea, vomiting)		Battigelli and Perini 1955
12	Rat	2 wk 4-5 d/wk 6 hr/d	Hepatic Renal		2000 (moderate lesions) 2000 (degeneration and necrosis of tubules		Morgan et al. 1982
13	Rat	2 or 3 d 24 hr/d	Resp Hemato Hepatic Renal Other	2000 2000 500 500 200	1000 (fatty infiltration of liver) 500 (reversible weight loss)	1000 (kidney failure)	Burek et al. 1981
14	Rat	5 d 6 hr/d	Renal		5000 (necrosis)		Chellman et al. 1986a
15	Mouse	1 d 6 hr/d	Hepatic		1500 (increased SGPT)		Chellman et al. 1986b
16	Mouse	11 d 22 hr/d	Hepatic Other	100	150[a] (necrosis) 150[a] (decreased body weight gain)		Landry et al. 1985
17	Mouse	2 wk 5 d/wk 6 hr/d.	Renal		1500 (increased DNA synthesis, basophilia)		Chellman et al. 1986b
18	Mouse	11 d 5.5 hr/d	Hemato Renal Other	1600	2400 (enlarged spleen) 2400 (degeneration and regeneration of tubules) 2400 (decreased body weight gain)		Landry et al. 1985

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
19	Mouse	12 d 6 hr/d	Hepatic	1000	2000 (degeneration, necrosis)		Morgan et al. 1982
			Renal	500	1000 (basophilia, regeneration)		
20	Dog	3 d 23.5 hr/d	Resp	500			McKenna et al. 1981a
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Derm/Oc	500			
			Other	500			
21	Cat	3 d 23.5 hr/d	Resp	500			McKenna et al. 1981a
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Derm/Oc	500			
			Other	500			
Neurological							
22	Human	1 d				39,000 (convulsions, ataxia, staggering, double vision)	Morgan Jonesa 1942
23	Human	1-2 wk 2-5 d/wk 1,3 or 7.5 hr/d		150			Stewart et al. 1980
24	Human	1 d 3 hr/d			200[b] (4% decrement in performance)		Putz-Anderson et al. 1981a

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Neurological							
25	Human	1 d 4 hr/d				29000[b] (vertigo, confusion, tremors, weakness)	Battigelli and Perini 1955
26	Rat	2 or 3 d 24 hr/d		500		1000 (withdrawn appearance, lethargy)	Burek et al. 1981
27	Rat	5 d 6 hr/d				5000 (tremors, ataxia)	Chellman et al. 1986a
28	Rat	2 wk 4-5 d/wk 6 hr/d		3500		5000 (hindlimb paralysis, forelimb incoordination, cerebellar lesions)	Morgan et al. 1982
29	Mouse	12 d 6 hr/d				1000 (severe cerebellar degeneration, ataxia)	Morgan et al. 1982
30	Mouse	11 d 5.5 hr/d		150		400 (degeneration in cerebellum)	Landry et al. 1985
31	Mouse	11 d 22 hr/d		50[c]		100[a] (cerebellar degeneration)	Landry et al. 1985
32	Mouse	2 wk 5 d/wk 6 hr/d				1500 (motor incoordination, degeneration)	Jiang et al. 1985
33	Dog	3 d 23.5 hr/d		200		500 (neuropathy, histological lesions)	McKenna et al. 1981a
Developmental							
34	Rat	13 d 6 hr/d Gd 7-19				1500[a] (delayed development)	Wolkowski-Tyl et al. 1983a

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Developmental							
35	Mouse	12 d 6 hr/d Gd 6-17				500 (heart defects in fetuses)	Wolkowski-Tyl et al. 1983a
36	Mouse	12 d 6 hr/d Gd 6-17		250		500 (heart defects in fetuses)	Wolkowski-Tyl et al. 1983b
Reproductive							
37	Rat	5d 6 hr/d				3000 (persistent decreased fertility)	Working et al. 1985a
38	Rat	5 d 6 hr/d			3000 (reversible disruption of spermatogenesis)		Working et al. 1985b
39	Rat	9 d 4-5 d/wk 6 hr/d				3500 (irreversible lesions in testes)	Chapin et al. 1984
40	Rat	5 d 6 hr/d			3000 (sperm toxicity)		Chellman et al. 1987
41	Rat	2 or 3 d 24 hr/d		200	500[a] (degeneration of epididymides)		Burek et al. 1981
42	Rat	5 d 6 hr/d			5000 (testicular lesion, granuloma epididymis)		Chellman et al. 1986a
43	Rat	5 d 6 hr/d				3000[a] (post implantation loss)	Chellman et al. 1986c
44	Rat	5 d 6 hr/d			1000[a] (decreased fertility)	3000 (severely reduced fertility)	Working and Bus 1986
45	Rat	2 wk 4-5 d/wk 6 hr/d			2000 (testicular degeneration)		Morgan et al. 1982

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Reproductive							
46	Dog	3 d 23.5 hr/d		500			McKenna et al. 1981a
47	Cat	3 d 23.5 hr/d		500			McKenna et al. 1981a
INTERMEDIATE EXPOSURE							
Death							
48	*Rat*	*12 mo* 5 d/wk 6 hr/d		*1000*			CIIT 1981
49	Mouse	6 mo 5 d/wk 6 hr/d		1000			CIIT 1981
50	Mouse	12 mo 5 d/wk 6 hr/d		225		1000[a] (increased mortality)	CIIT 1981
51	Dog	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
Systemic							
52	Rat	90 d 5 d/wk 6 hr/d	Resp Cardio Hemato Hepatic Renal Derm/Oc Other	1500 1500 1500 1500 1500 	 1500 (increased liver weight, infarct) 375[a] (decreased body weight)		Mitchell et al. 1979

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
53	Rat	6 mo 5 d/wk 6 hr/d	Other		1000 (decreased body weight gain)		CIIT 1981
54	Rat	12 mo 5 d/wk 6 hr/d	Hepatic Renal Derm/Oc Other	1000 1000 1000 225	1000 (decreased body weight gain)		CIIT 1981
55	Mouse	6 mo 5 d/wk 6 hr/d	Hepatic Renal Derm/Oc Other	 1000 1000 225[d]	1000[a] (necrosis) 1000 (decreased body weight gain		CIIT 1981
56	Mouse	12 mo 5 d/wk 6 hr/d	Hepatic Renal Other	225 225 225	1000 (necrosis) 1000[a] (hyperplasia) 1000 (decreased body weight gain)		CIIT 1981
57	Mouse	90 d 5 d/wk 6 hr/d	Resp Cardio Hemato Hepatic Renal Other	1500 1500 1500 750 1500	1500 (vacuolization) 1500 (decreased body weight gain)		Mitchell et al. 1979
58	Dog	90 d 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Hepatic Renal Derm/Oc Other	400 400 400 400 400 400 400 400			McKenna et al. 1981b

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Immunological							
59	Mouse	6 mo 5 d/wk 6 hr/d			1000 (lymphoid depletion of spleen)		CIIT 1981
Neurological							
60	Human	2-3 wk or more 5 d/wk 8-16 hr/d (occup)				265[b] (neurological symptoms)	Scharnweber et al. 1974
61	Mouse	6 mo 5 d/wk 6 hr/d				1000[a] (tremor, paralysis)	CIIT 1981
62	Mouse	12 mo 5 d/wk 6 hr/d				1000 (tremor, paralysis)	CIIT 1981
63	Mouse	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
Reproductive							
64	Rat	6 mo 5 d/wk 6 hr/d				1000[a] (testicular atrophy)	CIIT 1981
65	Rat	20 wk 5-7 d/wk 6 hr/d			475 (reduced fertility)[a]	1500[a] (sterility)	Hamm et al. 1985
66	Rat	12 mo 5 d/wk 6 hr/d		225		1000 (testicular atrophy)	CIIT 1981

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Reproductive							
67	Mouse	12 mo 5 d/wk 6 hr/d		1000			CIIT 1981
68	Dog	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
CHRONIC EXPOSURE							
Death							
69	Rat	24 mo 5 d/wk 6 hr/d		1000			CIIT 1981
70	Mouse	24 mo 5 d/wk 6 hr/d		225		1000 (increased mortality)	CIIT 1981
71	Mouse	18 mo 5 d/wk 6 hr/d				1000 (increased mortality)	CIIT 1981
Systemic							
72	Rat	24 mo 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Hepatic Renal Derm/Oc Other	1000 1000 1000 1000 1000 1000 1000 225	1000 (decreased body weight gain)		CIIT 1981

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
73	Rat	18 mo 5 d/wk 6 hr/d	Other		1000 (decreased body weight gain)		CIIT 1981
74	Mouse	18 mo 5 d/wk 6 hr/d	Hepatic Renal Other		1000 (degeneration) 1000 (hyperplasia) 1000 (decreased body weight gain)		CIIT 1981
75	Mouse	24 mo 5 d/wk 6 hr/d	Resp Cardio Hemato Hepatic Renal Derm/Oc Other	1000 1000 1000 225 225 1000 225[e]	 1000 (degeneration) 1000 (hyperplasia) 1000 (decreased body weight gain)		CIIT 1981
Immunological							
76	Mouse	18 mo 5 d/wk 6 hr/d			1000 (splenic atrophy)		CIIT 1981
Neurological							
77	Rat	24 mo 5 d/wk 6 hr/d		1000			CIIT 1981
78	Mouse	24 mo 5 d/wk 6 hr/d		225		1000 (neurotoxicity, cerebellar lesions)	CIIT 1981
79	Mouse	18 mo 5 d/wk 6 hr/d				1000 (neurotoxicity, cerebellar lesions	CIIT 1981

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Reproductive							
80	Rat	24 mo 5 d/wk 6 hr/d		225		1000 (testicular atrophy)	CIIT 1981
81	Rat	18 mo 5 d/wk 6 hr/d				1000 (testicular atrophy)	CIIT 1981
82	Mouse	24 mo 5 d/wk 6hr/d		225	1000 (testicular degeneration)		CIIT 1981
83	Mouse	18 mo 5 d/wk 6 hr/d			1000 (testicular degeneration)		CIIT 1981
Cancer							
84	Mouse	24 mo 5 d/wk 6 hr/d				1000[f] (kidney tumors)	CIIT 1981

[a]Presented in Table 1-2.
[b]Presented in Table 1-1.
[c]Used to derive acute inhalation MRL. Dose adjusted for intermittent exposure. Uncertainty Factor of 100 (10 for intraspecies variability, 10 for interspecies variability) applied resulting in an MRL of 0.46 ppm. The MRL is presented in Table 1-1.
[d]Used to derive intermediate inhalation MRL. Dose adjusted for intermittent exposure. Uncertainty Factor of 100 (10 for interspecies variability, 10 for intraspecies variability) applied resulting in an MRL of 0.40 ppm. The MRL is presented in Table 1-1.
[e]Used to derive chronic inhalation MRL. Dose adjusted for intermittent exposure. Uncertainty Factor of 100 (10 for interspecies variability, 10 for intraspecies variability) applied resulting in an MRL of 0.40 ppm. The MRL is presented in Table 1-1.
[f]Cancer Effect Level (CEL).

Cardio = Cardiovascular; CNS = central nervous system; d = day; Derm/Oc = Dermal/Ocular; Gastro = Gastrointestinal; Gd = Gestational day; Hemato = Hematological; hr = hour; LC_{50} = lethal concentration; 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = Respiratory; wk = week.

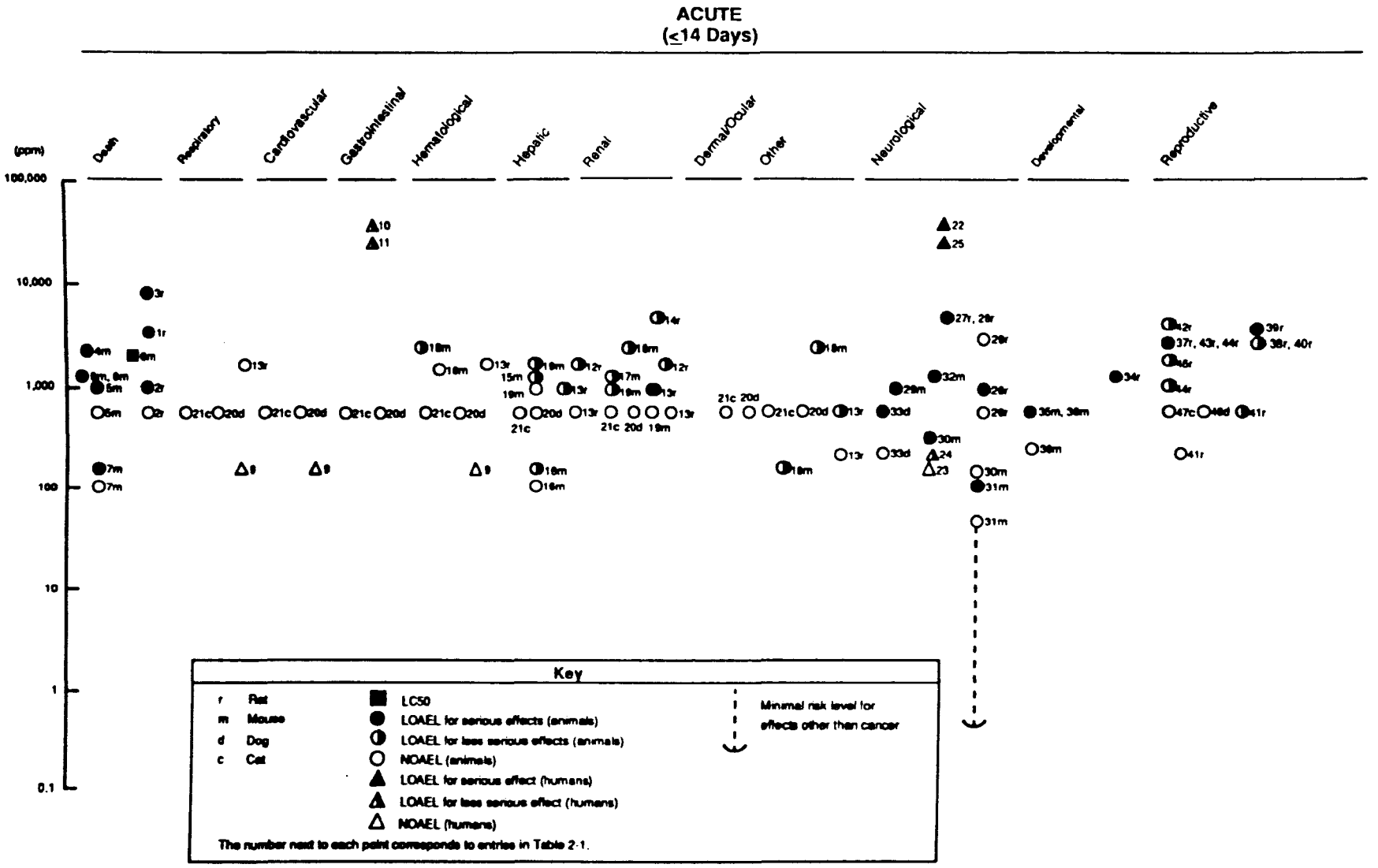


FIGURE 2-1. Levels of Significant Exposure to Chloromethane - Inhalation

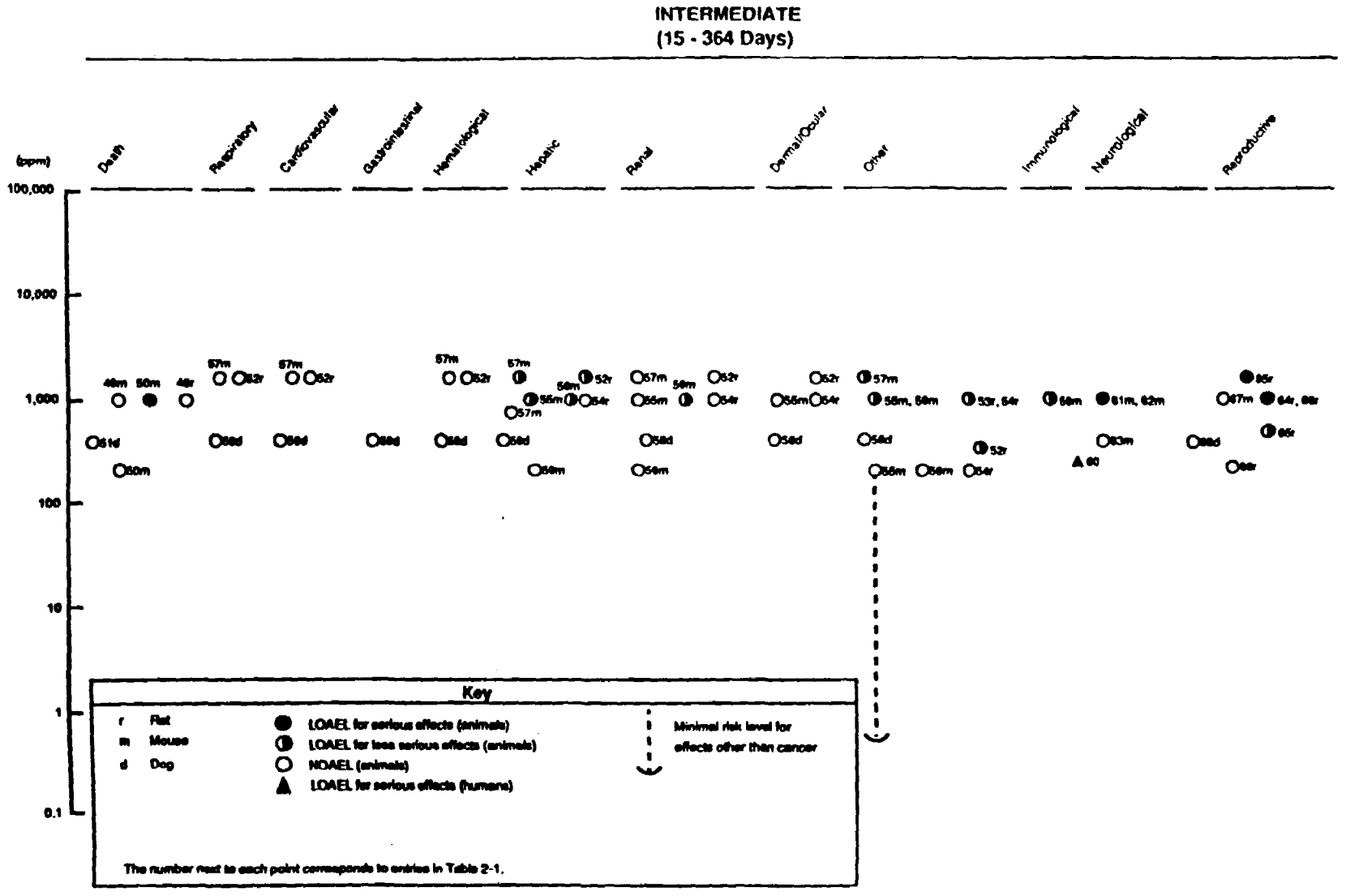


FIGURE 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (Continued)

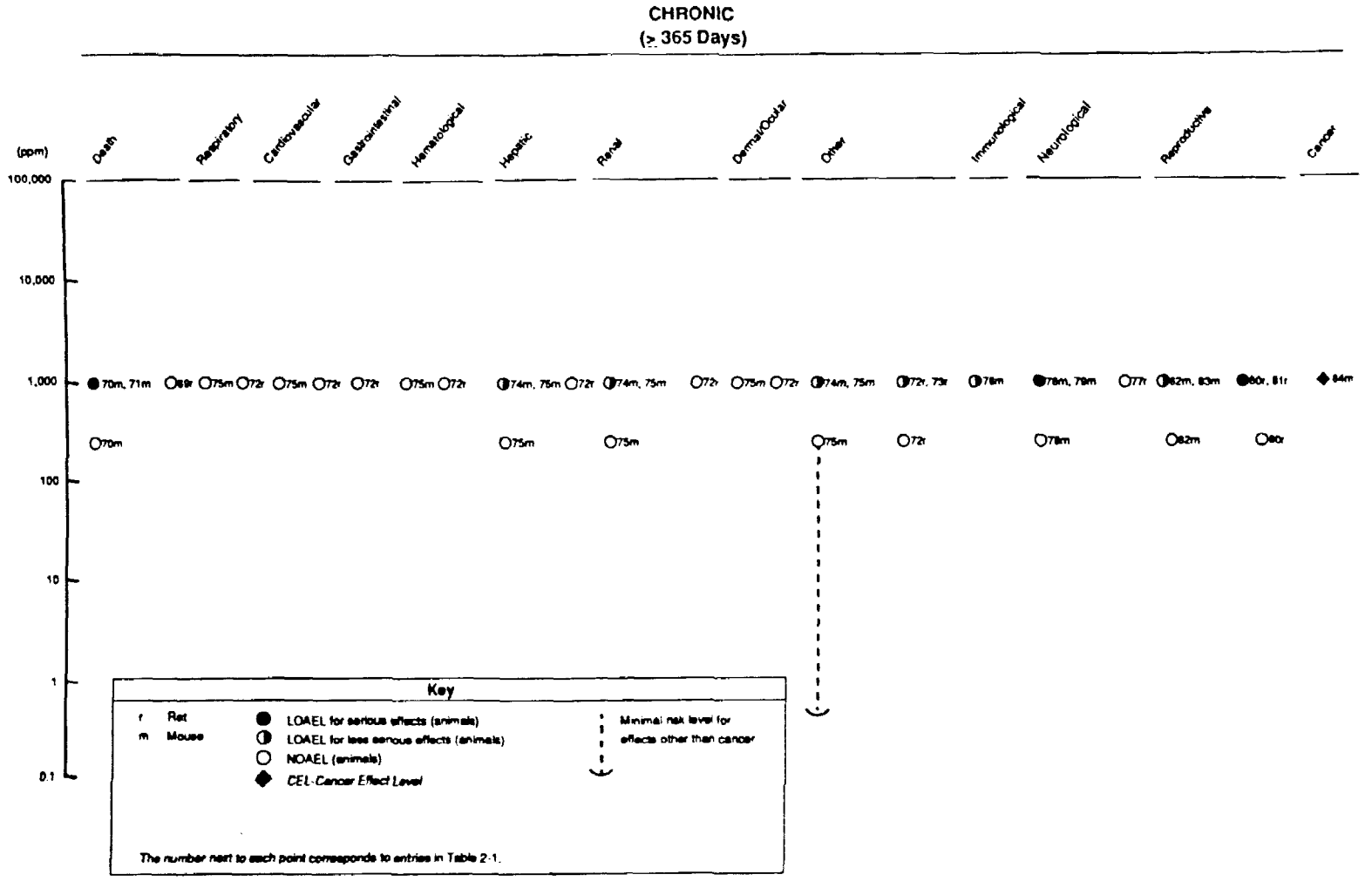


FIGURE 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (Continued)

in significantly increased mortality after exposure for 1 year. This became so dramatic that the 1000 ppm exposure groups were terminated at 21 and 22 months of exposure. No deaths occurred in male dogs (four per group) exposed to 400 ppm chloromethane or greater for 90 days (McKenna et al. 1981b). Female dogs were not tested. The highest levels that did not cause death and all reliable levels that caused death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Respiratory Effects. Case reports generally have not described respiratory effects in humans exposed to chloromethane. No effects on pulmonary function were observed in volunteers who participated in a study of neurological and neurobehavioral effects of acute inhalation exposure of up to 150 ppm chloromethane (Stewart et al. 1980). This study, however, had several limitations such as small sample size, multiple dosing schemes, and confusing protocol. Specifically, groups of two to four men and two to four women were exposed to 20, 100, or 150 ppm or to concentrations that were increased from 50 to 150 ppm in the same group for 1, 3, or 7.5 hours/day for 2-5 days/week for 1 or 2 weeks. Several subjects, both male and female, dropped out of the study before some of the experiments were completed, and other subjects were added. Furthermore, the same subjects were used for different protocols during different weeks of the study. Despite the limitations, however, chloromethane exposure did not appear to have any effect on pulmonary function.

Acute exposure of dogs to 15,000 ppm caused an initial rise in heart rate and blood pressure, followed by markedly reduced respiration, decreased heart rate, and a progressive fall in blood pressure until the dogs died within 4-6 hours (von Oettingen et al. 1949, 1950). These effects may have resulted from vasodilation due to depression of the central nervous system. Pulmonary congestion was a common finding among the various species exposed to chloromethane until death (Dunn and Smith 1947; Smith and von Oettingen 1947a). As discussed above in Section 2.2.1.1, however, limitations of these reports preclude precise determination of concentration-duration-response relationships. Furthermore, more recent studies using very pure chloromethane (99.5-99.9%) failed to find any exposure-related histopathological lesions in the lungs of male dogs and male cats exposed acutely to 500 ppm chloromethane (McKenna et al. 1981a), rats exposed acutely to 2000 ppm (Burek et al. 1981), male dogs exposed to 400 ppm and rats and mice exposed to up to 1500 ppm chloromethane for intermediate durations (CIIT 1981; McKenna et al. 1981b; Mitchell et al. 1979), or rats and mice exposed chronically to up to 1000 ppm (CIIT 1981). The highest NOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Cardiovascular Effects. Cardiovascular effects of chloromethane have been described in case reports of humans exposed to chloromethane occupationally or accidentally due to refrigerator leaks (Gummert 1961;

Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Spevak et al. 1976; Verriere and Vachez 1949). These effects include electrocardiogram abnormalities, tachycardia and increased pulse rate, and decreased blood pressure. The precise concentrations and durations of exposure are not known. A retrospective epidemiological study of workers exposed to chloromethane in a butyl rubber manufacturing plant found no statistical evidence that the rate of death due to diseases of the circulatory system was increased in the exposed population when compared with U.S. Mortality rates (Holmes et al. 1986). In a study of neurological and neurobehavioral effects of acute inhalation exposure in volunteers, no abnormalities of cardiac function or electrocardiograms were found at concentrations up to 150 ppm (Stewart et al. 1980).

Dogs exposed acutely to 15,000 ppm had an initial rise in heart rate and blood pressure, followed by markedly reduced respiration, decreased heart rate, and a progressive fall in blood pressure until death, which occurred within 4-6 hours (von Oettingen et al. 1949, 1950). These effects may have resulted from vasodilation due to depression of the central nervous system. Chloromethane exposure does not appear to result in histopathological lesions in the heart, as demonstrated by acute studies in male dogs and cats exposed to 500 ppm chloromethane (McKenna et al. 1981a), by intermediate duration studies in male dogs exposed to 400 ppm and in rats and mice exposed to up to 1500 ppm chloromethane (McKenna et al. 1981b; Mitchell et al. 1979), and by chronic studies in rats and mice exposed to up to 1000 ppm (CIIT 1981). The highest NOAEL values for cardiovascular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Gastrointestinal Effects. Numerous case reports of humans exposed to chloromethane vapors as a result of industrial leaks and defective refrigerators have described symptoms of nausea and vomiting (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Hansen et al. 1953; Kegel et al 1929; Mackie 1961; Morgan Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Verriere and Vachez 1949). In all cases, these symptoms were accompanied by central nervous system toxicity, which was usually severe. It is not clear, therefore, if the nausea and vomiting were secondary to the neurotoxic effects of chloromethane. Two of the reports (Battigelli and Perini 1955; Morgan Jones 1942) provided exposure concentration data. The LOAELs for gastrointestinal effects in humans are recorded in Table 2-1 and plotted in Figure 2-1.

Histopathological examination of animals exposed to various concentrations of chloromethane for acute, intermediate, or chronic durations did not show evidence of gastrointestinal damage (CIIT 1981; McKenna et al. 1981a,b). The highest NOAELs for gastrointestinal effects in animals are recorded in Table 2-1 and plotted in Figure 2-1.

Hematological Effects. No hematological effects were found in volunteers who participated in a study of neurological and neurobehavioral

effects of acute inhalation exposure of up to 150 ppm chloromethane (Stewart et al. 1980). Case reports of human overexposure have also generally been negative for hematological effects.

Spleen enlargement, suggestive of extramedullary hematopoiesis, and hemoglobinuria, suggestive of intravascular hemolysis, were found in female mice exposed intermittently to a high concentration (2400 ppm) of chloromethane for 11 days (Landry et al. 1985). These effects were not seen when female mice were exposed continuously to a lower concentration (150 ppm) (Landry et al. 1985). Male mice were not used in this study. No exposure-related effects on hematological parameters were found in male dogs or cats exposed continuously for 3 days to 500 ppm (McKenna et al. 1981a), or in rats exposed continuously for 3 days to 2000 ppm (Burek et al. 1981). In addition, male dogs exposed to 400 ppm and rats or mice exposed to 1500 ppm for 90 days (McKenna et al. 1981b; Mitchell et al. 1979), and rats and mice exposed for 6, 12, 18, or 24 months to up to 1000 ppm (CIIT 1981) did not have hematological effects. LOAEL and NOAEL values for spleen enlargement, and the highest NOAEL values for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Hepatic Effects. Case reports of humans exposed to chloromethane have described clinical jaundice (Kegel et al. 1929; Mackie 1961; Weinstein 1937). A case of jaundice and cirrhosis of the liver was attributed to chloromethane exposure in a man who had been a refrigeration engineer for 10 years and had frequently been exposed to chloromethane vapors (Wood 1951). There was no reason to believe that these liver effects were due to other causes such as infective hepatitis or to alcohol consumption.

Hepatic effects have also been observed in animals exposed to chloromethane, and mice appear to be more susceptible than rats. Rats exposed to 1000-1500 ppm for acute, intermediate, or chronic durations had either no liver effects or relatively mild to moderate changes, such as loss of normal areas of basophilia, cloudy swelling, increased liver weight, fatty infiltration, and increased levels of SGPT, SGOT, and serum bilirubin (Burek et al. 1981; Chellman et al. 1986b; CIIT 1981; Mitchell et al. 1979; Morgan et al. 1982). No necrosis was seen. Acute, intermediate, or chronic exposure of mice to 1000-1500 ppm generally resulted in necrosis and degeneration (CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan et al. 1982). Female mice exposed acutely to a relatively high intermittent concentration (2400 ppm) had milder liver effects than those exposed to a continuous lower concentration (150 ppm) (Landry et al. 1985). Although no liver effects were observed in male dogs and cats (McKenna et al. 1981a,b), the exposure concentrations (400 or 500 ppm) may not have been high enough to produce liver toxicity in these species. The highest NOAEL values and all reliable LOAEL values for liver effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Renal Effects. Case reports of humans exposed to chloromethane have described such indicators of renal toxicity as albuminuria, increased serum creatinine and blood urea nitrogen, proteinuria, and anuria (Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Verriere and Vachez 1949). Exposure concentrations at which these effects occur are not known.

Effects on the kidney have also been observed in rats and mice. In acute studies, rats exposed intermittently to 2000-2500 ppm had degeneration and necrosis of the proximal convoluted tubules (Chellman et al. 1986a; Morgan et al. 1982), while rats exposed continuously to 1000 ppm had evidence of renal failure (Burek et al. 1981). In intermediate and chronic studies in which rats were exposed intermittently to ≤1500 ppm, however, no effects on the kidneys were observed (CIIT 1981; Mitchell et al. 1979; McKenna et al. 1981b). Areas of basophilia, which were interpreted as evidence of regeneration, were found in kidneys of mice exposed acutely to 1000 ppm (Morgan et al. 1982) and 1500 ppm (Chellman et al. 1986b). An extensive study by CIIT (1981) did not find kidney lesions in mice killed after 6 months of exposure, but hyperplasia and kidney tumors were observed after 12, 18, and 24 months of exposure. The highest NOAEL values and all reliable LOAEL values for kidney effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Dermal/Ocular Effects. Case reports of humans exposed to chloromethane have described such symptoms as blurred and double vision (Baker 1927; Borovska et al. 1976; Gummert 1961; Kegel et al. 1929; Mackie 1961). These symptoms probably reflect effects on the nervous system rather than effects on the eye itself.

Ophthalmological examination of male cats and dogs exposed to 500 ppm continuously for 3 days (McKenna et al. 1981a), male dogs exposed to 400 ppm for 90 days (McKenna et al. 1981b), or of rats and mice exposed to 1000 ppm for up to 24 months (CIIT 1981) failed to reveal eye lesions. However, mucopurulent conjunctivitis with total destruction of the eye in some cases was found in mice exposed to ≥375 ppm for 90 days (Mitchell et al. 1979). These lesions were attributed to exposure because no lesions were found in controls; however, the failure of longer-term studies to detect eye lesions at higher concentrations makes the findings of Mitchell et al. (1979) questionable. If the eye lesions were due to chloromethane exposure, the effect was probably due to direct contact of the vapor with the eye, rather than a consequence of inhalation. The highest NOAEL values for dermal/ocular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Other Systemic Effects. Other than neurological effects, which are discussed in a separate section, studies and case reports of humans exposed to chloromethane have not described other systemic effects.

The only other consistent systemic effect of chloromethane exposure in animals is reduced body weight gain, which was observed in rats and mice

exposed to chloromethane for acute, intermediate, and chronic durations (Burek et al. 1981; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979). The highest NOAEL values and all reliable LOAEL values for other systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. The highest NOAEL in both intermediate and chronic duration studies, below which no LOAEL exists, is 225 ppm in the CIIT (1981) study. Based on the NOAEL of 225 ppm, intermediate and chronic duration inhalation MRLs of 0.40 ppm were calculated as described in the footnote in Table 2-1. The MRL is presented in Table 1-1.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to chloromethane.

In animals, the only effects that could possibly be considered immunological effects were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed to 1000 ppm chloromethane for up to 2 years (CIIT 1981). The lymphoid depletion was first observed in mice killed after 6 months of exposure, while the splenic atrophy was observed in mice killed after 18 months. This LOAEL value for immunological effects in mice is recorded in Table 2-1 and plotted in Figure 2-1 for both intermediate and chronic duration categories. The lower exposure level in this study (225 ppm) cannot be considered a NOAEL for immunological effects, however, because more sensitive tests for immune function were not conducted. In addition, cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than did control cats (McKenna et al. 1981a). The lesions, however, were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease could not be ruled out. It is not known whether the exacerbation would represent an immunological effect.

2.2.1.4 Neurological Effects

Numerous case reports of humans exposed to chloromethane vapors as a result of industrial leaks and defective refrigerators have described neurological effects (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Gummert 1961; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; Morgan Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). In addition, a couple who had stored insulated boards made of polystyrene foam in the basement of their home had symptoms of neurotoxicity (Lanham 1982). (Chloromethane is used in the production of some polystyrene foam, from which it is slowly emitted.) In general, symptoms develop within a few hours after exposure and include fatigue, drowsiness, staggering, headache, blurred and double vision, mental confusion, tremor, vertigo, muscular cramping and rigidity, sleep disturbances, and ataxia. These symptoms may persist for several months, and depression and personality changes may develop, although

complete recovery generally occurs eventually. In cases of more severe poisoning, convulsion, coma, and death may ensue. Microscopic examination of the brain of an individual who died revealed accumulation of lipoid-filled histiocytes in the leptomeninges of the hemispheres, hyperemia of the cerebral cortex, and lipoid droplets in the adventitia cells of the capillaries throughout the brain (Kegel et al. 1929).

Although the precise concentrations and durations of exposure resulting in neurological effects were generally not known, a few reports were able to define exposure concentrations. In cases in which workers were exposed acutely to leaks while repairing refrigeration systems, exposures were ≥29,000 ppm (Battigelli and Perini 1955; Morgan Jones 1942). In a report of six cases, workers were exposed occupationally to relatively low levels (TWA 265 ppm) for 2-3 weeks before the onset of typical symptoms (Scharnweber et al. 1974). In addition, the concentration of chloromethane in the home of the couple who stored polystyrene foam insulation boards in their basement was in excess of 200 ppm (Lanham et al. 1982). In a study of volunteers, no exposure-related neurological abnormalities or abnormal EEGs, and no effects on cognitive tests or subjective response were found at acute exposures of up to 150 ppm (Stewart et al. 1980), while, although not statistically significant, a 4% decrement in performance in behavioral tests was found at an acute exposure level of 200 ppm (Putz-Anderson et al. 1981a). Although some of these studies had limitations, taken as a whole they indicate that the threshold for neurological and behavioral effects in humans appears to be about 200 ppm.

Chloromethane exposure also results in neurological effects in animals. Rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed to chloromethane until death all displayed signs of severe neurotoxicity, including paralysis and convulsions (Smith and von Oettingen 1947a,b). As discussed in Section 2.2.1.1, these studies have several limitations that preclude determination of concentration-duration-response relationships, but are useful for demonstrating the universal response of animals to the neurotoxic effects of chloromethane. More recent studies using very pure chloromethane have also demonstrated neurotoxic effects of acute inhalation exposure of rats, mice, and male dogs (Burek et al. 1981; Chellman et al. 1986a,b; Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982; McKenna et al. 1981a). Effects include ataxia, tremors, limb paralysis and incoordination, and cerebellar lesions consisting of degeneration of the granular layer. Mice appear to be more sensitive than rats, developing similar but more severe effects at lower exposure concentrations (Morgan et al. 1982). In addition, under identical exposure conditions, male dogs, which developed hind limb stiffness and tremors and had brain and spinal cord lesions, appeared to be more sensitive than male cats, which had brain lesions consistent with viral-induced central nervous system disease (McKenna et al. 1981a). Neurotoxic effects occurred at lower concentrations in continuously exposed mice than in intermittently exposed mice (Landry et al. 1985).

Mice exposed to 1000 ppm for 6 or 12 months developed signs of neurotoxicity (tremor and paralysis) but had no histopathological lesions (CIIT 1981). After exposure for 18 or 24 months, however, reduced numbers of neurons in the granular cell layer of the cerebellum and degenerative changes in the spinal cord were observed. This study also demonstrates the greater sensitivity of mice to the neurotoxicity of chloromethane, as no clinical signs or histological evidence of neurotoxicity were observed in rats similarly exposed.

The highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. The 50 ppm concentration in mice exposed continuously for 11 days (Landry et al. 1985) is the highest NOAEL below which no LOAEL exists. At 100 ppm, the mice had cerebellar lesions. Based on the NOAEL of 50 ppm, an acute inhalation MRL of 0.46 ppm was calculated as described in the footnote in Table 2-1. This MRL is presented in Table 1-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to chloromethane.

Maternal toxicity, evidenced by decreased body weight gain and retarded development of fetuses, was observed in rats exposed to 1500 ppm chloromethane for 6 hours/day during gestational days 7-19 (Wolkowski-Tyl et al. 1983a). The fetal effects consisted of reduced fetal body weight and crown-rump length and reduced ossification of metatarsals and phalanges of the anterior limbs, thoracic centra in the pubis of the pelvic girdle, and metatarsals of the hind limbs. Concentration-related higher incidences of heart malformations were also found among fetuses of mice exposed to chloromethane for 6 hours/day during gestational days 6-17 (Wolkowski-Tyl et al. 1983a,b). The heart malformations consisted of absence or reduction of atrioventricular valves, chordae tendineae, and papillary muscles. The heart anomaly may have been an artifact of the sectioning technique, due to the examination of fixed as opposed to unfixed fetal tissue, or a misdiagnosis, as suggested by John-Greene et al. (1985), because they failed to find the defect when they attempted to increase the incidence of heart malformations by continuously exposing the dams to a higher concentration, but only during gestational days 11.5-12.5. They also found much interanimal variability in the appearance of the papillary muscles in control mice. This period (gestational days 11.5-12.5) was chosen as the critical period for development of the embryonal heart (John-Greene et al. 1985). However, Wolkowski-Tyl (1985) countered that the inability of John-Greene et al. (1985) to detect the abnormality was due to the different exposure protocol and that the critical period is more appropriately gestational day 14. Until the controversy is resolved, it is prudent to consider chloromethane a developmental toxicant in mice. NOAEL and LOAEL values for developmental effects in mice 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 chloromethane.

Chloromethane is a reproductive toxicant in male rats. In acute exposure experiments (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1987; Morgan et al. 1982; Working et al. 1985a,b; Working and Bus 1986), inhalation exposure of male rats resulted in disruption of spermatogenesis (delayed spermiation, disorganization of the seminiferous epithelium, decreased mid and late spermatids, increased abnormal sperm, decreased fertility), inflammation of the epididymides, and sperm granulomas in the epididymides. Inhalation exposure of male rats also resulted in preimplantation and postimplantation loss (see Section 2.2.1.7 on Genotoxic Effects below) in unexposed females mated to the exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). In a 20-week reproduction study in rats, reduced fertility was found in males at 475 ppm, and complete sterility was found at 1500 ppm (Hamm et al. 1985). Germinal epithelial degeneration and atrophy of the seminiferous tubules was found in male rats exposed to 1000 ppm chloromethane at the 6-month interim kill (CIIT 1981). The incidence of these lesions increased at later kills such that all males exposed to 1000 ppm had lesions at 18 months. Testicular lesions were also found in mice similarly exposed for 18 months. No testicular effects were found in cats or dogs exposed acutely for 3 days or in dogs exposed for 90 days (McKenna et al. 1981a,b). It is possible that male dogs and male cats are not sensitive to the reproductive effects of chloromethane, but the concentrations may not have been high enough to produce the effect. The highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to chloromethane.

In animals, chloromethane exposure has resulted in dominant lethal mutations in the sperm of male rats (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Experiments on the mechanism of the postimplantation loss observed in the females mated to the exposed males indicated that the dominant lethal effect may be secondary to epididymal inflammation, rather than a direct genotoxic effect of chloromethane itself (Chellman et al. 1986c). Chloromethane did not result in unscheduled DNA synthesis in hepatocytes, spermatocytes, or tracheal epithelial cells when male rats were exposed to 3500 ppm, 6 hours/day for 5 days, but did produce a marginal increase in unscheduled DNA synthesis in hepatocytes when rats were exposed to 15,000 ppm for 3 hours (Working et al. 1986).

2.2.1.8 Cancer

A retrospective epidemiology study of 852 male workers exposed to chloromethane in a butyl rubber manufacturing plant produced no statistical evidence that the rates of deaths due to cancer at any site were increased in the exposed population when compared with U.S. Mortality rates (Holmes et al. 1986). The subjects had worked in the plants for at least 1 month from 1943. No specific exposure levels were given in this study.

A high incidence of renal tumors was found in male mice that were exposed to 1000 ppm chloromethane and died or were killed from 12 months on (CIIT 1981). Tumors consisted of renal cortex adenomas and adenocarcinomas, papillary cystadenomas, tubular cystadenomas, and papillary cystadenocarcinomas. No evidence of carcinogenicity was found in male mice exposed to 50 or 225 ppm or in female mice or male and female rats exposed to any concentration (1000 ppm or less) in this study. The cancer effect level is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

Only one animal study was located in which chloromethane was administered orally. In this study, the hepatotoxic effects of chloroform, carbon tetrachloride, dichloroethane, and chloromethane were compared (Reynolds and Yee 1967). Rats were given chloromethane in mineral oil by gavage at a single dose of 420 mg/kg. Only the livers were examined for effects, but no liver necrosis was found in the rats given chloromethane. Higher doses of chloromethane were not administered because of the known anesthetic and lethal effects of the compound.

Other than the study described above, no studies were located regarding the following health effects in humans or animals after oral exposure to chloromethane.

2.2.2.1 Death

2.2.2.2 Systemic Effects

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

2.2.3 Dermal/Ocular Exposure

Other than the study by Mitchell et al. (1979) described in Section 2.2.1.2 above, in which possible ocular effects were observed in mice following exposure to chloromethane vapors, no studies were located regarding the following effects in humans or animals after dermal/ocular exposure.

2.2.3.1 Death

2.2.3.2 Systemic Effects

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

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Chloromethane is absorbed readily from the lungs of humans following inhalation exposure. Alveolar breath levels of chloromethane reached equilibrium within 1 hour during a 3- or 3.5-hour exposure of men and women (Putz-Anderson et al. 1981a,b). Mean ± SD alveolar breath levels were 63±23.6 ppm in 24 men and women exposed to 200 ppm and 36±12 ppm in 8 men and women exposed to 100 ppm for 3 hours. Mean ± SD blood levels were 11.5±12.3 ppm for the 200 ppm exposed group and 7.7±6.3 ppm for the 100 ppm exposed group. The results suggest that uptake was not proportional to exposure concentration, but individual levels were quite variable based on the standard deviations. A high correlation between alveolar air and blood levels ($r=0.85$, $p \leq 0.01$) was found.

Blood and alveolar air levels of chloromethane also reached equilibrium during the first hour of exposure in six men exposed to 10 or 50 ppm for 6 hours (Nolan et al. 1985). The levels in blood and expired air were proportional to the exposure concentrations. Based on elimination data, the subjects were divided into two groups, fast and slow metabolizers. The difference between inspired and expired chloromethane concentrations

indicated that the fast metabolizers absorbed 3.7 μg/min/kg and the slow metabolizers absorbed 1.4 μg/min/kg.

In experiments in rats, uptake of chloromethane reached equilibrium within 1 hour and was proportional or nearly proportional to exposure concentrations of 50-1000 ppm for 3-6 hours (Landry et al. 1983a,b). Absorbed doses were calculated to be 67 mg/kg for rats exposed to 1000 ppm and 3.8 mg/kg for rats exposed to 50 ppm (ratio of 17.6 compared to predicted ratio of 20 if proportional to exposure concentration). The rate of uptake was 165 mg/min/kg for 1000 ppm and 10 mg/min/kg for 50 ppm (ratio of 16.5). Where the uptake was not completely proportional to exposure, the difference in the ratio of absorbed doses from the predicted ratios may be due to the lower respiratory minute volume in the rats exposed to 1000 ppm and to different amounts remaining in the body at the end of exposure and the amounts metabolized (Landry et al. 1983b). Blood chloromethane concentrations also reached equilibrium within 1 hour and were proportional to exposure concentration in dogs exposed to 50 or 1000 ppm (Landry et al. 1983a) or 15,000 or 40,000 ppm (von Oettingen et al. 1949, 1950) for 6 hours.

At relatively low exposure concentrations, absorption of chloromethane from the lungs appears to be proportional to exposure concentration in rats and humans, but at higher concentrations, some process, such as metabolism or excretion, becomes saturated, limiting the rate of uptake. In dogs, however, it appears that absorption is proportional to exposure concentration through a wide range of exposure levels.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to chloromethane.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to chloromethane.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to chloromethane.

After absorption of chloromethane, distribution of chloromethane and/or its metabolites is extensive in animals. Total uptake of radioactivity (as μmol [^{14}C]-chloromethane equivalents/g wet weight) in whole tissue homogenates following exposure of rats to 500 ppm for 6 hours was 1.21 for lung, 4.13 for liver, 3.43 for kidney, 2.29 for testes, 0.71

for muscle, 0.57 for brain, and 2.42 for intestine (Kornbrust et al. 1982). Little difference in the pattern of distribution was found at an exposure concentration of tissue homogenate macromolecules 1500 ppm as compared with 500 ppm. Upon acid precipitation of protein, 80% of the radioactivity present was found in the acid soluble (unbound) fraction. The remainder was found to have been metabolically incorporated into lipid, RNA, DNA, and protein, rather than bound to the macromolecules as a result of direct alkylation. Tissue levels of chloromethane (in mg%) in dogs exposed to chloromethane for 6 hours were 4.5 in liver, 4.1 in heart, and 3.7 in brain at 15,000 ppm and 9.3 in liver, 8.1 in heart, and 9.9 in brain at 40,000 ppm (von Oettingen et al. 1949, 1950).

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals after oral exposure to chloromethane.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to chloromethane.

2.3.3 Metabolism

Information regarding metabolism of chloromethane in humans is limited. In a group of six workers exposed to TWA 8-hour workroom concentrations of 30-90 ppm, the urinary excretion of S-methylcysteine, which is formed as a result of conjugation of chloromethane with glutathione, showed wide variations, with little correlation to exposure levels (van Doorn et al. 1980). In four of the workers all values were higher than in controls, and appeared to build up during the course of the week. Two of the workers had only minor amounts of S-methylcysteine in the urine, but these workers experienced the highest exposure concentrations. It appeared that two distinct populations of individuals exist: fast metabolizers with lower body burdens and higher excretion, and slow metabolizers with higher body burdens and lower excretion (van Doorn et al. 1980). The difference may be due to a deficiency of the enzyme glutathione-S-transferase that catalyzes the conjugation of chloromethane with glutathione. Other possible reasons for the differences in chloromethane elimination among subjects include differences in biliary excretion and fecal elimination of thiolated conjugates. For the sake of simplicity, however, the two distinct populations will be referred to as fast and slow eliminators. Two distinct populations were also found based on venous blood and expired concentrations of chloromethane in volunteers (Nolan et al. 1985). The urinary excretion of S-methylcysteine in the volunteers exposed to chloromethane was variable, was not significantly different between pre- and post-exposure levels, and did not correlate with exposure levels. Two distinct populations of slow and fast eliminators were also identified. No change was detected in the S-methylcysteine

concentration or in the total sulfhydryl concentration in the urine of four workers before and after a 7-hour shift in a styrene production plant by De Kok and Antheunius (1981), who concluded that S-methylcysteine is not a human metabolite of chloromethane. It is possible, however, that the workers examined by de Kok and Antheunius (1981) were slow eliminators.

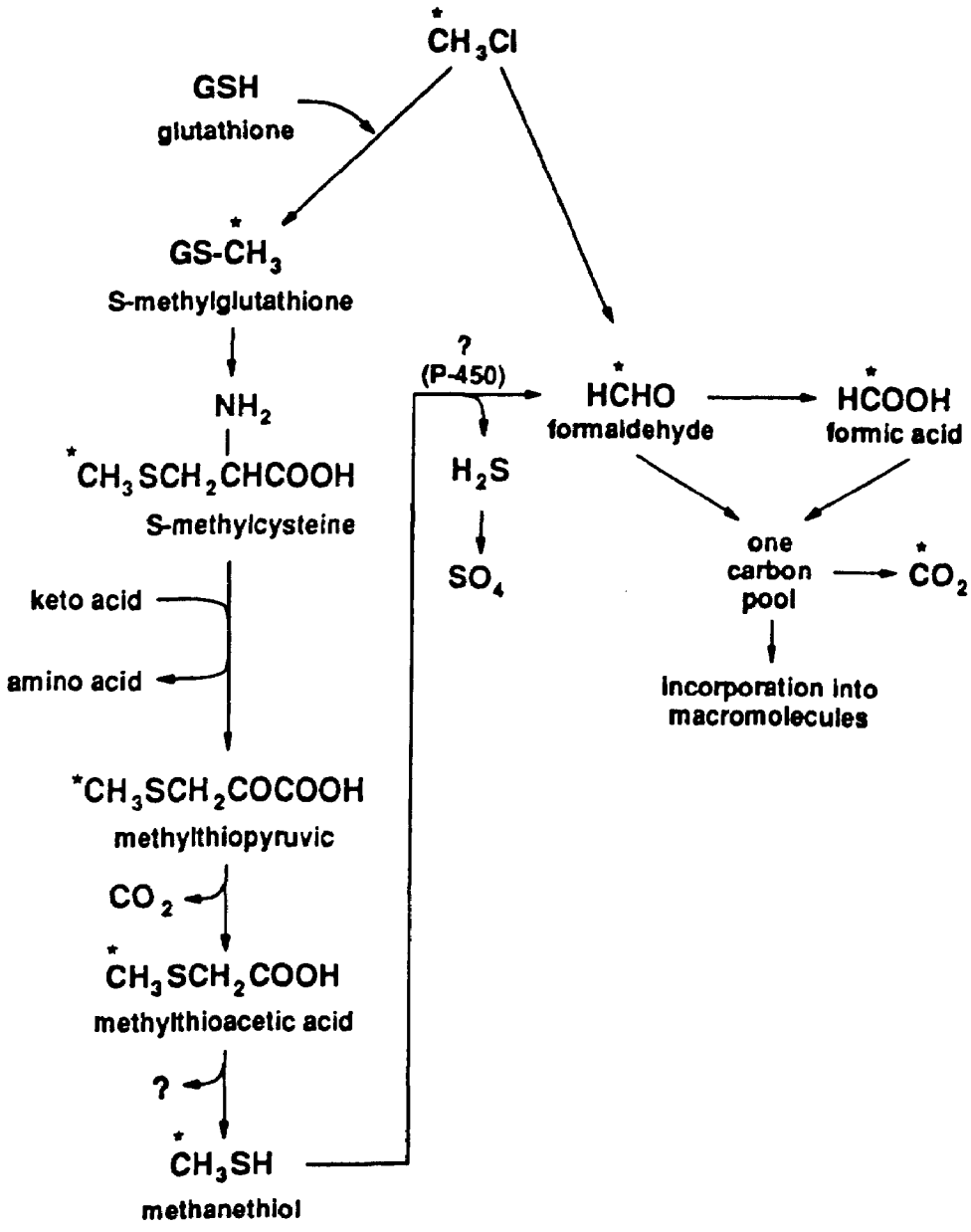
The metabolism of chloromethane has been studied in rats, mice, and dogs in vivo after inhalation exposure and in vitro. Based on these studies, the metabolic pathway shown in Figure 2-2 was proposed (Kornbrust and Bus 1983). According to this scheme, metabolism involves conjugation with glutathione to yield S-methylglutathione, S-methylcysteine, and other sulfur-containing compounds (Dodd et al. 1982; Kornbrust and Bus 1984; Landry et al. 1983a,b; Redford-Ellis and Gowenlock 1971a,b). These compounds can be excreted in the urine (Landry et al. 1983a), and S-methylglutathione may be further metabolized to methanethiol. Cytochrome P-450 dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms enter the one-carbon pool for incorporation into macromolecules or formation of CO_2 (Heck et al. 1982; Jaeger et al. 1988; Kornbrust et al. 1982; Kornbrust and Bus 1983). Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination. Production of methanethiol and formaldehyde, and lipid peroxidation due to glutathione depletion have been suggested as possible mechanisms for the toxicity of chloromethane, but the precise mechanisms are not known (Jaeger et al. 1988; Kornbrust and Bus 1983, 1984).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Very little unchanged chloromethane is excreted in the urine. In volunteers exposed to chloromethane, no chloromethane was found in the urine in one study (Stewart et al. 1980), and urinary excretion was <0.01%/min in another study (Morgan et al. 1970). The excretion patterns of chloromethane following prolonged exposure will differ from those observed in these experiments, which followed single breath exposure; therefore, these data are not useful for monitoring occupational exposure. Volunteers exposed to 10 or 50 ppm eliminated chloromethane from blood and the expired air in a biphasic manner when exposure ceased (Nolan et al. 1985). The half-life for the β-phase was 50-90 minutes, with differences possibly due to different metabolic rates. These results suggest that chloromethane is unlikely to accumulate in tissues during repeated intermittent exposures.

In rats exposed to chloromethane for 6 hours and dogs exposed for 3 hours at concentrations of 50 or 1000 ppm, blood levels rose rapidly and reached equilibria proportionate or nearly proportionate to exposure levels (Landry et al. 1983a). Blood concentrations declined rapidly in a biphasic, nonconcentration-dependent manner when exposure was stopped. The disappearance from blood was consistent with a linear 2-compartment open model. Half-lives for the α-phase were 4 minutes in rats, and 8 minutes in



* Indicates the position of the radioactive label.

Source: Kornbrust and Bus, 1983

FIGURE 2-2. Proposed Scheme for the Metabolism of Chloromethane

dogs; half-lives for the β-phase were 15 minutes in rats and 40 minutes in dogs. The disappearance of chloromethane from blood probably represents metabolism rather than excretion of parent compound. As discussed above in Section 2.3.3 on metabolism, chloromethane is conjugated with glutathione and cysteine, leading to urinary excretion of sulfur-containing compounds. Further metabolism of the S-methyl cysteine metabolite of chloromethane leads to formation of formaldehyde and formate, both of which are metabolized by single-carbon metabolic pathways resulting in incorporation into tissue macromolecules and production of carbon dioxide.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to chloromethane.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to chloromethane.

2.4 RELEVANCE TO PUBLIC HEALTH

Information regarding health effects of chloromethane in humans and animals is available only for the inhalation route of exposure. Oral and dermal routes of exposure are of concern because chloromethane is ubiquitous in the environment. Because it is highly volatile, however, chloromethane in water or soil will likely exist ultimately in the air (see Chapter 5).

The central nervous system is the major target of chloromethane toxicity in both humans and animals, as demonstrated by such signs and symptoms as dizziness, staggering, blurred vision, ataxia, muscle incoordination, convulsions, and coma after acute exposure to high levels. High acute exposures can also result in death of humans and animals. The liver and kidney are also common targets of chloromethane toxicity in humans and animals after acute or longer-term exposure. Toxic manifestations seen in humans, but generally not in animals, include cardiovascular and gastrointestinal effects, which may be secondary to the neurotoxicity. Effects that have been observed in animals, but not reported in humans, include testicular atrophy, infertility, and sterility of male rats, kidney tumors in male mice, and possibly developmental effects (heart defects) in mice.

Death. Case reports of humans who have died from exposure to chloromethane involved the inhalation of fumes that leaked from home refrigerators or industrial cooling and refrigeration systems (Baird 1954; Borovska et al. 1976; Kegel et al. 1929; McNally 1946; Thordarson et al. 1965). Exposure concentrations were probably very high, perhaps >30,000 ppm, because the leaks occurred in rooms with little or no ventilation. Exposure to high concentrations, even as high as 600,000 ppm, can result in

neurological effects (Morgan Jones 1942), but need not result in death if exposure is discontinued and/or medical attention is received in time. Since the use of chloromethane as a refrigerant in refrigeration devices has declined, exposure from leaks is of less concern than in the past, although some old refrigerators are probably still in use. Concentrations of chloromethane in the environment, even at hazardous waste sites, are not likely to be high enough to cause death.

Acute inhalation lethality data in animals indicate that high intermittent concentrations can be tolerated better than lower continuous concentrations (Burek et al. 1981; Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982). This phenomenon may be related to the conversion of chloromethane to a toxic metabolite or to diurnal susceptibility (Landry et al. 1985). Acute and chronic inhalation studies also indicated that mice are more sensitive than rats to the lethal effects of chloromethane (Chellman et al. 1986a,b; CIIT 1981). The greater susceptibility of mice may be due to differences in the ability of chloromethane to react with glutathione in the two species. Chloromethane conjugated with glutathione in liver, kidney, and brain to a much greater extent in mice than in rats (Kornbrust and Bus 1984). Pretreatment of mice with buthionine-S,R-sulfoximine (BSO), which depletes glutathione, thereby preventing its reaction with chloromethane, protected mice from the lethal effects of chloromethane (Chellman et al. 1986b). Thus, the reaction of chloromethane with glutathione to produce S-methylglutathione appears to be a toxifying rather than a detoxication mechanism (Chellman et al. 1986b). While the exact mechanism for the lethal effects of chloromethane is unclear, subsequent metabolism of S-methylglutathione may result in the formation of methanethiol and formaldehyde (Kornbrust and Bus 1983), which have been postulated to be toxic intermediates (Chellman et al. 1986b; Kornbrust and Bus 1982). Alternatively, chloromethane can elicit lipid peroxidation as a consequence of depletion of glutathione (Kornbrust and Bus 1984). Conjugation of chloromethane with glutathione probably occurs in humans because S-methylcysteine appears to be a human metabolite (see Section 2.3.3). No information was located regarding the extent to which chloromethane reacts with glutathione in humans or the ability of chloromethane to elicit lipid peroxidation in humans. The clinical signs and histopathological lesions noted with death in humans are similar to those in animals, suggesting a commonality of mechanism, but it is difficult to determine which animal species best serves as a model for extrapolating results to humans.

Systemic Effects. Cardiovascular effects, such as electrocardiogram abnormalities, tachycardia and increased pulse rate, and decreased blood pressure, and gastrointestinal effects such as nausea and vomiting, have been described in case reports of humans exposed to chloromethane vapors occupationally or accidentally due to refrigerator leaks (Baird 1954; Baker 1927; Battigelli and Perini 1955; Borovska et al. 1976; Gummert 1961; Hansen et al. 1953; Kegel et al. 1929; Mackie 1961; McNally 1946; Morgan Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Verriere and Vachez

1949). These case reports also describe neurological effects; therefore, the cardiovascular and gastrointestinal effects may be secondary to the neurotoxic effects of chloromethane. Exposure concentrations were probably very high, perhaps ≥30,000 ppm, because the leaks occurred in rooms with little or no ventilation.

Increased heart rate and blood pressure followed by decreased heart rate and blood pressure, possibly due to vasodilation resulting from depression of the central nervous system, occurred in dogs exposed by inhalation to high concentrations of chloromethane (15,000 and 40,000 ppm) (von Oettingen et al. 1949, 1950). The dogs died within 4-6 hours. Cardiovascular effects have not been described in other species after acute, intermediate, or chronic exposure by inhalation.

The only hematological effects described in animals were spleen enlargement, suggestive of extramedullary hematopoiesis, and hemoglobinuria, suggestive of intravascular hemolysis in mice exposed acutely to chloromethane by inhalation (Landry et al. 1985). It is not clear if similar hematological effects would occur in humans.

Case reports of humans exposed to chloromethane vapors have described clinical jaundice and cirrhosis of the liver (Kegel et al. 1929; Mackie 1961; Weinstein 1937; Wood 1951), but exposure concentrations were not known. Hepatic effects have also been observed in animals exposed by inhalation to chloromethane at concentrations ≥1000 ppm in acute, intermediate, and chronic duration experiments (Burek et al. 1981; Chellman et al. 1986a; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan et al. 1982).

Milder liver effects occurred in mice exposed acutely to an intermittent but relatively high concentration than to a low but continuous concentration (Landry et al. 1985). The greater susceptibility to continuous exposure may result from relatively greater metabolism to a toxic intermediate or from diurnal susceptibility. Hepatic effects were more severe in mice (necrosis and degeneration) than in rats (cloudy swelling, fatty infiltration, increased SGPT and SGOT with no necrosis). Furthermore, no hepatic lesions were observed in rats over the course of 2 years of inhalation exposure to 1000 ppm, while mice similarly exposed had necrotic lesions after 6 months (CIIT 1981). The greater susceptibility of mice to the hepatotoxic effects of chloromethane may be related to the greater ability of chloromethane to conjugate with hepatic glutathione in mice than in rats (Dodd et al. 1982; Kornbrust and Bus 1984). The reaction of chloromethane with glutathione appears to be a toxifying rather than a detoxication mechanism (Chellman et al. 1986b). While the exact mechanism for the hepatotoxic effects of chloromethane is unclear, chloromethane can elicit lipid peroxidation as a secondary consequence of depletion of glutathione (Kornbrust and Bus 1984). Comparison of lipid peroxidation in the S-9 fraction from mouse and rat livers revealed much greater lipid peroxidation in mouse liver than in rat liver. The findings that mice

exposed to 2500 ppm chloromethane expired ethane to an extent comparable to that produced by 2 mL/kg carbon tetrachloride, and developed moderate to severe hepatocellular hydropic degeneration provide further evidence that the mechanism of hepatotoxicity may involve lipid peroxidation.

Indicators of renal toxicity, such as albuminuria, increased serum creatinine and blood urea nitrogen, proteinuria, and anuria have been described in case reports of humans exposed to high levels of chloromethane vapors due to refrigerator leaks (Kegel et al. 1929; Mackie 1961; Spevak et al. 1976; Verriere and Vachez 1949).

Effects on the kidney have also been observed in animals exposed by inhalation for acute, intermediate, and chronic durations. In acute studies, rats developed more severe effects (evidence of renal failure) when 1000 ppm chloromethane was administered continuously (Burek et al. 1981) than when a 2-fold higher concentration was administered intermittently (degeneration and necrosis of convoluted tubules) (Morgan et al. 1982; Chellman et al. 1986a). The greater susceptibility of mice to continuous exposure than to intermittent exposure for lethal and hepatotoxic effects (Landry et al. 1985), however, did not hold true for renal toxicity. Only the mice exposed intermittently to the highest concentration had degenerative and regenerative changes in the tubules. No explanation for this apparent contradiction was offered. Degeneration and regeneration of renal tubules were also found in other acute duration studies in mice (Jiang et al. 1985; Morgan et al. 1982), and hyperplasia and kidney tumors were found after 12 months of exposure and later in a 2-year study (CIIT 1981). The biological significance of the proliferative kidney lesions in mice is discussed more fully in the subsection on Cancer below.

The possible relationship between the degenerative effects in the kidneys of mice and granular layer lesions in the brain, which are also observed in mice was discussed by Jiang et al. (1985). People who die of renal insufficiency (not due to chloromethane exposure) often have granular cell necrosis. Since the brain and kidney lesions in mice in this study were unrelated in severity, however, the brain lesions were probably not a direct consequence of chloromethane-induced kidney lesions. Although chloromethane depleted glutathione in the kidney, comparison of lipid peroxidation in the S-9 fractions revealed much less lipid peroxidation in kidney than in liver, suggesting that the mechanism for renal toxicity does not involve stimulation of tissue lipid peroxidation (Kornbrust and Bus 1984).

Because some refrigerators more than 30 years old are still in use, leaks of chloromethane vapor at concentrations high enough to produce hepatic effects, renal effects, and neurotoxicity with consequent cardiovascular and gastrointestinal effects in humans are possible. It is not known whether exposure of humans to chloromethane outside or at hazardous waste sites could result in hepatic and renal effects.

Immunological Effects. No studies were located regarding immunological effects in humans after inhalation exposure to chloromethane. The only effects in animals that could possibly be considered immunological were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed by inhalation for up to 2 years (CIIT 1981). Since more sensitive tests for immune function were not conducted, the biological significance of the splenic effects cannot be assessed. Furthermore, splenic alterations were not observed in rats in the same study. In another study, cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than the control (McKenna et al. 1981a). The lesions were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease, however, could not be ruled out. It is not known whether the exacerbation would represent an immunological effect.

Neurological Effects. Neurological effects have been described in numerous case reports of humans exposed to chloromethane vapors as a result of industrial leaks and leaks from defective home refrigerators (Baird 1954; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; Morgan Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). Depending on the extent of exposure and the availability of medical treatment, the signs and symptoms can range from staggering and blurred vision to coma, convulsions, and death. Such effects as abnormal gait, tremors, and personality changes may persist for several months or more, but complete recovery may also occur eventually. In cases in which exposure was quantitated, concentrations were generally $\geq$29,000 ppm (Battigelli and Perini 1955; Morgan Jones 1942). Symptoms of blurred vision, fatigue, vertigo, nausea, vomiting, tremor, and unsteadiness, however, developed in a man and a woman a few days after they stored insulated boards containing polystyrene foam in the basement of their house (Lanham 1982). The concentration of chloromethane in the house was found to be in excess of 200 ppm (exact levels not reported). It should be noted, however, that this exposure probably represented an unusual situation because the rate of air turnover in the couples' home was an order of magnitude lower than the typical rate. In addition, a small not statistically significant decrement in performance in behavioral tests was found in volunteers exposed to 200 ppm (Putz-Anderson et al. 1981a).

Severe neurological signs (ataxia, tremors, limb paralysis, incoordination, convulsions) have been observed in rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed acutely by inhalation to high concentrations of chloromethane (Burek et al. 1981; Chellman et al. 1986a,b; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). Signs of neurotoxicity developed after 6 and 12 months, and degeneration of the granular cell layer of the cerebellum was observed after 18 months in mice exposed by inhalation for 2 years (CIIT 1981). Cerebellar lesions have also been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice were more

susceptible than rats (Morgan et al. 1982; CIIT 1981), and dogs were more susceptible than cats to the neurological effects of chloromethane (McKenna et al. 1981a). Mice were more sensitive to neurological effects after continuous exposure to low concentrations than after intermittent exposure to higher concentrations of chloromethane (Landry et al. 1985). The greater sensitivity of mice to continuous exposure may be a consequence of metabolism of chloromethane to a toxic intermediate or diurnal susceptibility.

The mechanism by which chloromethane produces neurological effects is unclear. Pretreatment of mice with BSO to deplete glutathione protected mice from cerebellar damage due to inhalation exposure to chloromethane (Chellman et al. 1986b), suggesting that the reaction of chloromethane with glutathione to form S-methylglutathione is required for the degenerative changes in the brain to occur. In the metabolic scheme proposed by Kornbrust and Bus (1983), subsequent metabolism of S-methylglutathione produces methanethiol as an intermediate. Methanethiol produces signs and symptoms of neurotoxicity (tremors, convulsions, coma) similar to those seen in animals or humans acutely exposed to chloromethane (Chellman et al. 1986b). The possibility of a relationship between degenerative effects in the kidneys and granular layer lesions in the brain, which were also observed in mice was discussed by Jiang et al. (1985). Granular cell necrosis is often seen in people who die of renal insufficiency (not due to chloromethane exposure). Since the brain and kidney lesions in mice in this study were unrelated in severity, however, Jiang et al. (1985) concluded that the brain lesions were probably not a direct consequence of chloromethane-induced kidney lesions.

Because refrigerators more than 30 years old are still in use, leaks of chloromethane vapor at concentrations high enough to produce neurological effects in humans are possible. These exposures have generally occurred in rooms with poor ventilation. It is not known whether exposure of humans to chloromethane in the outside environment or at hazardous waste sites could result in neurological effects.

Developmental Effects. No studies were located regarding developmental effects in humans exposed to chloromethane by any route.

Pregnant rats exposed to 1500 ppm chloromethane by inhalation during gestation had decreased body weight gain and produced fetuses with delayed development (Wolkowski-Tyl et al. 1983a). The investigators also found increased incidences of heart malformations in the fetuses of mouse dams exposed by inhalation to 500 ppm chloromethane during gestational days 6-17. Heart malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during gestational days 11.5-12.5, which was considered to be the critical period for development of the embryonal heart (John-Greene et al. 1985). According to Wolkowski-Tyl (1985), however, the critical period of embryonal heart development is more appropriately gestational day 14. The developmental toxicity of

chloromethane in mice is therefore controversial. It is not known whether chloromethane could produce developmental effects in humans.

Reproductive Effects. No studies were located regarding reproductive effects in humans exposed to chloromethane by any route. Acute, intermediate, and chronic inhalation exposures of male rats to chloromethane have resulted in such reproductive effects as inflammation of the epididymis and sperm granuloma formation in epididymides, disruption of spermatogenesis, and decreased fertility at about 500 ppm, and at higher concentrations (1000 or 3000 ppm), sterility (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a,b, 1987; CIIT 1981; Hamm et al. 1985; Morgan et al. 1982; Working et al. 1985a,b; Working and Bus 1986). Testicular effects of chloromethane have been manifested as preimplantation loss in unexposed female rats mated with males exposed to chloromethane (Working et al. 1985a). Testicular lesions were also observed in mice after 18 months of exposure to chloromethane (CIIT 1981). Studies on the mechanism of chloromethane-induced testicular effects suggested that preimplantation loss was due to cytotoxicity of chloromethane to sperm in the testes at the time of exposure, rather than to a genotoxic effect on the sperm (Chellman et al. 1986a,c, 1987; Working and Bus 1986; Working et al. 1985a,b).

Although testicular effects were observed in mice in the CIIT (1981) study, the incidence was much lower and occurred much later in mice than it did in rats. The mechanism for testicular and epididymal effects has been studied only in rats. It is not known whether chloromethane could produce reproductive effects in humans.

Genotoxic Effects. Chloromethane has been tested for genotoxicity in a number of *in vitro* and *in vivo* systems (Tables 2-2 and 2-3). Positive results have generally been found in the reverse mutation assay in *Salmonella typhimurium* with and without metabolic activation (Andrews et al. 1976; DuPont 1977; Simmon et al. 1977). In addition, a positive result was obtained in *S. typhimurium* for 8-azaguanine resistance (Fostel et al. 1985). Chloromethane gave positive results for gene mutation, sister chromatid exchange, and transformation in cultured mammalian cells, including human lymphoblast cells (Fostel et al. 1985; Hatch et al. 1982, 1983; Working et al. 1986). Chloromethane also produced recessive lethal mutations in fruitflies (Valencia no date). Chloromethane, therefore, appears to be a direct-acting genotoxicant *in vitro*. Although chloromethane was positive for unscheduled DNA synthesis in rat hepatocytes, spermatocytes, and tracheal epithelial cells *in vitro*, a marginally positive response was found only in hepatocytes of rats exposed to chloromethane *in vivo*, and only at very high concentrations (Working et al. 1986). Chloromethane exposure consistently produced dominant lethal mutations in the sperm of rats, as measured by postimplantation loss in females mated to the exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, did not result in

TABLE 2-2. Genotoxicity of Chloromethane *In Vitro*

End Point	Species (Test System)	Result: With Activation	Result: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	*Salmonella typhimurium* (desiccator test for exposure to gases)	+	+	Simmon et al. 1977
	S. typhimurium TA1535 (gas exposure)	+	+	Andrews et al. 1976
	S. typhimurium (gas exposure)			
	TA1535	+	+	DuPont 1977
	TA100	+	+	
	TA1537	-	-	
	TA18	-	-	
	S. typhimurium TA677 (gas exposure)	ND	+	Fostel et al. 1985
Mammalian cells:				
Gene mutation	Human lymphoblasts	ND	+	Fostel et al. 1985
Sister-chromatid exchange	Human lymphoblasts	ND	+	Fostel et al. 1985
DNA strand breaks	Human lymphoblasts	ND	-	Fostel et al. 1985
Unscheduled DNA synthesis	Rat hepatocytes	NA	+	Working et al. 1986
	Rat spermatocytes	ND	+	Working et al. 1986
	Rat tracheal epithelial cells	ND	+	Working et al. 1986
DNA viral transformation	Primary hamster embryocells	ND	+	Hatch et al. 1982, 1983

+ = positive result; - = negative result; ND = no data; NA = not applicable.

TABLE 2-3. Genotoxicity of Chloromethane *In Vivo*

End Point	Species (Test System)	Results	Reference
Recessive lethal	*Drosophila melanogaster* (gas exposure)	+	Valencia no date
Dominant lethal	Rat (inhalation)	+	Working et al. 1985a
	Rat (inhalation)	+	Chellman et al. 1986c
	Rat (inhalation)	+	Rushbrook 1984
Unscheduled DNA synthesis	Rat (inhalation)		
	hepatocytes	(+)	Working et al. 1986
	spermatocytes	-	Working et al. 1986
	tracheal epithelial cells	(+/-)	Working et al. 1986

+ = positive result; - = negative result; (+) = marginally positive result; (+/-) = equivocal results.

postimplantation loss, it was suggested that the dominant lethal mutation was probably due to chloromethane-induced epididymal inflammation, possibly by production by inflammatory cells of a superoxide capable of damaging DNA, rather than by a genotoxic effect of chloromethane itself (Chellman et al. 1986c). The ability of inflammatory cells to produce superoxides capable of genetic damage has been demonstrated (Weitzman and Stossel 1981). Since studies using ^{14}C-chloromethane indicated that the carbon atom from chloromethane becomes incorporated into normal macromolecules via the one-carbon pool rather than binding to macromolecules as an alkylating agent (Kornbrust et al. 1982; Peter et al. 1985), and since the dominant lethal effect may be secondary to inflammation, it is possible that *in vivo* genotoxicity may be secondary to other toxic effects of chloromethane. Nevertheless, the *in vitro* studies demonstrate the direct genotoxicity of chloromethane. Although chloromethane produced genotoxic effects in human lymphocytes in culture, it is not known whether chloromethane could produce dominant lethal mutations or other genotoxic effects in humans exposed by any route.

Cancer. The only information regarding carcinogenicity in humans after exposure to chloromethane comes from a negative epidemiological study of butyl rubber workers which showed no statistically significant increase in the rate of death due to cancer in this population (Holmes et al. 1986).

Chloromethane has been tested for carcinogenicity in animals only by the inhalation route. No evidence of a carcinogenic effect was found in rats or in female mice (CIIT 1981). In a 2-year inhalation study, a statistically significant increased incidence of kidney tumors developed in 1000 ppm-exposed B6C3F1 male mice. Renal hyperplasia was also observed after 12 months of exposure. In an acute study, significant increases in cell proliferation occurred in the kidneys of male B6C3F1 mice, as measured by incorporation of tritiated thymidine into DNA of the kidneys (Chellman et al. 1986b). Such proliferation may be involved in the development of kidney tumors, a hypothesis supported by the evidence that chloromethane is probably not an alkylating agent but acts by an epigenetic mechanism (Kornbrust et al. 1982; Peter et al. 1985). Female B6C3F1 mice exposed to 1500 ppm chloromethane also had increased cell proliferation in the kidney (Chellman et al. 1986b), but did not develop kidney tumors in the CIIT (1981) study; however, the exposure concentrations in the CIIT (1981) study were lower than in the study by Chellman et al. (1986b). In addition, greater evidence of regeneration of renal tubular cells, presumably in response to cell death, was found in B6C3F1 males than in females of the same strain exposed to 500 and 1000 ppm chloromethane for 12 days (Morgan et al. 1982). In mice exposed to 2000 ppm, however, there was no sex difference. It is possible, therefore, that at relatively low concentrations, female mice are less sensitive than male mice to the renal toxicity of chloromethane.

Since data that chloromethane exposure was associated with tumors were found in only one sex of one species in only one study, the evidence that

chloromethane is a carcinogen is limited. It is not known whether cancer could develop in humans exposed to chloromethane by any route.

2.5 BIOMARKERS OF EXPOSURE AND EFFECTS

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 or cell 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 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 (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 chloromethane 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 chloromethane 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. 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 or Quantify Exposure to Chloromethane

Several studies have unsuccessfully attempted to correlate exposure levels of chloromethane in air with urinary excretion of S-methylcysteine. In a group of six workers exposed to TWA 8-hour workroom concentrations of 30-90 ppm, the excretion of S-methylcysteine in urine showed wide variations, with little correlation with exposure levels (van Doorn et al. 1980). On the basis of variable excretion of S-methylcysteine in six male volunteers exposed to 10 or 50 ppm chloromethane for 6 hours, Nolan et al. (1985) concluded that measurement of S-methylcysteine in urine is not a valid method for monitoring exposure to chloromethane.

In an evaluation of the use of blood and breath analysis of chloromethane to monitor exposure in volunteers exposed to up to 150 ppm chloromethane, breath levels immediately after exposure to 20 or 100 ppm correlated with exposure, but subsequent samples were difficult to interpret (Stewart et al. 1980). Exposure to 100 ppm could not be distinguished from exposure to 150 ppm. The excretion patterns following prolonged exposure will differ from those observed in these experiments (Morgan et al. 1970), which followed single breath exposure (see Section 2.3.4.1); therefore, the data are not useful for monitoring occupational exposure. This conclusion probably applies to prolonged environmental exposure as well. Symptoms resembling drunkenness and food poisoning, along with a sweet odor of the breath, may alert physicians that a person has been exposed to chloromethane.

2.5.2 Biomarkers Used to Characterize Effects Caused by Chloromethane

Attempts to correlate blood levels and expired air concentrations of chloromethane with health effects of occupational and experimental inhalation exposure have been unsuccessful. In a study of 73 behavioral measures of task performance, 4 indices of exposure and 8 indicators of neurological function in workers exposed to a mean concentration of 34 ppm chloromethane, effects on cognitive time-sharing and finger tremor were found, but correlation coefficients indicated that chloromethane in breath was not a sensitive indicator of performance (Repko et al. 1977). A 4% decrement in performance of behavioral tests was found in volunteers exposed to 200 ppm chloromethane for 3 hours, but blood and alveolar air levels of chloromethane were highly variable (Putz-Anderson et al. 1981a). Furthermore, the decrement in performance was small and not statistically significant.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Inhalation exposure of volunteers to 200 ppm chloromethane along with oral dosing with 10 mg diazepam produced an additive impairment in performance on behavioral tests (Putz-Anderson et al. 1981a). Since both of these compounds are known to be central nervous system depressants, workers who are exposed to chloromethane in industry or during cleanup of

hazardous waste sites, or people who live near hazardous waste sites where chloromethane is present and are treated with diazepam or exposed to other central nervous system depressants, including alcohol, may have aggravated symptoms. The only other studies that show an effect of other compounds on the toxicity of chloromethane are those in which the effects of BW755C, an anti-inflammatory agent, and BSO, a depletor of glutathione, were administered to rats or mice exposed to chloromethane by inhalation to study the mechanism of chloromethane-induced toxicity (Chellman et al. 1986a,b). These studies are discussed in Section 2.2. It is unlikely that these compounds would be found with chloromethane at hazardous waste sites.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Two distinct populations of humans with differences in elimination of chloromethane have been identified. Some volunteers exposed by inhalation to chloromethane had distinctly higher chloromethane concentrations in alveolar breath samples than others (Stewart et al. 1980). In humans exposed to chloromethane by inhalation, the chloromethane was eliminated from the blood and expired air more slowly by the subjects who had higher venous blood and expired air concentrations than by those who had lower concentrations (Nolan et al. 1985). This finding was believed to be due to differences in metabolic rate. In six workers exposed to chloromethane occupationally, the excretion of S-methylcysteine showed wide variations, and there was little or no correlation between exposure levels and excretion (van Doorn et al. 1980). In four of the workers, all concentrations of S-methylcysteine were higher than in controls, and appeared to increase during the course of the week. The other two workers had only small amounts of S-methylcysteine in the urine, but these workers had experienced the highest exposure concentrations. These results support the speculation that there are two distinct populations: fast eliminators, with lower body burdens and higher excretion, and slow eliminators, with higher body burdens and lower excretion. Because chloromethane is eliminated relatively rapidly, the observation of two distinct populations may have no toxicological significance (Nolan et al. 1985). Based on studies in mice, the reaction of chloromethane with glutathione, however, may lead to the formation of toxic compounds in humans that exert their action before they are eliminated. If slow eliminators have a deficiency of glutathione-S-transferase, the enzyme that catalyzes the conjugation of glutathione with chloromethane, or low levels of glutathione, they would be expected to be less susceptible to the toxic effects of chloromethane. The extent to which chloromethane reacts with glutathione in humans, however, is not known.

As discussed in Section 2.7, workers treated with diazepam and exposed to chloromethane had an additive impairment in performing behavioral tests (Putz-Anderson et al. 1981a). These results imply that people who are occupationally exposed to chloromethane and treated with diazepam, or perhaps other drugs that depress the central nervous system, may have aggravated symptoms.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 chloromethane 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 chloromethane.

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.

2.8.1 Existing Information on Health Effects of Chloromethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chloromethane are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of chloromethane. 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.

As seen from Figure 2-3, information regarding the health effects of exposure of humans to chloromethane is available only for inhalation or occupational exposure. Exposure to chloromethane from accidental leaks from refrigeration units or from occupational sources also involves dermal exposure; however, the primary route in these situations is inhalation. Effects observed in humans after exposure to chloromethane include liver and renal effects, neurological and behavioral effects, cardiovascular and gastrointestinal effects possibly secondary to the neurological effects, and death. These effects have been described for both acute exposure and for longer-term occupational exposure, which can include intermediate and chronic durations. An epidemiological study found no association between exposure to chloromethane and cancer at any site. No information was available regarding immunological, developmental, reproductive, or genotoxic effects in humans exposed to chloromethane by any route.

The health effects of chloromethane exposure in animals generally have been well studied for the inhalation route, although only a single comprehensive chronic study in rats and mice has been performed. Health effects of acute, intermediate, and chronic inhalation exposure in animals include death and increased mortality, liver and kidney pathology, and

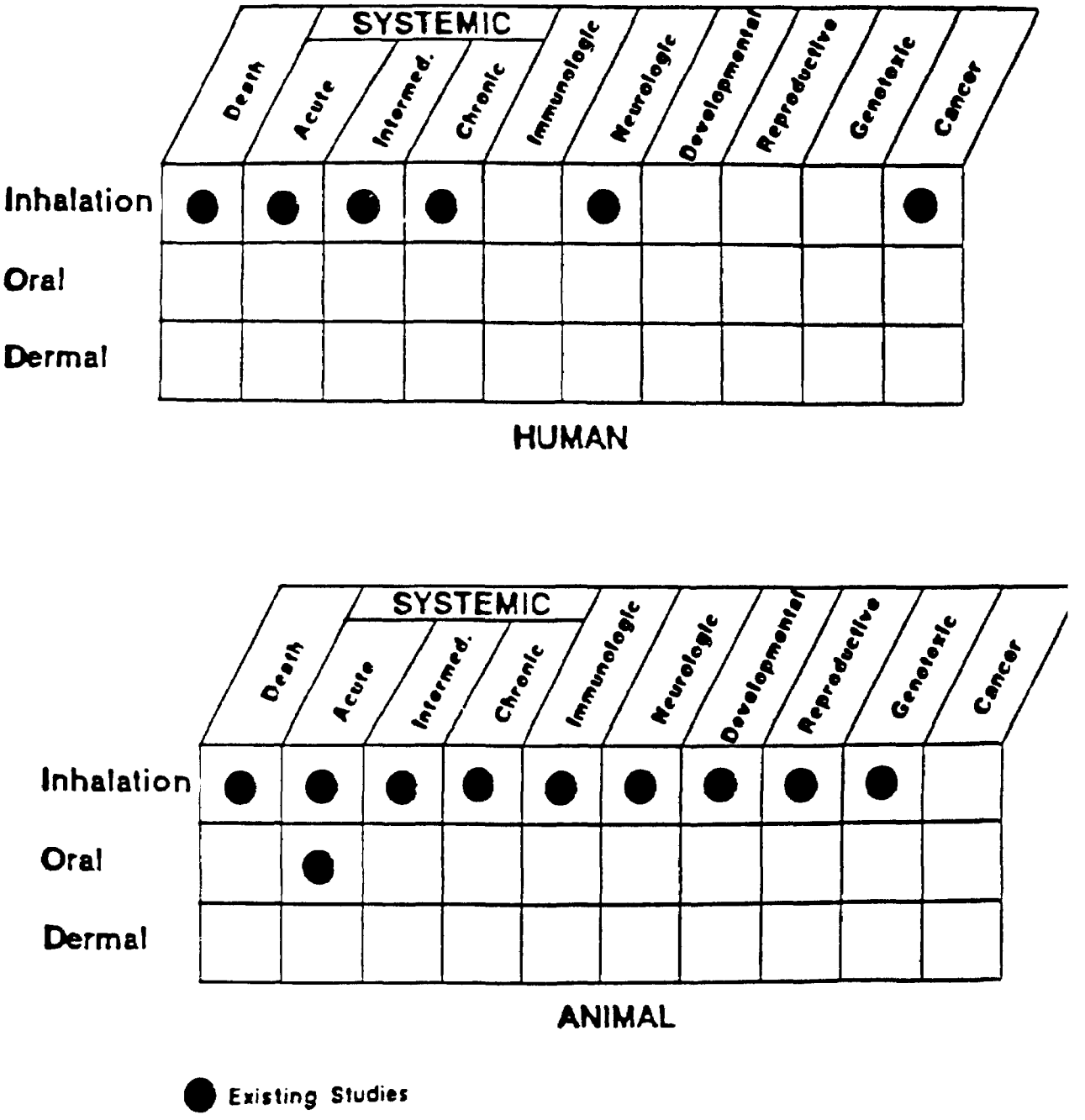


FIGURE 2-3. Existing Information on Health Effects of Chloromethane

neurological, possible developmental, reproductive, and genotoxic effects. Inhalation exposure of mice to chloromethane for 2 years resulted in increased incidences of kidney tumors. The only oral study in animals attempted to compare the hepatotoxicity of chloromethane with carbon tetrachloride and chloroform. The dose of chloromethane administered, however, was too low to produce hepatic effects, and administration of higher doses was precluded due to neurotoxicity.

2.8.2 Identification of Data Needs

With the exception of a single dose oral study, no information was located regarding the health effects of chloromethane in humans or animals after oral or dermal exposure. It is not possible to predict whether effects following oral or dermal exposure to chloromethane would be similar to those following inhalation exposure, partially because the pharmacokinetic disposition of chloromethane has not been compared for the three routes of exposure. Differences in absorption, distribution, and metabolic pathways could lead to differences in toxic response and different target organs following the three routes of exposure. Therefore, studies using oral and dermal routes of exposure would provide information regarding possible similarities between target organs and responses seen following inhalation exposure and those seen following oral and dermal exposures. The oral and dermal routes of exposure are of concern because chloromethane is ubiquitous in the environment. Chloromethane is highly volatile, however, and chloromethane in water or soil will likely volatize to the air (Chapter 5).

Acute-Duration Exposure. Case reports of humans exposed acutely to high concentrations of chloromethane have described severe neurological effects, sometimes followed by death. Effects on the cardiovascular system, liver, and kidney have also been described in case reports of humans exposed for brief periods or for more prolonged periods occupationally. Acute inhalation exposure levels of chloromethane causing death in animals are available for rats and mice. Numerous acute inhalation studies have identified the liver and kidney as target organs in rats and mice, the spleen as a target organ in mice, the central nervous system as a target system in rats, mice, and dogs, and the testes and epididymides as target organs in rats. In addition, the respiratory and cardiovascular systems may be targets in dogs. These studies have shown that species differences in susceptibility exist, and that generally animals are more susceptible to relatively low exposures given continuously than to relatively high exposures given intermittently. Some studies provide information on the mechanism of hepatic, renal, and neurological effects in mice and reproductive effects in mice. The data for acute inhalation exposures in animals were sufficient to derive an acute inhalation MRL for chloromethane based on a NOAEL for neurological effects in mice. Only one acute oral study was conducted. In this study, rats were dosed orally with chloromethane, and livers were examined for pathology (Reynolds and Yee 1967). The administered dose was too low to cause hepatic effects, and

higher doses were not administered because of the neurotoxic effects of chloromethane. Therefore, an acute oral MRL can not be derived. No studies were located regarding effects in humans or animals after dermal exposure to chloromethane. Pharmacokinetic data are insufficient to identify target organs of chloromethane after oral and dermal exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment. Therefore, acute studies in animals exposed by oral or dermal routes would provide information to identify target organs and dose-response relationships for these routes. This information is important because there are populations surrounding hazardous waste sites that might be exposed to chloromethane for similar durations.

Intermediate-Duration Exposure. Information regarding effects in humans after intermediate-duration exposure to chloromethane is limited to findings of neurological symptoms in humans occupationally exposed. Inhalation studies have been conducted in rats, mice, and dogs, and have identified the liver as a target organ in rats and mice, the testes as a target organ in rats, and the kidney, spleen, and central nervous system as targets in mice. The data were sufficient to derive an intermediate-duration inhalation MRL. No studies were located regarding effects in humans or animals after intermediate-duration oral or dermal exposure, and pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment. Therefore, intermediate-duration studies in animals exposed by oral or dermal routes would provide information to identify target organs and dose-response relationships for these routes. This information is important because there are populations surrounding hazardous waste sites that might be exposed to chloromethane for similar durations.

Chronic Exposure and Cancer. No information was located regarding effects of chloromethane in humans after chronic exposure by any route. A 2-year inhalation study has been conducted that exposed both sexes of rats and mice to several concentrations of chloromethane and comprehensively examined endpoints of toxicity (CIIT 1981). The liver, kidney, spleen, and brain were identified as target organs in mice, and the testes were identified as target organs in rats and mice. Data were sufficient to derive a chronic inhalation MRL. No studies were located regarding effects in humans or animals after chronic oral or dermal exposure to chloromethane, and pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment. Therefore, chronic-duration studies in animals exposed by oral or dermal routes would provide information to identify target organs and dose-response relationships for these routes.

This information is important because there are populations surrounding hazardous waste sites that might be exposed to chloromethane for similar durations.

The carcinogenic effects of chloromethane were also examined in this study. Male mice, but not female mice nor rats of either sex, developed increased incidences of kidney tumors at the highest exposure level. The rats and mice were exposed to the same concentrations, but differences in ventilation rate, the ability to conjugate chloromethane with glutathione and to further metabolize the glutathione conjugate, and body weight make it probable that mice received a higher internal dose than rats. It is possible, therefore, that the exposure concentration was not high enough in rats to produce kidney tumors. Additional chronic inhalation studies in rats using concentrations that would result in internal doses similar to those received by the mice might show that chloromethane can induce tumors in rats. No studies were located regarding the carcinogenic effects of chloromethane in animals after oral and dermal exposure, and pharmacokinetic data are insufficient to support the carcinogenic potential across routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment. Additional chronic studies in rats, mice, and other species would reduce uncertainties in extrapolating information from animal studies to humans.

Genotoxicity. The available genotoxicity studies for mutation in Salmonella typhimurium, for mutation, sister-chromatid exchange, and DNA strand breaks in human lymphoblasts, for unscheduled DNA synthesis in rat hepatocytes, spermatocytes, and tracheal epithelial cells, for DNA viral transformation in primary hamster embryo cells, and for recessive lethal mutation in Drosophila melanogaster indicate that chloromethane is genotoxic. Studies of the mechanism of dominant lethal mutations in rat sperm resulting from inhalation exposure of male rats to chloromethane suggest that the dominant lethal effects may be secondary to inflammation of the epididymis. Because the dominant lethal effect may have been secondary to inflammation and because chloromethane does not appear to be an alkylating agent, some investigators have suggested that chloromethane is only a weak direct-acting genotoxicant. Further genotoxicity studies might resolve this issue.

Reproductive Toxicity. No information was available regarding reproductive effects of chloromethane in humans, but several inhalation studies have demonstrated that chloromethane is a reproductive toxicant in male rats. In addition, the mechanism of the reproductive effects has been studied in rats. The reproductive effects of chloromethane have been studied extensively only in rats because testicular lesions in mice occurred at lower incidences and later time periods than in rats in the 2-year inhalation study by CIIT (1981). Testicular effects were not observed in male dogs and cats exposed to chloromethane by inhalation, but the exposure concentrations may not have been high enough. Species differences in

sensitivity exist for other end points; therefore, testing for reproductive effects in other species at higher exposure levels might provide information on whether reproductive effects are confined to rats and mice or apply to other species, even humans. No studies were located regarding the reproductive effects of chloromethane in animals after oral and dermal exposure, and pharmacokinetic data are insufficient to support the potential for reproductive effects across routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment.

Developmental Toxicity. No information was located regarding developmental effects in humans after exposure to chloromethane by any route. The teratogenicity of inhalation exposure to chloromethane has been studied in rats and mice. In rats, delayed fetal development was found at the same concentration that resulted in maternal toxicity. The results in mice are controversial. Additional studies in mice and other species might resolve the controversy and provide information on the possible developmental effects of chloromethane in other species.

No studies were located regarding the developmental effects of chloromethane in animals after oral and dermal exposure, and pharmacokinetic data are insufficient to support the potential for developmental toxicity across routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment.

Immunotoxicity. The only effects that could be possibly considered immunological effects were lymphoid depletion of the spleen and splenic atrophy observed in mice, but not rats exposed by inhalation to chloromethane for 2 years (CIIT 1981). In addition, cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than the control (McKenna et al. 1981a). The lesions, however, were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease could not be ruled out. It is not known whether the exacerbation would represent an immunological effect. More sensitive measures of immunotoxicity could be studied to determine whether exposure to chloromethane by any route produces immunological effects.

Neurotoxicity. The neurotoxic effects of inhalation exposure to chloromethane are well defined in animals and humans, but the mechanism is unclear. No studies were located regarding the neurotoxic effects of chloromethane in animals after oral and dermal exposure, and pharmacokinetic data are insufficient to support the potential for neurological toxicity across routes of exposure. As discussed above, although the potential for humans to be exposed to chloromethane is greater

for the inhalation route than for the oral and dermal routes, chloromethane is ubiquitous in the environment. The mechanism for the induction of cerebellar lesions in mice exposed by inhalation may involve conjugation of chloromethane with glutathione, with further metabolism leading to production of methanethiol. Methanethiol produces similar central nervous system effects as seen in animals and humans exposed to chloromethane. The relative importance of conjugation with glutathione in other species has not been determined. As S-methylcysteine appears to be a metabolite in humans, conjugation with glutathione probably operates in humans. In addition, sensitive neurobehavioral toxicity studies in monkeys may provide valuable information for determining the threshold for the neurotoxic effects and in elucidating the possible mechanism of action of chloromethane-induced neurotoxicity. Monkeys represent a better model than do rodents for extrapolating animal data on neurobehavioral effects to humans.

Epidemiological and Human Dosimetry Studies. A retrospective epidemiological study was conducted in workers exposed to chloromethane in a butyl rubber manufacturing facility (Holmes et al. 1986). No association was found between chloromethane exposure and death due to cardiovascular disease or cancer at any site. In a study of workers from fabricating plants, occupational exposure to chloromethane below 100 ppm produced subtle, quantifiable behavioral effects, but the threshold for changes in functional capacity could not be determined precisely (Repko et al. 1977). An experimental study by Stewart et al. (1980) found no effects on pulmonary function, cardiac function or ECG, and no hematological, neurological, or behavioral effects in volunteers exposed by inhalation to chloromethane, but the protocol was too confusing to clearly define the exposures. A slight decrement in performance of behavioral tasks was found in volunteers exposed to 200 ppm for 3 hours (Putz-Anderson et al. 1981a). Further epidemiological studies could be conducted to confirm or refute the lack of an association between increased cancer risk and occupational exposure and to better define the threshold for neurobehavioral effects.

Biomarkers of Exposure and Effect. A number of studies have unsuccessfully tried to relate blood and alveolar air levels of chloromethane and urinary levels of S-methylcysteine with exposure. The blood and alveolar air levels of chloromethane and the urinary levels of S-methylcysteine are highly variable. Symptoms resembling drunkenness and food poisoning, along with a sweet odor on the breath, may alert a physician that a person has been exposed to chloromethane, but such symptoms could easily be mistaken for the conditions they resemble. Further studies designed to identify a metabolite or biomarker that can be monitored for exposure to chloromethane would facilitate future medical surveillance.

Attempts to correlate blood levels and expired air concentrations of chloromethane with health effects of occupational and experimental inhalation exposures of humans have also been unsuccessful. Blood and alveolar levels are highly variable and are not sensitive indicators of neurological function or behavior. Further studies designed to identify a

metabolite or biomarker that can be correlated with the known subtle neurological effects would facilitate future medical surveillance that could lead to early detection and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. Experimental inhalation studies in animals and humans indicate that chloromethane is rapidly taken up from the lungs into the blood, widely distributed throughout the body and extensively metabolized, with the carbon atom being incorporated into natural biological macromolecules, CO_2 being excreted in the expired air, and other metabolites being excreted in the urine. Differences in the rate and extent of absorption, metabolic pathways, and disposition may result in differences in the toxic manifestations of a chemical following exposure by oral or dermal routes. Thus, further studies of the rate and extent of absorption, distribution, metabolism, and excretion in animals following exposure by the oral and dermal routes, would provide information to fully characterize the pharmacokinetics of chloromethane in animals. Oral and dermal routes of exposure are of concern because chloromethane is ubiquitous in the environment. Chloromethane is highly volatile, however, and chloromethane in water or soil will likely volatilize to the air (see Chapter 5).

Comparative Toxicokinetics. Studies on the pharmacokinetics of chloromethane following inhalation exposure have been conducted in rats, mice, dogs, and humans. Kinetics of chloromethane in humans were similar to those in rats and dogs, with data for each species consistent with 2-compartment models. The plateau concentrations of slow human metabolizers were less than those in rats and dogs. The half-life for the beta phase of excretion was 15 minutes for rats, 50 minutes for rapid human metabolizers and dogs, and 90 minutes for slow metabolizers. Species difference can be explained by differences in respiratory minute volumes and basal metabolic rates (rat > dog > human). Studies in rats and mice indicate that chloromethane conjugates with glutathione. Since S-methylcysteine is probably a metabolite of chloromethane in humans, conjugation with glutathione probably operates in humans. Glutathione reacts with chloromethane to a greater extent in mice than in rats, but the extent to which chloromethane reacts with glutathione in humans is not known. Although chloromethane reacts with glutathione in human erythrocytes (Redford-Ellis and Gowenlock 1971b), determination of the extent of glutathione depletion in human liver and/or kidney would probably involve exposure of humans to chloromethane and invasive methods of investigation. Information on the extent of glutathione depletion in humans is important because the reaction of chloromethane with glutathione is believed to represent a toxifying mechanism that leads to the formation of other toxic compounds. Studies to determine the specific metabolites (or parent compound) that are responsible for the neurotoxicity, testicular toxicity, and kidney tumorigenesis in animals and the identification of the same metabolites in humans would help in the prediction of toxic effects in humans and the identification of the appropriate animal model to further study the effect. Identification of further similarities between animals

and humans with respect to toxicokinetics would provide information to identify the most appropriate species to serve as a model for predicting toxic effects in humans.

2.8.3 On-going Studies

Very little on-going research was identified. As reported in a recent abstract, the activity of glutathione transferase was determined in human erythrocytes exposed to chloromethane in vitro (Hallier and Peter 1988). The method may be useful for identifying the subpopulations of fast and slow metabolizers. As reported in another recent abstract, a significant sex-specific difference was found in the content of microsomal cytochrome P450 in kidneys (male>female), but not in livers, of mice of three different strains (Jaeger 1988). Glutathione-S-transferase activities in liver and kidney cytosol incubated with methyl chloride were greater in female mice than male mice. These data may help to elucidate the reasons for the sex-specific renal toxicity observed in mice.

3. CHEMICAL AND PHYSICAL INFORMATION

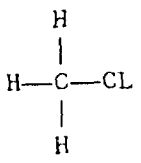
3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of chloromethane are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of chloromethane are presented in Table 3-2.

TABLE 3-1. Chemical Identity of Chloromethane

	Value	Reference
Chemical name	Chloromethane	CAS 1988
Synonyms	Methyl chloride monochloromethane	CAS 1988; SANSS 1988
Trade names	Artic R 40 Freon 40	HSDB 1988; SANSS 1988
Chemical formula	CH_3Cl	CAS 1988
Chemical structure		SANSS 1988
Identification numbers:		
CAS Registry	74-87-3	CAS 1988
NIOSH RTECS	PA6300000	RTECS 1988
EPA Hazardous Waste	U045	HSDB 1988
OHM-TADS	7216794	OHM-TADS 1988
DOT/UN/NA/IMCO Shipping	UN 1063	HSDB 1988; RTECS 1988
HSDB	883	HSDB 1988
NCI	No data	

CAS = Chemical Abstracts Services; EPA = Environmental Protection Agency; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance 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 Chloromethane

Property	Value	Reference
Molecular weight	50.49	
Color	Colorless gas	Ahlstrom and Steele 1979
Physical state	Gas	Ahlstrom and Steele 1979
Melting point	-97.7°C	Ahlstrom and Steele 1979
Boiling point	-23.73°C	Ahlstrom and Steele 1979
Density:		
Liquid at 20/4°C	0.920 g/mL	Ahlstrom and Steele 1979
Gas at 0°C, 1 atm	1.74 (air=1)	Ahlstrom and Steele 1979
Odor	Ethereal, nonirritating	Ahlstrom and Steele 1979
Odor threshold		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	5325 mg/L	Horvath 1982
	4800 mg/L	Ahlstrom and Steele 1979
Organic solvents[a]:		
Benzene	4723	Ahlstrom and Steele 1979
Carbon tetrachloride	3756	Ahlstrom and Steele 1979
Glacial acetic acid	3679	Ahlstrom and Steele 1979
Absolute alcohol	3740	Ahlstrom and Steele 1979
Partition coefficients:		
Log octanol/water	0.91 (experimental)	Hansch and Leo 1985
Log K_{OC}	0.7 (estimated)	PCGEMS equ 4-10
Log BCF	0.46 (estimated)	PCGEMS equ 5-5
Vapor pressure:		
at 20°C	3670 mmHg	Ahlstrom and Steele 1979
at 25°C	4310 mmHg	Riddick et al. 1986
Henry's law constant:		
at 25°C	8.82×10^{-3} atm-m^3/mol	Gossett 1987
Autoignition temperature	632°C	Ahlstrom and Steele 1979
Flashpoint, open cup	<0°C	Ahlstrom and Steele 1979
Flammability limits	10.7-17.4 vol %	Ahlstrom and Steele 1979
Conversion factors:		
ppm (v/v) to mg/m^3 in air at 25°C	ppm (v/v) x 2.064 = mg/m^3	
mg/m^3 to ppm (v/v) in air at 25°C	mg/m^3 x 0.4845 = ppm (v/v)	

[a]Gas, 20°C, 1 atm, mL CH_3Cl/100 mL solvent.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Chloromethane is both an anthropogenic and naturally occurring chemical. Anthropogenic sources include industrial production, polyvinyl chloride burning, and wood burning; natural sources include the oceans, microbial fermentation, and biomass fires (e.g., forest fires, grass fires). Chloromethane is produced industrially by either reaction of methanol and hydrogen chloride (HCl) or by chlorination of methane (Ahlstrom and Steele 1979; Key et al. 1980; Edwards et al. 1982a). While the reaction of methanol with HCl is the most common method, the process chosen depends, in part, on the HCl balance at the site (the methane route produces HCl, the methanol route uses it) (Ahlstrom and Steele 1979; Edwards et al. 1982a). Typically, manufacturing plants that produce chloromethane also produce higher chlorinated methanes (methylene chloride, chloroform, and carbon tetrachloride).

The methanol-HCl process involves combining vapor-phase methanol and HCl at 180-200°C, followed by passage over a catalyst where the reaction occurs (Ahlstrom and Steele 1979). Catalysts include alumina gel, gamma alumina, and cuprous or zinc chloride on pumice or activated carbon. The exit gases from the reactor are quenched with water to remove unreacted HCl and methanol. The quench water is stripped of the dissolved methanol and chloromethane and the remaining dilute HCl solution is used in-house or treated and discharged (Ahlstrom and Steele 1979). The chloromethane is then dried by treatment with concentrated sulfuric acid, then compressed, cooled, and stored.

In the methane chlorination process, a molar excess of methane is mixed with chlorine, and the mixture is then fed to a reactor, which is operated at 400°C and 200 kPa pressure (Ahlstrom and Steele 1979; Key et al. 1980). The exit gases can then be scrubbed with chilled chloromethanes (mono- to tetrachloromethane) to remove most of the reaction chloromethanes from unreacted methane and HCl. The by-product HCl is removed by water wash, stripped of any chloromethanes, and either used in-house or sold; the unreacted methane is recycled through the process. The condensed chloromethanes are then scrubbed with dilute NaOH to remove any HCl, dried, compressed, cooled, then fractionally distilled to separate the four chloromethanes. While there are some variations to this process, including the use of catalysts, the above description is a general overview of the basic steps in the process.

Six domestic manufacturers of chloromethane are Dow Corning Corp. (Carrollton, KY; Midland, MI), Dow Chemical Co. (Plaquemine, LA; Freeport, TX), LCP Chemicals (Moundsville, WV), General Electric Co. Silicone Products Division (Waterford, NY), Occidental Chemical Co. (Belle, WV), and Vulcan Materials (Lake Charles, LA) (CMR 1986; USITC 1987). Vista Chemical Co.'s plant in Geisman, LA, will be completed in 1991 (CMR 1989). LCP Chemicals in Moundsville, WV, can use either process, and the others use the methanol hydrochlorination process (Key et al. 1980). Total United States production

of chloromethane was 373 million pounds ($1.7x10^{11}$ g) in 1987 (USITC 1987), which is less than the 1985 production of 511 million pounds ($2.2x10^{11}$ g) (CMR 1986) and the 1984 production of 482 million pounds (USITC 1985). World-wide production was ≈790 million pounds ($3.6x10^{11}$ g) in 1980 (Edwards et al. 1982b). It is difficult to estimate the total production levels for chloromethane because many of the producers consume their output internally as a feedstock for other chemicals, including silicones and higher chlorinated methanes. Total production, therefore, may be higher than the above estimates.

In addition to direct manufacture, chloromethane is also produced naturally and from a number of human activities. The amount of chloromethane produced naturally far exceeds the amount manufactured (at least by a factor of 10). Most chloromethane produced on earth comes from the ocean; estimates of oceanic production volumes vary, but generally fall within the range $(3-5)x10^{12}$ g/year (6.6-11 billion pounds/year) (Fabian 1986; Rasmussen et al. 1980; Singh et al. 1979; Yung et al. 1975). Other sources of natural chloromethane include biomass burning (both natural and resulting from human activity, e.g., forest fires, wood burning, cigarette smoking, volcanoes, burning plastic, coal burning), which accounts for $(0.2-0.4)x10^{12}$ g/year (0.44-0.88 billion pounds/year) (Chopra 1972; Crutzen et al. 1979; Edgerton et al. 1984, 1986; Fabian 1986; Kadaba et al. 1978; Khalil et al. 1985; Kleindienst et al. 1986; Palmer 1976; Rasmussen et al. 1980; Tassios and Packham 1985), microbial activity (Fabian 1986; Harper and Hamilton 1988; Harper 1985; Harper et al. 1988), chlorination of drinking water and wastewater (Coleman et al. 1976; Lurker et al. 1983), and some trees (Isidorov et al. 1985). Some controversy exists concerning wood burning as a source of chloromethane (DeGroot 1989). The total production of chloromethane from sources other than manufacture account for approximately $(3.2-8.2)x10^{12}$ g/year (7-18 billion pounds).

4.2 IMPORT

No information concerning the import of chloromethane in the United States was located in the literature (chloromethane is not reported separately by the U.S. International Trade Commission). Approximately 4% of production is exported (CMR 1986).

4.3 USE

Chloromethane is used mainly (72%) in the production of silicones (CMR 1986) where it is used to methylate silicon. This process involves the reaction of silicon with chloromethane and heat to form mono-, di-, and trichlorosilicon (Browning 1985). Chloromethane is also used in the production of agricultural chemicals (8%), methyl cellulose (6%), quaternary amines (5%), butyl rubber (3%), and for miscellaneous uses including tetramethyl lead (2%) (CMR 1986). Virtually all of the uses for chloromethane are consumptive in that the chloromethane is reacted to form

another product during use. Thus, chloromethane is consumed when used and is no longer available for release, disposal, or reuse.

4.4 DISPOSAL

No information was located in the literature concerning the disposal of chloromethane. Since most chloromethane is used consumptively, little remains to be disposed of. Nonetheless, some chloromethane is present in waste, since it has been detected in hazardous waste landfills. These concentrations may result from the landfilling of still bottoms or other residues from the manufacture and use of chloromethane. Its presence in municipal waste landfills may suggest that consumer products containing chloromethane are landfilled (e.g., propellants for aerosol cans, old refrigerators). In a study of the products of initial combustion using mixtures of chloromethane under simulated incinerator conditions, chloromethane was destroyed under oxygen-rich conditions (Taylor and Dellinger 1988). Under oxygen starved conditions, however, chloromethane can combine with other components of the mixture to form, among other compounds, chlorinated ethanes, hexachlorobenzene, and octachlorostyrene.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chloromethane is a natural and ubiquitous constituent of the oceans and atmosphere (both troposphere and stratosphere). It is a product of biomass combustion, and is produced by wood rotting fungi. Chloromethane has been detected in surface waters, drinking water, groundwater, and soil. It is present in at least 18 out of 1177 hazardous waste sites on the National Priorities List (NPL) in the United States (VIEW Database 1989). The frequency of these sites in the United States can be seen in Figure 5-1. Chloromethane is a constituent of municipal and industrial solid waste leachate, and is a component of industrial waste discharges as well as being present in the effluents of publicly owned treatment works (POTWs). Chloromethane in air has an estimated half-life of ≈1.5 years and is the dominant organochlorine species in the atmosphere. In water, chloromethane is expected to volatilize rapidly from shallow bodies of water with a half-life of 25 hours calculated for a pond and 18 days for a lake. It is not expected to sorb to sediments or bioconcentrate. Chemical hydrolysis and biodegradation are not expected to be significant processes. In soil, chloromethane is expected to volatilize from the surface, but when present in a landfill, will probably leach to groundwater. In groundwater, hydrolysis may be the only removal mechanism available to chloromethane with a half-life of ≈2 years. Air concentrations of chloromethane are generally in the sub-ppb range, but urban locations appear to have elevated concentrations when compared to background concentrations. Although detailed information is lacking, water concentrations are likely to vary considerably depending on the season and geographic location. Very little information is available concerning chloromethane concentrations in soil. The general population is not expected to be exposed to concentrations of chloromethane much above 3 ppb in urban locations. In rural locations, the exposure concentration will be ≈0.7-0.9 ppb. Occupational exposure to chloromethane may result in exposures of up to ≈10 ppm based upon the incomplete database; however, the database for occupational exposure is dated (1980 or earlier) and not comprehensive enough to allow reliable predictions of average or probable occupational exposure levels. The population with the highest potential exposures probably would include those people who work in chloromethane manufacturing or use industries.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Most releases of chloromethane will be to air, since it is a gas at ambient temperatures and manufacturing practices suggest that little will be discharged by any other route. Chloromethane discharged to water will volatilize rapidly, based on the Henry's law constant; however, the amount volatilized will vary depending on a number of factors including the temperature, turbulence, and depth of the receiving water. Chloromethane will be released from both manufacturing and use (fugitive emissions) as well as production resulting from human activities (e.g., grass and plastics

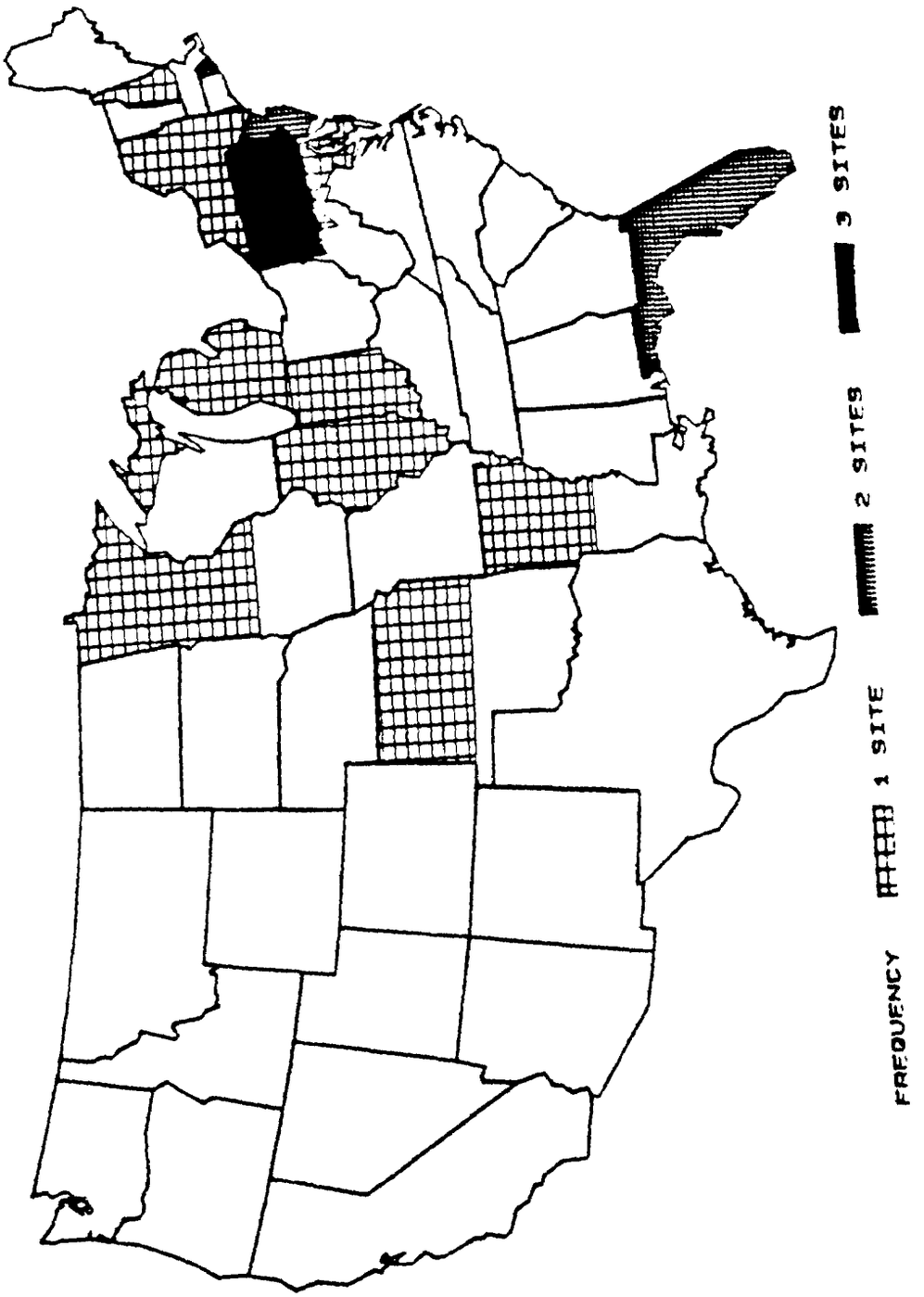


FIGURE 5-1. Frequency of Sites With Chloromethane Contamination

burning, water chlorination) and natural production. All of the sources amount to 7-18 billion pounds ($3.2\text{-}8.2\times10^{12}$ g) annually on a world-wide basis and sources include the oceans, forest fires, wood burning, coal burning, cigarette smoking, volcanos, burning plastic (Chopra 1972; Crutzen et al. 1979; Edgerton et al. 1984, 1986; Edwards et al. 1982a, 1982b; Khalil et al. 1985; Kleindienst et al. 1986; Palmer 1976; Rasmussen et al. 1980; Singh et al. 1979, 1981a, 1981b, 1982, 1983; Tassios and Packham 1985; Yung et al. 1975), fungal activity (Fabian 1986; Harper and Hamilton 1988; Harper 1985; Harper et al. 1988; Wuosmaa and Hager 1990), and some trees (Isidorov et al. 1985). Chloromethane present in wastewaters also may be released to air during aeration (Pincince 1988). By comparison, 1980 world-wide production of chloromethane was ≈794 million pounds (3.6×10^{11} g) (Edwards et al. 1982b), of which ≈6% was released to the environment from production, storage, transport, and use emissions (Edwards et al. 1982) or in other words world-wide releases of 44 million pounds (2.0×10^{10} g) resulted from manufacturing and use activities in 1980. United States production of chloromethane in 1987 was 373 million pounds (1.7×10^{11} g), resulting in estimated releases of 21 million pounds (9.5×10^{9} g). Thus, over 98% of ambient air concentrations of chloromethane appear to come from releases from natural sources rather than releases from manufacturing or use. Chloromethane concentrations are elevated in the ambient air of cities in the United States (Singh et al. 1982, 1983) (Section 5.4.1). The authors suggested that this elevation may be the result of manufacturing and use sources as well as combustion sources.

5.2.2 Water

Chloromethane is released to water from a number of sources including industrial discharges and effluents from municipal waste treatment plants, but insufficient information is available to quantify the releases. During the manufacture of chloromethane, process water contacts the reaction mixtures (see Section 4.1) (Ahlstrom and Steele 1979; Edwards et al. 1982a; Key et al. 1980). This water is stripped during manufacture and treatment to remove most of the dissolved chloromethane, then discharged (some chloromethane manufacturing plants use the process water on-site as a source of dilute hydrochloric acid rather than discharging it). Data regarding the use and fate of process water in use applications were not found in the available literature; however, spent process water is probably treated (including aeration) prior to discharge. Nonetheless, chloromethane has been found in wastewater effluents, possibly as a result of its formation (Coleman et al. 1976; Gould et al. 1983) or incomplete removal during industrial wastewater treatment (Snider and Manning 1982). Chloromethane has been detected in the leachate of both municipal (Gould et al. 1983; Sabel and Clark 1984) and hazardous waste landfills (Brown and Donnelly 1988; Kosson et al. 1985; Venkataramani et al. 1984). It was reportedly found in at least 18 of 1177 NPL hazardous waste sites (VIEW Database 1989) in unspecified medium and in the water at 7 of 357 hazardous waste sites in the Contract Laboratory Program Statistical Data Base at a concentration range of 5.4-500 ppb (CLPSDB 1987).

5.2.3 Soil

Chloromethane is probably released to soil during the landfilling of sludges and other wastes (e.g., still bottoms) generated from industrial processes and municipal sewage treatment; however, no specific information concerning chloromethane containing wastes was located in the literature. Chloromethane has been detected in the leachate of both municipal (Sabel and Clark 1984) and hazardous waste landfills (Brown and Donnelly 1988; Kosson et al. 1985; Venkataramani et al. 1984), indicating that disposal of these materials apparently results in contamination of soils. The Contract Laboratory Program Statistical Data Base reports that chloromethane has been detected in the soil at 8 of 357 hazardous waste sites at a concentration of 5-500 ppb (CLPSDB 1987).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The physical properties of chloromethane that affect its transport and partitioning in the environment are: water solubility, ≈5000 ppm; log octanol/water partition coefficient, 0.91; Henry's law constant, 8.82×10^{-3} atm-m^3 mol; vapor pressure, 4310 mm Hg at 25°C; log sediment sorption coefficient ≈0.7; and log BCF ≈0.46 (see Table 3-2). Most chloromethane discharged to the environment will be released to air where it will be subjected to transport and diffusion into the stratosphere (Singh et al. 1979, 1982, 1983). The relatively uniform concentration of chloromethane in the northern and southern hemispheres (Singh et al. 1979, 1982, 1983) indicates its widespread distribution and the importance of transport processes in its distribution. The water solubility of chloromethane indicates that small amounts may be removed from the atmosphere by precipitation; however, no information confirming this was located in the literature.

The dominant transport process from water will be volatilization. The results of two EXAMS model runs and the value of the Henry's law constant (calculated from the solubility and the vapor pressure) suggest that volatilization will be significant in surface waters. EXAMS is an environmental model that predicts the behavior of a chemical in surface waters. Using the code test data developed by the Athens Environmental Research Laboratory of the EPA for a pond, the half-life for volatilization was calculated to be 25 hours. For a lake, the half-life was calculated to be 18 days. Input data included molecular weight, vapor pressure, Henry's law constant, octanol/water partition coefficient, sediment sorption coefficient, and water solubility. The volatilization rates predicted by the EXAMS model appear to be in agreement with the observation of Lurker et al. (1983) who reported chloromethane concentrations in wastewater and in the air above the wastewater at the Memphis North Wastewater Treatment Plant in Memphis, Tennessee. Based on the log octanol/water partition

coefficient and the sorption coefficient and BCF calculated from it (see Table 3-2), chloromethane is not expected to concentrate in sediments or in biota.

In soil, the dominant transport mechanism for chloromethane that is present near the surface probably will be volatilization (based on its Henry's law constant, water solubility, and vapor pressure), but no experimental information was located in the literature to confirm this. The actual volatilization rate for a chemical in soil is influenced by a number of factors including surface roughness, soil type, rainfall, leaching, depth of incorporation, temperature, and ground cover (Jury et al. 1987). Since chloromethane is not expected to sorb to soils, any chloromethane present in lower layers of the soil will be expected to leach to lower horizons as well as diffuse to the surface and volatilize. The presence of chloromethane in groundwater confirms the importance of leaching as a transport route (Greenberg et al. 1982; Jury et al. 1987; Page 1981).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The dominant tropospheric removal mechanism for chloromethane is generally regarded to be hydrogen abstraction by hydroxyl radical (Dilling 1982; Fabian 1986; Gusten et al. 1984; Lovelock 1975; Rasmussen et al. 1980; Robbins 1976; Singh et al. 1979). The hydroxyl radical reaction with chloromethane has been experimentally determined in a number of studies (Butler et al. 1978; Cox et al. 1976; Davis et al. 1976; Howard and Evenson 1976; Jeong and Kaufman 1980, 1982; Jeong et al. 1984; Paraskevopoulos et al. 1981; Perry et al. 1976). The data of Howard and Evenson (1976) [discharge flow-laser magnetic resonance], Perry et al. (1976) [flash photolysis-resonance fluorescence], Davis et al. (1976) [flash photolysis-resonance fluorescence], Paraskevopoulos et al. (1981) [flash photolysis-resonance adsorption], and Jeong and Kaufman (1980, 1982) [discharge flow-resonance fluorescence] are in agreement (Atkinson 1985; NASA 1981). The recommended rate constants for the hydroxyl radical reaction are 4.36×10^{-14} and 4.3×10^{-14} cm^3 $molecule^{-1}$ sec^{-1}, respectively, at 298 K (Atkinson 1985; NASA 1981). The Arrhenius form recommended by Atkinson (1985) was:

$$k = (3.50^{+0.71}_{-0.58}) \times 10^{-18} T^2 \exp[(-585 \pm 59)/T],$$

where k is the rate constant in cm^3 $molecule^{-1}$ sec^{-1} and T is the Kelvin temperature; that recommended by NASA (1981) based on the same data set without the Paraskevopoulos et al. (1981) data was:

$$k = 3.49 \times 10^{-18} T^2 \exp(-582/T)$$

over the range 247-483 K. The equations yield rate constants that vary <1% over the valid temperature range of the equation.

The high quality of the early measurements of the rate constants for the chloromethane reaction with hydroxyl radicals has allowed calculation of tropospheric lifetimes by a number of researchers (Crutzen and Gidel 1983; Dilling 1982; Fabian 1986; Khalil and Rasmussen 1981; Singh et al. 1979). Using the most recent estimates of global hydroxyl radical concentrations [$(0.1\text{-}1)\times10^6$ molecules cm^{-3}, Fabian (1986)], a half-life of ≈1.5 years has been calculated, although estimates vary from 1-2 years (Khalil and Rasmussen 1981) to 2-3 years (Crutzen and Gidel 1983; Singh et al. 1979).

A complex atmospheric model, a hydroxyl radical concentration of $(0.5\text{-}3)\times10^6$ molecules cm^{-3} in the troposphere, and UV absorption cross sections [calculated by Robbins (1976)] for photochemical reactions have been used to estimate the mixing height of chloromethane to be ≈50 km. Another atmospheric model (and probably high estimates of hydroxyl radical concentrations) has been used to estimate the importance of the stratospheric photochemical dissociation of chloromethane to chlorine and methyl radicals (Robbins 1976). In this model, photochemical dissociation will compete with hydroxyl radical reactions above 30 km, but photochemical processes below 30 km will be insignificant compared to hydroxyl radical reaction rates. The products of photochemical destruction have been reported to be CHClO and HCl along with CO (Sanhueza and Heicklen 1975).

5.3.2.2 Water

In water, chloromethane can degrade either by hydrolysis or biodegradation. Although few data are available on the biodegradation of chloromethane in water, neither hydrolysis nor biodegradation in surface waters appears to be rapid when compared with volatilization. Chloromethane hydrolysis proceeds via an S_N2 mechanism (bimolecular) in which no intermediate ions are formed and methanol and HCl are the only products. The kinetics of chloromethane hydrolysis have been measured by Heppolette and Robertson (1959) and Laughton and Robertson (1956) by bubbling chloromethane into water and following the reaction by measuring the conductance of the water. The rate constant for hydrolysis of chloromethane at 50°C was reported to be 7.6×10^{-7} sec^{-1}, which yields a half-life of 10.5 days. When extrapolated to 20°C and neutral conditions using the thermodynamic constants calculated by Heppolette and Robertson (1959), a rate constant of 1.04×10^{-8} sec^{-1} and a half-life of ≈2 years are calculated. This rate is expected to be unaffected by pH ranges normally encountered in the environment. This hydrolysis half-life is too long to be of any environmental significance in surface waters, especially considering the rapid volatilization of chloromethane from surface water (Mabey and Mill 1978). In groundwater, however, hydrolysis may be the only degradation mechanism available and, hence, may be a significant removal process under these conditions. Biodegradation may also occur in groundwater, but rates are highly variable.

Very little information is available concerning the biodegradation of chloromethane in water. Both cell-free preparations of methane

monooxygenase, prepared from Methylococcus capsulatus (Bath), and whole-cell preparations oxidized chloromethane (Stirling and Dalton 1979). Formaldehyde was the product of metabolism. In pure cultures of a Hyphomicrobium sp., obtained by culturing with a chloromethane-minimal medium, hydrolytic dehalogenation was not observed, but cell growth and chloride formation occurred simultaneously (Hartmans et al. 1986). Strain GJ10 of Xanthobacter autotrophicus could not use chloromethane in a growth medium containing other carbon sources (Janssen et al. 1985). These reports show that under pure culture conditions, some microbial strains can degrade chloromethane. Since these conditions, however, do not occur in the environment, these same species may not degrade chloromethane in the environment. Biodegradation of chloromethane is not ruled out, however, by the available information. Based on the reactions of other chloroalkanes, chloromethane may degrade anaerobically via dechlorination to form methane (Vogel et al. 1987). An estimated half-life of less than 11 days has been predicted for anaerobic biodegradation of chloromethane in groundwater, based upon laboratory data obtained under conditions favorable for anaerobic biodegradation (Wood et al. 1985).

5.3.2.3 Soil

No information concerning soil transformation and degradation was located in the literature. In lower soil horizons, hydrolysis may be a significant process since no other removal mechanism has been identified.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Chloromethane has been the subject of numerous studies conducted to determine the atmospheric chloride balance. In the development of a database for ambient air monitoring, over 242 sites in the United States had been monitored for chloromethane in a 5-year period (Eichler and Mackey 1986). Table 5-1 presents monitoring data for chloromethane for urban/suburban and rural/remote air masses. The ranges and averages presented in Table 5-1 cannot be compared directly since the measurements taken at urban/suburban locations were all taken at ground level, while many of the rural/remote analyses were made at higher altitudes. The volatile organic carbon (VOC) database contained 706 data points (300 cities from 42 states) and further reported the following analysis of the data for chloromethane (Shah and Singh 1988):

Average	740 ppt
Upper Quartile	721 ppt
Median	652 ppt
Lower Quartile	607 ppt

Since the average value, which is higher than the upper quartile (75% value) may be skewed because of a few high values, the median may be a better

TABLE 5-1. Detection of Chloromethane in Air[a]

Media Type/Location	Sampling Dates	# of Samples	Sample Type	Analytical Method	Concentration (ppt) Range	Concentration (ppt) Mean	% Occurrence	Reference
Urban/Suburban Air								
Los Angeles, CA	4/9-21/79	NS	Continuous	GC/ECD	1037-7761	3001	100	Singh et al. 1981
Phoenix, AZ	4/23/79-5/6/79	NS	Continuous	GC/ECD	1231-5685	2391	100	Singh et al. 1981
Oakland, CA	6/28/79-7/10/79	NS	Continuous	GC/ECD	483-5000	1066	100	Singh et al. 1981
Houston, TX	5/15-24/80	NS	Continuous	GC/ECD	531-2284	955	100	Singh et al. 1982a
St. Louis, MO	5/30/80-6/8/80	NS	Continuous	GC/ECD	531-1015	732	100	Singh et al. 1982a
Denver, CO	6/16-26/80	NS	Continuous	GC/ECD	519-1157	763	100	Singh et al. 1982a
Riverside, CA	7/2-12/80	NS	Continuous	GC/ECD	437-1593	703	100	Singh et al. 1982a
Staten Island, NY	3/27/80-4/5/80	NS	Continuous	GC/ECD	466-1280	701	100	Singh et al. 1982a
Pittsburgh, PA	4/8-16/80	NS	Continuous	GC/ECD	450-852	665	100	Singh et al. 1982a
Chicago, IL	4/21-30/80	NS	Continuous	GC/ECD	575-1311	856	100	Singh et al. 1982a
Los Angeles, CA	4/29/76-5/4/76	NS	Grab	GC/ECD	708-944	834	100	Singh et al. 1977
Stanford Hills, CA	11/24-30/75	NS	Grab	GC/ECD	700-1700[a]	1022	100	Singh et al. 1977
Rural/Remote Air								
Pullman, WA	12/74-2/75	7[b]	Grab	GC/MS	503-566	530	100	Grimsrud and Rasmussen 1975
Alaska	5/24-30/75	45[c]	Grab	GC/MS	505-970[d]	NS	100	Robinson et al. 1977
Point Barrow, AK	5/7 & 13/82	51[e]	Grab	GC/ECD	634-660	647	100	Rasmussen and Khalil 1983
Pacific Northwest	3/11/76	34[c]	Grab	GC/ECD	428-611[d]	569	100	Cronn et al. 1977
Point Arina, CA	12/8/79-2/18/81	NS	Continuous[f]	GC/ECD	674-898	754	100	Singh et al. 1981b
Point Reyes, CA	12/2-12/75	NS	Grab	GC/ECD	680-1700[a]	1260	100	Singh et al. 1977
Yosemite, CA	5/12-17/75	NS	Grab	GC/ECD	654-999	713	100	Singh et al. 1977
Palm Springs, CA	5/24-27/76	NS	Grab	GC/ECD	645-2128	1058	100	Singh et al. 1977

[a]Marine air may influence levels.
[b]Samples were taken in downtown Pullman, Washington State University campus, 1.2, 1.8, 2.4, 3.0, and 3.6 km in altitude.
[c]Samples were taken at altitudes up to 14.5 km.
[d]Read from a graphical presentation of the data.
[e]Samples were taken at altitudes up to 4.3 km.
[f]4-6 samples were taken in a 24-hour period on each of 17 sampling days.

GC/ECD = gas chromatography/electron capture detector; GC/MS = gas chromatography/mass spectroscopy; ND = not detected; NS = not specified.

representation of the database. The data by types of air mass were also reported so that the influence of urban centers could be estimated (Shah and Singh 1988):

Air Mass	Median Concentration	Data Points
Remote	713 ppt	5
Rural	923 ppt	2
Suburban	641 ppt	599
Urban	810 ppt	100

From these data and the data presented in Table 5-1, it appears that source contributions from industrial processes do not significantly impact the ambient concentration of chloromethane, although some elevation may occur. There are many fewer data points, however, for rural/remote data than for urban/suburban data so that a direct comparison is difficult. The ambient air levels of chloromethane in cities in the United States are slightly elevated above background levels, probably due to higher numbers of combustion sources (Singh et al. 1982, 1983). Average urban levels reported by these authors were 660-960 ppt, while background levels were 600-700 ppt.

5.4.2 Water

Chloromethane has been detected in surface water, groundwater, drinking water, municipal and hazardous waste landfill leachate, and industrial effluents (Table 5-2). When detected, concentrations appear to be in the ppb-ppt range, possibly due to the rapid volatilization of chloromethane. Chloromethane apparently is formed during the chlorination of drinking water. It was 1 of 13 compounds found in the drinking water of all five cities (Philadelphia, PA; Miami, FL; Seattle, WA; Ottumwa, IA; Cincinnati, OH) studied as part of the EPA National Organics Reconnaissance Survey (NORS) (Coleman et al. 1976). Most of the compounds detected were reported to be highly specific to the locality and raw water supply. Those compounds found in all supplies studied may be widespread.

No specific information concerning sources of chloromethane in fresh surface water was located in the literature. Chloromethane concentrations in surface water may be the result of rain out from the atmosphere as well as the result of human activity (e.g., industrial effluents, chlorinated secondary effluent from POTWs). Industrial effluents may be a significant source. Seven positive detections of chloromethane in industrial effluents out of over 4000 samples from 46 industrial categories and subcategories were reported in the EPA database (Bursey and Pellizzari 1982). Concentrations ranged from 6-4194 μg/L in these effluents. Thirty-four species of fungi can produce chloromethane biosynthetically (Harper et al. 1988). The presence of these fungi near lakes and streams may be a source of chloromethane. The significance of this source to surface water, however, cannot be estimated.

TABLE 5-2. Detection of Chloromethane in Water and Sediments

Media Type/Location	Sampling Dates	# of Samples	Sample Type	Analytical Method	Concentration (ppb) Range	Mean	% Occurrence	Reference
Surface Water								
Delaware River and Raritan Canal	NS	NS	Grab	NS	ND	NS	0	Granstrom et al.1984
Lake Ontario	7/82-5/83	10[a]	Grab	GC/MS	<1	<1	0	Otson 1987
Lake Ontario	NS	NS	NS	NS	Detected	NS	NS	Great Lakes Water Quality Board 1983
Surface Waters in New Jersey	NS	605	NS	NS	<0.1-222	NS	4	Page 1981
Groundwater								
New Jersey	NS	1058[b]	NS	NS	<0.1-6	NS	0.3	Page 1981; Greenberg et al. 1982
Minnesota[c]	NS	13	NS	NS	Detected	NS	69	Sabel and Clark 1984
Minnesota	NS	7	NS	NS	Detected	NS	29	Sabel and Clark 1984
Massachusetts	NS	NS	NS	NS	Detected	44	NS	Burmaster 1982
Drinking Water								
Miami, FL	NS	NS	Grab	GC/MS	Detected	NS	NS	Coleman et al. 1976
Seattle, WA	NS	NS	Grab	GC/MS	Detected	NS	NS	Coleman et al. 1976
Ottumwa, IA	NS	NS	Grab	GC/MS	Detected	NS	NS	Coleman et al. 1976
Philadelphia, PA	NS	NS	Grab	GC/MS	Detected	NS	NS	Coleman et al. 1976
Cincinnati, OH	NS	NS	Grab	GC/MS	Detected	NS	NS	Coleman et al. 1976 Kopfler et al. 1977
Landfill Leachate								
Minnesota[d]	NS	6	NS	NS	Detected	NS	66	Sabel and Clark 1984
Wisconsin[d]	NS	5	NS	NS	170	170	20	Sabel and Clark 1984
Love Canal, NY[e]	NS	NS	NS	NS	180	180	NS	Shuckrow et al. 1982
Kin-Buc Landfill, NJ[e]	NS	NS	NS	NS	3.1	3.1	NS	Shuckrow et al. 1982
Hazardous Waste Sites	NS	NS	NS	GC/MS	5.4-500	115	NS	CLPSBD 1987
11 National Priority List Sites	NS	NS	NS	NS	Detected	NS	NS	NPLTDB 1989
Urban Runoff								
15 United States cities	NS	86	Grab	GC/MS	ND	ND	0	Cole et al. 1984

TABLE 5-2 (Continued)

Media Type/Location	Sampling Dates	# of Samples	Sample Type	Analytical Method	Concentration (ppb) Range	Mean	% Occurrence	Reference
Effluents								
Petroleum refinery effluents[f]	NS	17	Grab	GC/MS	<100->100	NS	NS	Snider and Manning 1982
Petroleum refinery effluents[g]	NS	17	Grab	GC/MS	<10	NS	NS	Snider and Manning 1982

[a]10 locations on Lake Ontario.
[b]408 wells.
[c]Groundwater under municipal solid waste landfills.
[d]Municipal solid waste leachate.
[e]Industrial landfill.
[f]Biotreatment effluents.
[g]Final effluent.

GC/ECD = gas chromatography/electron capture detection; GC/MS = gas chromatography/mass spectroscopy; ND = not detected; NS = not specified.

The presence of chloromethane in groundwater may also result from both natural and anthropogenic sources. Since chloromethane has been detected in the groundwater near municipal waste sites containing the chemical (Sabel and Clark 1984), waste deposits of chloromethane on land may lead to groundwater contamination. Chloromethane appears to be a constituent of both municipal and industrial waste landfills. In these landfills, volatilization may be hindered so that leaching to groundwater can become an important transport pathway. Additionally, chloromethane may be the product of anaerobic metabolism of higher chlorinated methanes also present in the soil (Vogel et al. 1987).

5.4.3 Soil

The only information located in the literature concerning the presence of chloromethane in soil was the natural formation of chloromethane by a number of fungi (Harper et al. 1988) and its presence in both landfill leachate and groundwater. Thus, chloromethane is present in soils, but no concentrations can be inferred from these reports. The Contract Laboratory Program Statistical Data Base reported that the soil at hazardous waste sites contained chloromethane at mean concentrations ranging from 5-500 ppb (CLPSDB 1987).

5.4.4 Other Media

As presented in Section 5.2.1, chloromethane is present in wood smoke, cigarette smoke, coal burning, volcanoes, and burning plastic (Chopra 1972; Crutzen et al. 1979; Edgerton et al. 1984, 1986; Fabian 1986; Kadaba et al. 1978; Khalil et al. 1985; Kleindienst et al. 1986; 1983; Palmer 1976; Rasmussen et al. 1980; Singh et al. 1982; Tassios and Packham 1985). It was suggested that 1 cm^3 of chloromethane gas (2.2 mg) was produced for each gram of cellulose burned (glowing combustion) (Palmer 1976). Concentrations of chloromethane in smoke from combustion processes, however, are highly variable and depend on both the fuel (i.e., the amount of inorganic chlorine present in the fuel) and temperature of the burn. Thus, quantification of chloromethane in these media will be representative of the specific source and the exact conditions of the burn rather than general emission levels. Chloromethane has not been detected in auto exhaust (detection limit of 1 ppm) (Hasanen et al. 1979).

Chloromethane was present in 2 of 8 samples of mothers' milk from Bayonne and Jersey City, NJ; Bridgeville, PA; and Baton Rouge, LA (Pellizzari et al. 1982). No concentrations were reported and no information was given concerning the source of the chloromethane in the milk. Chloromethane was present in the expired air of all three tested groups of 62 non-smoking adults, including a control, prediabetic, and diabetic group (Krotoszynski and O'Neill 1982). Since chloromethane is a ubiquitous constituent of air, it is reasonable that it would be found in the expired air of virtually all humans. The chlorine used to chlorinate

drinking water did not contain chloromethane, but other higher chloromethanes were present (Otson et al. 1986). Sources for the chlorine included both mercury and diaphragm cells and contamination by higher chloromethanes was uniform across several manufacturers.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Chloromethane is a ubiquitous constituent of air and probably drinking water. As such, the general population will be exposed to background levels at all times, while those living in urban centers will be exposed to slightly higher levels.

According to one report, persons living in Los Angeles, CA, Phoenix, AZ, and Oakland, CA, would have daily intakes of ≈120, 94, and 52 μg/day, respectively (Singh et al. 1981a). These intakes are based on a total respirable air volume of 20 m^3/day at 25°C and 1 atm pressure. Using the data of Shah and Singh (1988) for remote, rural, suburban, and urban air masses, daily intakes are estimated to be ≈31, 40, 28, and 35 μg/day, respectively. The intakes for rural and remote air masses are based on very small sample sizes and may be inaccurate. Dermal exposure and exposures from drinking water containing chloromethane are more difficult to estimate from the available information. Drinking water concentrations are not well described in the literature and may vary considerably both seasonally and geographically.

Historically (30 years ago or longer), large exposures have been associated with leaking refrigerators that used chloromethane as a refrigerant. While refrigeration grade chloromethane is apparently still available (Ahlstrom and Steele 1979), it is not known whether it is currently used in refrigeration equipment. Without this information, potential exposures cannot be estimated.

A large database of documented occupational exposure levels is available for chloromethane manufacturing; however, the information is dated (1980 and earlier) and may not represent current conditions. The available data are summarized in Table 5-3. In general, the occupational exposure data indicate that the majority of exposure concentrations are below 50 ppm, but excursions as high as 300 ppm can occur. Most exposure concentrations reported in the literature have occurred in the manufacturing industry, with very few reported in use industries. Based on the major use patterns (see Section 4.3), exposures in use industries will be similar to those in manufacturing industries since similar storage and transfer equipment is used and these are the major sources of leakage (Edwards et al. 1982a,b). NIOSH (1984) reported 30 industrial categories (SIC codes) where exposures to chloromethane may occur. Table 5-4 presents these categories along with the number of workers potentially exposed in each category. These data are based on 1972-1974 surveys. The more recent National Occupational Exposure Survey (NOES) reports much lower exposure incidents than the 40,538 estimated by the 1972-1974 survey (NIOSH 1984). According

TABLE 5-3. Occupational Monitoring of Chloromethane

Company	Year Sampled	Sample Type	Concentration (ppm) Range	Concentration (ppm) Mean[a]	Number of Samples	% Positive	Reference
Conoco Chemicals	1978	Area	0.8-5.9	NS	16	94	Cohen 1979
Conoco Chemicals	1978	Personal	<0.2-7.5	1.1	16	81	Cohen 1979
DuPont Company	1977	Area	<1.0-75.1	NS	15	93	Koketsu 1979
DuPont Company	1977	Personal	<0.16-12.4	NS	22	86	Koketsu 1979
Diamond Shamrock Chemical	1975	Area	0.14-101.7	NS	9	100	Egan et al. 1976
Diamond Shamrock Chemical	1975	Personal	0.04-34.7	NS	53	100	Egan et al. 1976
Union Carbide	1976-1980	Personal	0.1-15	NS	NS	100	Gorman and Froneburg 1981
Foxboro Company	1976	Area	<0.001	NS	2	0	Ruhe 1976
UCAR[b]	1978	Area	0.02-0.08	NS	5	100	Belanger 1980
Cities Service Company	1980	Area	52-313	NS	2	100	Markel and Froneburg 1983
Cities Service Company	1980	Personal	1.45-166	NS	11	100	Markel and Froneburg 1983
Dow Chemical Co.	1979	Area	1.47-19.8	NS	16	100	Crandall et al. 1980
Dow Chemical Co.	1979	Personal	0.35-39.6	NS	50	100	Crandall et al. 1980
Dow Chemical Co.	1975	Area	1-120[c]	NS	75	100	Repko et al. 1977
Survey of 4 Plants	1979	Area and Personal	<0.16-62.5	NS	82	82	Cohen 1980

[a]Geometric mean of the positive samples.
[b]University Corporation for Atmospheric Research, Mauna Loa, Hawaii.
[c]Range of average concentrations taken at various locations in the plant, concentrations measured with conductivity and infrared equipment.

NS = not specified.

TABLE 5-4. Numbers of Workers Potentially Exposed to Chloromethane and Standard Industrial Classification (SIC)

SIC Code	SIC Description	Number of Workers Potentially Exposed
07	Agricultural services and hunting	647
13	Oil and gas extraction	24
15	General building contractors	1301
16	Heavy construction contractors	405
17	Special trade contractors	1143
20	Food and kindred products	2720
21	Tobacco manufacturers	90
22	Textile mill products	8
24	Lumber and wood products	112
27	Printing and publishing	212
28	Chemicals and allied products	980
29	Petroleum and coal products	16
31	Leather and leather products	85
33	Primary metal industries	1223
34	Fabricated metal products	238
35	Machinery, except electrical	1292
36	Electrical equipment and supplies	451
37	Transportation equipment	1660
38	Instruments and related products	453
39	Miscellaneous manufacturing industries	418
41	Local and interurban passenger transit	73
44	Water transportation	93
45	Transportation by air	1115
48	Communication	424
50	Wholesale trade	486
53	Retail general merchandise	402
55	Automotive dealers and service stations	14,734
73	Miscellaneous business services	8960
79	Amusement and recreation services	342
80	Medical and other health services	431
	Total	40,538

Source: NIOSH 1984

to NOES, 8853 employees are exposed to chloromethane. Of these, 572 are female. Fifty-six percent of the total exposures were to the actual chemical, while 44% were to trade name products. Ninety-nine percent of the exposures to female employees were to the actual chemical and 1% to trade name products (NIOSH 1988).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

All humans are probably exposed to low concentrations of chloromethane because chloromethane is ubiquitous in the environment. Those with potentially high exposures appear to be workers employed in the manufacturing and use (by analogy) industries. Concentrations in these industries may reach 100,000 times background concentrations, but can go up to 1,000,000 times background concentrations. People with old refrigerators in which chloromethane is used as a refrigerant are another population with potentially high exposure. These refrigerators can leak and result in very high air concentrations of chloromethane. This latter population should be diminishing, since the number of refrigerators using chloromethane should be decreasing.

The concentrations of chloromethane reported at hazardous waste sites present in the Contract Laboratory Program Statistical Data Base are low (CLPSDB 1987), and, if indicative of the concentrations at NPL sites, they probably do not represent a source of potentially high exposures to those populations surrounding the sites.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 chloromethane 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 chloromethane.

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 Identification of Data Needs

Physical and Chemical Properties. Data regarding physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Most of the necessary data on physical and chemical

properties are available for chloromethane, and many of these have experimental descriptions accompanying them so that accuracy can be evaluated. A property of chloromethane that has not been measured is the odor threshold. The odor of chloromethane, however, is probably not a sufficient warning property for humans because severe neurological effects and death have occurred in people who were unaware of being exposed even to high concentrations in confined spaces. The known physical and chemical properties data form the basis of many of the input requirements for environmental models that predict the behavior of a chemical under specific conditions including hazardous waste landfills.

Production, Use, Release, and Disposal. Production methods for chloromethane are well described in the literature (including the patent literature) and there does not appear to be a need for further information. Uses of chloromethane have been recently documented, although a detailed description of all uses is not available. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden; however, it is difficult to obtain this information in the detail desired since generally it is considered to be confidential business information for those industries that manufacture chloromethane. Release information, which can be used to estimate environmental burdens and potentially exposed populations, is also not obtained easily.

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxics Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Environmental Fate. The fate of chloromethane in air is well described because extensive air photolysis and photooxidation studies are available that characterize these processes. In water, biodegradation studies in surface and groundwaters are lacking. Hydrolysis data are available, but reliable data have not been obtained at environmentally relevant temperatures. These kinds of studies are important because they would provide information about fundamental removal mechanisms for chloromethane in the environment and might aid in understanding the behavior of chloromethane at hazardous waste sites. Data regarding biodegradation in water may be difficult to obtain and may be irrelevant due to possible rapid volatilization from the aqueous media used in the experiments. In addition, transport mechanisms, particularly volatilization of chloromethane from soil surfaces and leaching to lower soil horizons, are not well described. These processes, however, are complex and unless theory for these improves, it is likely that any data for chloromethane would apply only to the specific sites where measurements are taken. The vapor pressure of chloromethane and its presence in groundwater suggest that these processes are important,

particularly at hazardous waste sites, and may account for some of the losses of chloromethane from the site.

Bioavailability from Environmental Media. Experimental inhalation studies in animals and humans indicate that chloromethane is bioavailable from the atmosphere. Although chloromethane in water or soil is likely to end up in the air because of its volatility, studies using the oral and dermal routes of exposure would help to determine the bioavailability of chloromethane from water, soil, and other environmental media.

Food Chain Bioaccumulation. The log K_{ow} for chloromethane is 0.91 and the bioconcentration factor calculated from this value is 2.98 (PCGEMS), indicating that chloromethane will not concentrate significantly in aquatic organisms. No information was available concerning the bioaccumulation of chloromethane at other trophic levels. Information concerning the accumulation of chloromethane in several trophic levels would be useful in estimating human dietary intake of chloromethane; however, based on the calculated BCF, little intake is expected.

Exposure Levels in Environmental Media. Extensive environmental monitoring data are available for air, while only some data are available for drinking water, surface water and groundwater. The air monitoring data describe the concentrations that populations are exposed to through inhalation of ambient air. The data for water are not sufficient to accurately characterize the concentrations of chloromethane present in drinking water, surface water, and groundwater. Virtually no data are available for soils. These data would be helpful in determining the ambient concentrations of chloromethane so that exposure of the general population as well as of terrestrial and aquatic organisms could be estimated.

Exposure Levels in Humans. The database for exposure levels in humans is limited to determinations of chloromethane in breast milk. A more complete database would be helpful in determining the current exposure levels and thereby estimating the average daily dose associated with various scenarios (e.g., living near a hazardous waste site). An environmental media monitoring program may provide the necessary information for estimating environmental exposures, while workplace monitoring at use sites, using personal dosimeters and remote sensing devices, would probably provide useful workplace information.

Exposure Registries. An exposure registry is not available. The development of a registry of exposures would provide a useful reference tool in assessing exposure levels and frequency. In addition, a registry would allow assessment of variations in exposure resulting from such variables as geography, season, regulatory actions, presence of hazardous waste landfills, or manufacturing and use facilities. These assessments, in

turn, would provide a better understanding of the need for various types of research or data acquisition.

5.7.2 On-Going Studies

No on-going studies were located in the literature.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring chloromethane 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 chloromethane. 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 chloromethane 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 a trade association 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.

6.1 BIOLOGICAL MATERIALS

Methods used to analyze biological samples for chloromethane are summarized in Table 6-1. S-Methylcysteine may be a metabolite of chloromethane in some humans (Nolan et al. 1985; Van Doorn et al. 1980). S-methylcysteine can be analyzed by diluting urine with water and treating the resulting solution with a buffer and a phthaldialdehyde solution to derivatize the S-methylcysteine (De Kok and Antheunius 1981; van Doorn et al. 1980). Analysis is performed on a reversed phase high performance liquid chromatography column using methanol sodium hydrogen phosphate gradient elution and a fluorescence detector. The reported detection limit is 1 mg/L.

Breast milk can be analyzed for chloromethane by expressing a 60 mL sample into a wide mouth bottle followed by freezing (Pellizzari et al. 1982). Analysis was performed by warming the sample then purging with helium flowing through a Tenax GC column to sorb the chloromethane and other volatiles. The Tenax was thermally desorbed onto a GC column and analyzed by mass spectrometry. No recoveries or accuracy information was reported.

6.2 ENVIRONMENTAL SAMPLES

In air, chloromethane can be analyzed by NIOSH Method 1001 (NIOSH 1987), which is suitable for air concentrations to ≈1 ppm. The method involves drawing a 0.4-3 L sample through a coconut charcoal tube followed by methylene chloride desorption and analysis by GC-FID. The method has a working range of 66-670 mg/m^3 for a 1.5 L sample and a detection limit of 0.01 mg/tube. Table 6-1 presents accuracy information for this method. For lower concentrations, the analytical methods necessary are more specialized. The use of coconut charcoal tubes preceded by an $MgClO_4$ drying tube has been described to measure chloromethane in air (Lindskog et al. 1988). From 1-2 L of air aredrawn through the tube then placed in dry ice. The chloromethane is thermally desorbed onto a liquid nitrogen cooled capillary column then flushed onto the GC column by warming the capillary column.

TABLE 6-1. Analytical Methods for Determining Chloromethane in Biological and Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy[a]	Reference
Urine	Dilution with water followed by derivatization with phthaldialdehyde (method for S-methyl cysteine)	HPLC/FD	1 mg/L	NS	De Kok and Antheunius 1981
Rat blood	Warming sample and immediate analysis of headspace air	GC/ECD	NS	NS	Landry et al. 1983a
Breast milk	Warming sample then purging to Tenax and thermal desorption to GC column.	GC/MS	NS	NS	Pellizzari et al. 1982
Expired air	Expired air collected in a 10 L gas sample bag and analyzed with added ethyl chloride or vinyl chloride as an internal standard	GC/ECD	NS	NS	Nolan et al. 1985
Air	Charcoal tube collection and CH_2Cl_2 desorption.	GC/FID	66 mg/m^3	95	NIOSH 1987
	Charcoal tube collection, thermal desorption.	GC/FID	NS	NS	Lindskog et al. 1988
Water	Purging sample with inert gas and trapping the chloromethane on a column followed by desorption onto GC column.	GC[b]	0.08 µg/L	91.4[c]	EPA 1982
	Same as above.	GC/MS	10 µg/L[d]	99±24[e]	EPA 1982; EPA 1988a
Soil/solid waste	Purging sample with inert gas and trapping the chloromethane on a column followed by desorption onto GC column.	GC[b] GC/MS	7.4 µg/kg[f]	NS	EPA 1986b EPA 1988a

[a]Average percent recovery.
[b]Electrolytic conductivity or microcoulometric detector.
[c]Laboratory water and effluents.
[d]Quantitation limit for Contract Laboratory Program.
[e]Laboratory water.
[f]Recoveries from solid samples will vary depending on the particular matrix.

ECD = Electron capture detector; FD = fluorescence detection; FID = flame ionization detector; GC/MS = gas chromatography/mass spectroscopy; HPLC = high performance liquid chromatography; NS = not specified.

Analysis is performed by GC with flame ionization detection. For very low concentrations, extreme care must be taken to ensure no contamination is introduced into the sampling and analysis method.

Chloromethane can be analyzed in municipal and industrial wastewater by EPA Test Method 601 - Purgeable Halocarbons or EPA Test Method 624 - Purgeables (EPA 1982). The method is adequate for measuring chloromethane in wastewaters; however, care must be taken in sampling the site since chloromethane is volatile and some of the chemical may be lost during the sampling process. Method 601 involves purging the sample with an inert gas and passing the gas through a trap containing 2,6-diphenylene oxide polymer (Tenax GC), silica gel, and coconut charcoal to adsorb the purged chloromethane and other halocarbons. After the purging is complete, the trap is heated to desorb the chloromethane from the trap. The desorbed chloromethane is analyzed by gas chromatography (GC) using an electrolytic conductivity or microcoulometric detector. Method 624 is similar to Method 601, but the trap material is made of 3% methyl silicone (OV-1) on packing material, 2,6-diphenylene oxide polymer (Tenax GC), and silica gel; analysis is made by gas chromatography/ mass spectroscopy (GC/MS). Over purging the sample may result in loss of some chloromethane. The average recovery from reagent water and effluents was 91.4±13.4% for Method 601 and 99±24% from wastewater for method 624. The Contract Laboratory Program analytical method involves screening the sample for component concentrations by rapidly transferring the room temperature sample to a volumetric flask, adding hexadecane and extracting the volatiles, including chloromethane, for 1 minute then qualitatively analyzing the sample by gas chromatography with flame ionization detection (EPA 1988a). The quantitative analysis method for the sample is by GC/MS and is essentially identical to EPA method 624 (EPA 1988a). Table 6-1 presents accuracy and detection limit data for the methods.

In soil and solid waste, EPA Method 5030 for soil and solid waste analysis of chloromethane (EPA 1986b) and the Contract Laboratory Procedure for soil analysis (EPA 1988a) involve the direct purge and trap method for low level samples or methanolic extraction for high level samples, based on a hexadecane extraction as described above. For low level samples, the soil/solid waste is placed in a purge impinger, mixed with water, purged with an inert gas, and trapped on a Texax GC and silica gel (EPA 1988a) or OV-1, Tenax GC, and silica gel column (EPA 1986b). The trap column is heated and purged to desorb the chloromethane and other volatiles onto the GC column. For medium level samples, the soil/solid waste is mixed with methanol and shaken. An aliquot of the methanol is removed, diluted with water and purged as described above for water samples. Over purging the sample may result in loss of some chloromethane. Analysis is performed by EPA Method 8000 (Gas Chromatography) and 8010 (Halogenated Volatile Organics) or Method 8240 (Gas Chromatography/Mass Spectrometry for Volatile Organics) (EPA 1986b), which is essentially identical to the Contract Laboratory Program method. Method 8010 uses a GC with an electrolytic

conductivity detector. Table 6-1 presents the detection limit for this method.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 chloromethane 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 chloromethane.

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 Identification of Data Needs

Methods for Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 2.5). Methods are available for the analysis of chloromethane in blood, expired air, and breast milk. In addition, a method exists for analysis of the metabolite S-methylcysteine in urine. Quantitative relationships have not been established between exposure and measurement of chloromethane or 2-methylcysteine in these biological media. The observed variability of metabolism (see discussion of metabolism of chloromethane in Section 2.3.3) suggests that a correlation of chloromethane levels in tissues with levels of chloromethane exposure is not likely to be found. It may be possible to use levels of yet unidentified metabolites in blood or urine as biomarkers of exposure. If reliable biomarkers of exposure were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods for the biomarkers, including ample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans.

No biomarker that can be associated quantitatively with effect has been identified (see Section 2.5). Thus, there are no analytical methods for the determination of biomarkers of effect for chloromethane.

Methods for Determining Parent Compound and Degradation Products in Environmental Media. Methods appear to be available for the analysis of chloromethane in all environmental media including groundwater, surface

water, waste water, soil, solid waste, and workplace and ambient air. Chloromethane degrades to a number of products in the environment including methanol and formaldehyde, both of which are natural products. While analytical methods exist for these compounds, they cannot be used as indicators of chloromethane degradation since methanol and formaldehyde have large natural sources.

6.3.2 On-going Studies

No on-going studies were located regarding analytical method development for chloromethane.

7. REGULATIONS AND ADVISORIES

The International Agency for Research on Cancer (IARC) and National and state regulations and guidelines pertinent to human exposure to chloromethane are summarized in Table 7-1.

Chloromethane is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, organic chemicals, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black (EPA 1988b).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Value	Reference
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
	National		
Regulations:			
a. Air:			
OSHA	TWA	50 ppm (8 hr)	29 CFR 1910.1000
	STEL	100 ppm	OSHA 1989
b. Nonspecific media:			
EPA OERR	Reportable quantity (statutory)	1 lb	40 CFR 302.4 EPA 1987a, 1988c
Guidelines:			
a: Air:			
ACGIH	TLV TWA	50 ppm	ACGIH 1988
	STEL	100 ppm	
NIOSH	TWA	100 ppm	NIOSH 1985
	Ceiling	200 ppm	
	Maximum peak	300 ppm (5 min in 3 hr)	
b. Other:			
EPA	Carcinogenic classification	Group C[b]	EPA 1987b
EPA	q_1^* for inhalation exposure (proposed)	6.32×10^{-3} $(mg/kg/d)^{-1}$	
	q_1^* for oral exposure (proposed)	1.26×10^{-2} $(mg/kg/d)^{-1}$	
	State		
Regulations:			
a. Air:	Accceptable ambient air concentrations		
Connecticut		2100 $\mu g/m^3$ (8 hr)	NATICH 1988
Kansas		74.12 $\mu g/m^3$ (annual)	NATICH 1988
Kentucky		52.5 mg/m^3 (8 hr)	State of Kentucky 1986
Michigan		1.6 $\mu g/m^3$ (annual)	NATICH 1988
North Dakota		1.05 mg/m^3 (8 hr)	NATICH 1988
		2.05 mg/m^3 (1 hr)	NATICH 1988
Nevada		2.5 mg/m^3 (8 hr)	NATICH 1988
New York		2100 $\mu g/m^3$ (1 yr)	NATICH 1988
Pennsylvania		2520 $\mu g/m^3$ (1 yr)	NATICH 1988
Virginia		1750 $\mu g/m^3$ (24 hr)	NATICH 1988
b. Water	Drinking water		NATICH 1988
Arizona		0.50 µg/L	
Kansas		0.19 µg/L	

[a]The agent is not classifiable as to its carcinogenicity to humans.
[b]Possible human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; STEL = Short-Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average.

8. REFERENCES

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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 (Kd) -- 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.

9. GLOSSARY

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.

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.

9. GLOSSARY

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

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 8-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.

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: PEER REVIEW

A peer review panel was assembled for chloromethane. The panel consisted of the following members: Dr. Anthony DeCaprio, Private Consultant; Dr. Theodore Mill, Physical Organic Chemistry Department, SRI International; Dr. Nancy Reiches, private consultant; and Dr. Nancy Tooney, Department of Biochemistry, Polytechnic University. These experts collectively have knowledge of chloromethane'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 Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act as amended.

A joint panel of scientists from ATSDR and EPA has 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 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 Agency for Toxic Substances and Disease Registry.