TOXICOLOGICAL PROFILE FOR CHLOROMETHANE

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Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Chloromethane was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance 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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey Koplan

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure,* by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

> *NOTE:* Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)
or 404-639-6357 *Fax:* 404-639-6359
E-mail: atsdric@,cdc.gov *Internet:* http://atsdr1.atsdr.cdc.gov:8080

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History--The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume *III-Medical Management Guidelines for Acute Chemical Exposures-is* a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29,4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX:770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone:800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19,4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233,104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone:919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone:202-347-4976 • FAX:202-347-4950 • e-mail: aoec@,dgs.dnsvs.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone:847-228-6850 • FAX:847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.\

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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PEER REVIEW

A peer review panel was assembled for chloromethane. The panel consisted of the following members:

1. Dr. Herbert Comish, Private Consultant, 830 W. Clark Road, Ypsilanti, MI;

2. Dr. Anthony DeCaprio, Associate Professor, State University of New York at Albany, Albany, NY;

3. Dr. Theodore Mill, Senior Scientist, SRI International, Menlo Park, CA; and

4. Dr. Nancy Tooney, Associate Professor, Brooklyn, NY.

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(1)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chloromethane and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup. Chloromethane has been found in at least 172 of the 1,467 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with chloromethane may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance 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. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to chloromethane, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CHLOROMETHANE?

Chloromethane (also known as methyl chloride) is a clear, colorless gas. It has a faint, sweet odor that is noticeable only at levels which may be toxic. It is heavier than air and is extremely flammable.

Chloromethane is produced in industry, but the it also occurs naturally, and most of the chloromethane that is released to the environment (estimated at up to 99%) comes from natural

sources. Chloromethane is always present in the air at very low levels. Most of the naturally occurring chloromethane comes from chemical reactions that occur in the oceans or from chemical reactions that occur when materials like grass, wood, charcoal, and coal are burned. It is also released to the air as a product of some plants or from rotting wood.

Chloromethane is produced industrially. In the past, chloromethane was widely used as a refrigerant, but refrigerators no longer use chloromethane because of its toxic effects. It was also used as a foam-blowing agent and as a pesticide or fumigant. A working refrigerator that is more than 30 years old may still contain chloromethane, and may be a source of high-level exposure. Today, nearly all commercially produced chloromethane is used to make other substances, mainly silicones (72% of the total chloromethane used). Other products that are made from reactions involving chloromethane include agricultural chemicals (8%), methyl cellulose (6%), quaternary amines (5%), and butyl rubber (3%). Chloromethane is completely used up so that by the end of the process there is no or little chloromethane left to be released, disposed of, or reused. It is, however, found as a pollutant in municipal waste streams from treatment plants and industrial waste streams as a result of formation or incomplete removal. There are also some manufacturing processes for vinyl chloride that result in chloromethane as an impurity in the vinyl chloride end product.

See Chapters 3 and 4 for more information on the nature and uses of chloromethane.

1.2 WHAT HAPPENS TO CHLOROMETHANE WHEN IT ENTERS THE ENVIRONMENT?

Chloromethane has been identified in air, surface water, groundwater, soil, and sediment. Most releases of chloromethane will be to the air. Chloromethane rapidly moves through the air and is present at very low concentrations throughout the atmosphere. Naturally occurring chloromethane is continuously released into the atmosphere from oceans, rotting wood, forest fires, and volcanoes. When grass, coal, or wood are burned, chloromethane is released to the air. The burning of grasslands and forests accounts for about 20% (ranging from 10 to 40%) of the total chloromethane in the air. Releases from the oceans account for another 80 to 90%.

Chemical companies release some chloromethane gas to the air during the production of chloromethane or when it is used to make other substances, but the amount is relatively very small (0.2 to 0.6%) compared to natural sources of the total chloromethane in the atmosphere.

Chloromethane breaks down very slowly (months to years) in the air. Chloromethane can dissolve in water, and small amounts of chloromethane in air may go into surface waters or groundwater when it rains. Chloromethane can also enter water from industrial or municipal waste streams or from water that comes in contact with municipal or hazardous waste sites. Chemical companies generally treat waste water to remove chloromethane.

Chloromethane is a gas at room temperature, and when present in water, most will evaporate rapidly to the air. Small amounts of dissolved chloromethane may move below the surface of the water or be carried to the groundwater. It breaks down very slowly (months to years) in plain water, but certain kinds of small organisms in water may break it down more quickly (days). When chloromethane comes in contact with soil it does not stick to the soil. Most of the chloromethane in soil will move to the air. Some may dissolve in water and move down through the soil layers to the groundwater or into well water. Chloromethane does not concentrate in sediments, or in animals and fish in the food chain.

See Chapters 4 and 5 for more information on how chloromethane moves through the environment.

1.3 HOW MIGHT I BE EXPOSED TO CHLOROMETHANE?

Most (99%) of the chloromethane in the environment comes from natural sources. 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 1 part of chloromethane in a billion parts of air (ppb). In cities, human activities, mostly combustion and manufacturing, add to the chloromethane in the air, resulting in somewhat higher levels, up to 1 ppb. Chloromethane exposures in the less than 5 ppb range are much lower (1,000 to 10,000 times lower) than the

exposure levels that have been shown to have toxic effects. Chloromethane is also present in some lakes and streams and has been found in drinking water (including well water) at very low levels in the parts per billion to part per trillion (ppt) range. Chloromethane may be formed to a small extent in tap water that has been chlorinated. You could be exposed to levels in air higher than the background levels if you live near a hazardous waste site or an industry that uses chloromethane. If chloromethane is present at waste sites, it can move through the soil into underground water. We have very little information on the levels of chloromethane in groundwater. Chloromethane is not generally found in food.

The people most likely to be exposed to increased levels of chloromethane in the air are those who work in chemical plants where it is made or used. Chloromethane is also an impurity in vinyl chloride when the vinyl chloride is produced by heating another chemical, 1,2-dichloroethane. Exposure to chloromethane can occur from this kind of vinyl chloride or the disposal of vinyl chloride waste from this process. The proper enforcement of workplace regulations and the recycling of chloromethane during the manufacturing process help prevent worker exposures to levels that would be considered harmful. In the past (more than 30 years ago), chloromethane was also widely used as the refrigerant in refrigerators. Some of these old refrigerators may still be in use or may be located in storage areas. Chloromethane may be released from leaks in these refrigerators, leading to potentially very high exposures, especially in areas with poor ventilation. Liquid contact could also occur following a leak in an older refrigerator containing chloromethane. Other general population sources of chloromethane exposure include cigarette smoke; polystyrene insulation; aerosol propellants; home burning of wood, grass, coal, or certain plastics; and chlorinated swimming pools. The chloromethane in the outdoor environment, however, is almost totally from natural sources.

In Chapter 5, you can find more information on how you might be exposed to chloromethane.

1.4 HOW CAN CHLOROMETHANE ENTER AND LEAVE MY BODY?

Chloromethane can enter your body through your lungs, if you breathe it in, or through your digestive tract if you drink water containing it. The chloromethane that you breathe in or drink rapidly enters the bloodstream from the lungs or the digestive tract and moves throughout the body to organs such as the liver, kidneys, and brain. Very little of the chloromethane that enters the body remains unchanged. The portion of the chloromethane that does not get changed in your body leaves in the air you breathe out. The rest is changed in your body to other breakdown products that mostly leave in the urine. The breakdown process takes anywhere from a few hours to a couple of days.

Breathing air that contains chloromethane vapor is the most likely way you would be exposed if you live near a hazardous waste site. Contact with liquid chloromethane is rare, but could occur in an industrial accident from a broken metal container. Prolonged skin contact with liquid chloromethane is unlikely, because it turns into a gas very quickly at room temperature. It is not known how much chloromethane liquid or gas will enter the body through contact with the skin, but the amount is probably very low.

See Chapter 2 for more information on how chloromethane can enter and leave the body.

1.5 HOW CAN CHLOROMETHANE AFFECT MY HEALTH?

If the levels are high enough (over a million times the natural levels in outside air), even brief exposures to chloromethane can have serious effects on your nervous system, including convulsions, coma, and death. Some people have died from breathing chloromethane that leaked from refrigerators in rooms that had little or no ventilation. Most of these cases occurred more than 30 years ago, but this kind of exposure could still happen if you have an old refrigerator that contains chloromethane as the refrigerant. Some people who were exposed to high levels of chloromethane while they were repairing refrigerators did not die, but they did have toxic effects like staggering, blurred or double vision, dizziness, fatigue, personality changes, confusion,

tremors, uncoordinated movements, nausea, or vomiting. These symptoms can last for several months or years. Complete recovery has occurred in some cases, but not in others. Exposure to chloromethane can also harm your liver and kidney, or have an effect on your heart rate and blood pressure. If you work in an industry that uses chloromethane to make other products, you might be exposed to levels that could cause symptoms resembling drunkenness and impaired ability to perform simple tasks.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Harmful liver, kidney, and nervous system effects have developed after animals breathed air containing high levels of chloromethane (one million times higher than natural levels). Some of these animals died from exposure to high levels of chloromethane. Similar effects were seen in animals that breathed low levels continuously and animals that breathed high levels for shorter periods with some breaks from exposure.

Animals that breathed relatively low test levels of chloromethane (but still one hundred thousand to one million times higher than background levels people are exposed to) over a long period (weeks to months) had slower growth and developed brain damage. Some male animals were less fertile or even sterile or produced sperm that were damaged. Females that became pregnant by the exposed males lost their developing young.

Male mice that breathed air containing chloromethane (one million ppb) 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 can cause sterility, miscarriages, birth defects, or cancer in humans. The Department of Health and Human Services (DHHS) has not classified chloromethane for carcinogenic effects. The International Agency for Research on Cancer (IARC) calls chloromethane a Group 3 compound, which means it cannot be determined whether or not it is a carcinogen because there is not enough human or animal data. The Environmental Protection Agency (EPA) considers chloromethane possibly carcinogenic to humans (i.e., Group C) based on limited evidence of carcinogenicity in animals.

See Chapter 2 for more information on how chloromethane can affect your health.

1.6 HOW CAN CHLOROMETHANE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children may be exposed to chloromethane from the same sources as adults. These sources include outside air, indoor air, and drinking water. Exposures are generally well below safe levels. The people most heavily exposed to chloromethane are workers in chemical plants where it is made or used. With proper safeguards to prevent children from entering these work areas, children would not be expected to have high exposures. Old refrigerators that used chloromethane as a refrigerant and that are leaking chloromethane, however, are a potential source that could result in high exposures to children.

There have been no studies on whether children are more or less susceptible than adults to harmful health effects from a given amount or chloromethane. We do not know if chloromethane affects the developing fetus or the development of young children. There is no information on exposure to high levels of chloromethane in children (for example, accidental poisoning), but we

expect similar effects to those seen in adults (including harmful effects on the nervous system and kidneys). We do not know if the effects for children would be similar to those in adults for lower levels or for longer exposures. There have been no studies where young animals were exposed to chloromethane. Animal studies have shown that female adult rats that were exposed to chloromethane during pregnancy had young that were smaller than normal, with underdeveloped bones, and possibly abnormal hearts (although this effect remains uncertain).

We do not know if chloromethane or its breakdown products in the body can cross the placenta and enter into the developing young. We also do not know if chloromethane or its breakdown products can enter into a nursing woman's milk. We do know that chloromethane is broken down and eliminated from the body very quickly in adults. Although we expect the breakdown and elimination of chloromethane to be the same in children as in adults, more studies are needed to answer this question and the other questions concerning the movement of chloromethane into the fetus or into nursing young through breast milk, and what amounts might result in harmful effects.

More information on the effects of chloromethane can be found in Chapters 2 and 5.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHLOROMETHANE?

If your doctor finds that you have been exposed to significant amounts of chloromethane, ask your doctor if children may also be exposed. When necessary your doctor may need to ask your state Department of Public Health to investigate.

Families can reduce the risk of exposure to chloromethane by properly disposing of the older types of refrigerators that used chloromethane as a refrigerant. If you live near a chemical plant that makes or uses chloromethane, or near a hazardous waste site that stores it, you should teach your children not to play in or around these sites. If family members work in a chemical facility that manufactures or uses chloromethane, they should become familiar with the safety practices that are used to prevent exposure to harmful levels. They should also become familiar with their

rights to obtain information from their employer concerning the use of chloromethane and any potential exposure they might be subject to at work.

You should teach your children about the dangers of breathing smoke from burning vinyl plastic or silicone rubber products, and should properly dispose of all such products. Chloromethane (as well as other toxic compounds) is released from burning polyvinyl chloride. If you are concerned that chloromethane may be in your drinking water, you can have your water tested and learn about the proper water filter to use to remove chloromethane (as well as other possible contaminants) from your drinking water. If you are concerned that products you are using might contain chloromethane, you can check the labels for ingredients or contact the manufacturer for additional information.

Chapter 5 contains additional information on the how you or your family might be exposed to chloromethane.

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

There are no known reliable medical tests 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.

See Chapters 2 and 6 for more information on tests to determine exposure to chloromethane.

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

The federal government develops regulations and recommendations (sometimes called advisories or guidelines) to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration

(FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for chloromethane include the following: To protect workers, OSHA has set a regulation of an average permissible exposure limit of 50 parts of chloromethane per million parts of workroom air (50 ppm) during each 8-hour work shift in a 40-hour workweek.

See Chapter 7 for more information on government recommendations to protect human health from the toxic effects of chloromethane.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-800-447-1544
Fax: (404) 639-6359

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

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2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of chloromethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

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 and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure- inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (l-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in Table 2-l and illustrated in Figure 2-1. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or

those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of chloromethane are indicated in Table 2-1 and Figure 2-1. Cancer effects could occur at lower exposure levels, but a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), has not been developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chloromethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 Inhalation Exposure

2.2.1.1 Death

Thirty or more years ago, chloromethane was used as a refrigerant, and many human deaths resulted from exposure to chloromethane vapors from leaks in 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 were admitted to hospitals with typical neurological signs and symptoms of chloromethane poisoning (confusion, staggering, slurred speech). These patients eventually became comatose, developed convulsions, and died. The concentrations and durations of these exposures were not known.

Exposure to high concentrations of chloromethane can result in moderate to severe neurological effects (see Section 2.2.1.4) but death does not always result if exposure ceases and medical attention is received in time. For example, refrigerator repairmen developed neurological symptoms after exposures to chloromethane from leaks at concentrations as high as 600,000 ppm, but no deaths resulted (Jones 1942). In other cases death did occur. Seventeen crew members (male) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (no estimates of exposure levels were reported). The refrigerator was located under the sleeping quarters of the crew. In the acute phase of the illness, nine patients exhibited abnormal neurological signs. Four died, one within 24 hours of the exposure. Two patients developed severe depression and committed suicide 11 and 18 months later. The fourth patient was" assessed as 75% disabled due to severe neurological and

psychiatric disturbances, and died 10 years postexposure at the age of 34. Autopsy revealed recent coronary occlusion which was not necessarily connected with the primary illness (Gudmundsson 1977). In a follow-up study, Rafnsson and Gudmundsson (1997) reported an excess mortality from cardiovascular diseases in this exposed population compared to a reference group. The excess mortality was more prominent for the deckhands who received the higher exposures to chloromethane. The results and conclusions from this study, however, are based upon the assumption that the reference group had similar lifestyle factors including smoking habits and diet (which may not have been the case). There was also a relatively low number of individuals with significant exposure.

Animals exposed to sufficiently high levels of chloromethane die 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 lethal concentrations of chloromethane (Dunn and Smith 1947; Smith 1947; Smith and von Oettingen 1947a, 1947b). Severe neurological effects, such as paralysis, convulsions, and opisthotonos, developed before death. Precise determination of concentration-duration-response relationships was not possible from these studies because of limitations including unknown purity of chloromethane, unconventional reporting of lethality data, and generally poor reporting of details. Nonetheless, these earlier studies demonstrated the universal response of animals to the neurotoxic and lethal effects of chloromethane.

More recent studies provide better dose-response information. Sprague-Dawley rats were exposed to 99.5% chloromethane at 0, 200, 500, 1,000, or 2,000 ppm for 48 or 72 hours. One-half of the animals were sacrificed immediately after exposure, and the remaining half were observed for 12 days postexposure prior to sacrifice. At 2,000 ppm for 48 hours, rats were either lethargic, moribund or dead. At 52 hours, rats exposed to 1,000 ppm remained lethargic; rats exposed to 2,000 ppm were all dead or moribund. At 72 hours of exposure, all rats receiving 2,000 ppm were dead. No male and 1 of 10 female rats died by 12 days postexposure to 1,000 ppm for 48 hours. Six of 10 male and 8 of 10 female rats died by 12 days postexposure to 1,000 ppm for 72 hours. No deaths occurred at 200 or 500 ppm for up to 72 hours of exposure. Cause of death was thought to be kidney failure (Burek et al. 1981).

Chellman et al. (1986a) studied the effects of 3-amino-l-[m-(trifluoromethyl)phenyl]-Zpyrazoline (BW755C), a potent anti-inflammatory agent, on chloromethane-induced lethality and reproductive toxicity in male Fischer 344 rats. Rats were exposed to 5,000 ppm chloromethane for 5 days or 7,500 ppm chloromethane for 2 days, 6 hours/day, with or without treatment with BW755C (10 mg/kg,

intraperitoneally 1 hour pre- and postexposure). Exposure to 7,500 ppm chloromethane for 2 days, 6 hours/day was fatal to 8 of 12 rats. No deaths occurred in 6 rats treated with both chloromethane and BW755C. One of 5 rats exposed to 5,000 ppm chloromethane died. No deaths occurred in 5 rats treated with both chloromethane and BW755C. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution or excretion of ^{14}C-chloromethane and administration of BW755C did not decrease hepatic glutathione content. The protection of BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis.

Morgan et al. (1982) investigated the lesions induced by inhalation exposure to chloromethane in C3H, C57BL/6, and $B6C3F_1$ mice and in Fischer 344 rats. Ten rats/sex were exposed to chloromethane for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure. Rats were exposed to 0, 2,000, 3,500, or 5,000 ppm. Animals were sacrificed 18 hours after the last exposure or immediately after exposure if found to be moribund. After 5 days, 6 males and 5 females exposed to 5,000 ppm, and 2 females exposed to 3,500 ppm, were killed in extremis. Five mice/sex were exposed to chloromethane for 12 days, 6 hours/day. Mice were exposed to 0, 500, 1,000, or 2,000 ppm. In mice exposed to 2,000 ppm, all male $B6C3F_1$ mice were moribund or died by day 2, one C57BL/6 male died on day 2, and others were moribund by day 5. All other mice survived except one male C3H mouse exposed to 1,000 ppm, which died by day 11. This study confirmed the existence of species, sex, and strain differences in susceptibility to chloromethane-induced toxicity. The authors further speculated that, although the mechanism of death is unknown, it may be associated with liver and kidney pathology.

Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver, kidney, and brain of male $B6C3F_1$ mice. In one experiment, groups of 5 mice were exposed to chloromethane at concentrations from 500 ppm to 2,500 ppm in increments of 500 ppm with or without pretreatment with buthionine-S,R,-sulfoximine (BSO), a depleter of glutathione (GSH), and were observed for death up to 18 hours after exposure. The resulting mortality data was used to estimate an approximate LC_{50} value. The LC_{50} in the non-pretreated rats was 2,200 ppm, while the LC_{50} for the pretreated rats was 3,200 ppm. The authors concluded that pretreatment with BSO, and hence GSH depletion, protected mice from the lethal effects of chloromethane. The GSH metabolic pathway appeared to be activating toxicity rather than detoxifying.

In two further experiments by Chellman et al. (1986b), 36 and 45 mice were exposed by inhalation to 1,500 ppm chloromethane for 2 weeks, 5 days/week, 6 hours/day, with or without daily pretreatment with BSO. In the two experiments using this protocol, 10 of 36 (28%) and 5 of 45 (11%) of the mice died by the end of the first day (6 hours) of exposure to 1,500 ppm chloromethane. In contrast, none of the BSO-pretreated mice died after the first exposure. The authors concluded that pretreatment with BSO, and hence GSH depletion, protected mice from the lethal effects of chloromethane. This provided further evidence that the GSH metabolic pathway activated toxicity rather than detoxified.

Jiang et al. (1985) characterized cerebellar lesions resulting from an acute inhalation exposure to chloromethane in female C57BL/6 mice. Ten mice each were exposed to room air or 1,500 ppm chloromethane for 2 weeks, 5 days/week, 6 hours/day. Two mice died, and several had motor incoordination. Only one exposure concentration was used, but the study was designed to study the neurological and kidney effects specifically, and therefore, used an exposure regimen known to produce these effects. The authors concluded that the brain lesions seen after exposure to chloromethane were probably not a direct consequence of renal lesions.

Landry et al. (1985) evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice Groups of 12 mice each were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously (C) 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently (I) 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. At 2,400-I ppm, the condition of the mice gradually deteriorated until they were killed in a moribund condition after 8 or 9 days of exposure. No deaths occurred in the 1,600-I ppm mice or in mice receiving lower intermittent exposures. The 400-C ppm exposed mice died or were sacrificed by day 4, and the 200-C ppm group by day 5, due to severe toxicity. Mice exposed to 150-C ppm were sacrificed in moribund condition by day 10.5. No deaths occurred in the mice exposed to ≤ 100-C ppm. The authors concluded that exposure duration affected susceptibility to chloromethane-induced neurotoxicity, with those continuously exposed exhibiting a non-proportionate greater susceptibility. The authors speculated that the greater susceptibility was due to a combination of glutathione depletion, the formation of a toxic metabolic intermediate, and the effects of nocturnal exposure.

Wolkowski-Tyl et al. (1983a) assessed the teratogenicity of an inhalation exposure to chloromethane in female Fischer 344 rats and B6C3F$_1$ mice. Groups of 33 mice per exposure level were exposed to 0, 100, 500 or 1,500 ppm chloromethane in whole-body exposure chambers, 6 hours daily on gestation days (Gd)

6-17. Actual chloromethane concentrations in the chambers were 0.05 (the ambient level; for the 0 dose), 102 (100 ppm), 479 (500 ppm), 1,492 (1500 ppm). At 1,492 ppm, there was severe maternal toxicity resulting in tremors, hunched appearance, difficulty righting, disheveled fur, bloody urine, and granular cell degradation in cerebellum with selective necrosis of neurons in the internal granular layer. All females in this group were sacrificed on gestation days 11-14 prior to the completion of exposure to Gd 17; two females died prior to necropsy (as early as Gd 9 after only 4 days of exposure). The authors concluded that in $B6C3F_1$ mice, an inhalation exposure to 1,492 ppm chloromethane resulted in severe maternal toxicity; exposure to 102 and 479 ppm chloromethane did not produce maternal toxicity. No chloromethane-related deaths were observed in female rats.

Wolkowski-Tyl et al. (1983b) assessed the reproductive and developmental effects of an inhalation exposure to chloromethane in C57BL/6 females mated to C3H males to produce $B6C3F_1$ offspring. After mating, 74-77 females were exposed to chloromethane at concentrations of 0, 250, 500, or 750 ppm on Gd 6-17. At 750 ppm, six dams were found dead and one was found moribund on Gd 15-18. The authors concluded that an inhalation exposure to chloromethane during Gd 6-17 resulted in maternal toxicity at 750 ppm, but not at 500 or 250 ppm. Exposure of pregnant mice to 250 ppm chloromethane produced neither maternal nor fetal toxicity nor teratogenicity.

Chellman et al. (1987) investigated the role of chloromethane-induced testicular and epididymal inflammation in the induction of sperm cytotoxicity and preimplantation loss in male Fischer 344 rats. The rats were exposed to 3,056 ppm chloromethane 6 hours/day for 5 consecutive days, with or without concurrent treatment with 3-amino-l-[m-(tri-fluoromethyl)phenyl]-2-pyrazoline (BW755C), an anti-inflammatory agent. None of the animals died during the course of exposure.

Working et al. (1985a) studied the effects of an inhalation exposure to chloromethane on germ cell viability in male Fischer 344 rats. Forty males each were exposed to 0, 1,000, or 3,000 ppm chloromethane for 5 days, 6 hours/day. No males died during the 5-day treatment period or 8-week breeding period.

In an evaluation of the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and $B6C3F_1$ mice, 120 animals per sex per exposure level were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure (n=10, 10, 20, 80 for rats; and n=10, 10, 10, 90 for mice; respectively). Actual measured concentrations

averaged over the 24-month exposure period were 0.3±4, 51±9, 224±16, and 997±65 ppm. During the acute exposure time frame (≤ 14 days), chloromethane exposure had no effect on the survival curves of male or female rats or mice at the exposure levels received. During the intermediate exposure time frame (15-364 days) there was some increased mortality beginning at 10 months in female mice exposed to 1,000 ppm chloromethane, but no effect on the survival of male mice or male or female rats. During the second half of the study (i.e., the chronic exposure of ≥365 days), there was increased mortality in 1,000 ppm exposed male mice beginning at 17 months with a large increase in mortality by 19 months. For 1,000 ppm female mice, increased mortality began at 10 months and continued to rise by 20 months. The 1,000 ppm mice groups were terminated at 21 months (2 males) and 22 months (18 females) due to high mortality. Chloromethane had no effect on the survival of male or female rats (CIIT 1981).

No deaths occurred in male dogs (4 per group) exposed to ≥400 ppm chloromethane for 90 days (McKenna et al. 1981b). Female dogs were not tested.

The LC_{50} values and all reliable LOAEL values for 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

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

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 a confusing protocol. Specifically, groups of two to four men and two to four women were exposed to 10, 100, or 150 ppm or to concentrations that were increased from 50-150 ppm in the same group for 1, 3, or 7.5 hours per day over 2-5 days per 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, chloromethane exposure did not appear to have any effect on pulmonary function.

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

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	2 or 3 d 24 hr/d				1000 (6-8/10 died by day 12 post- exposure to 1000 ppm for 72 hours)	Burek et al. 1981
2	Rat (Fischer- 344)	2-5 d 6 hr/d				5000 M (1/5 died)	Chellman et al. 1986a
3	Rat (Fischer- 344)	9 days 6 hr/d				3500 F (killed in extremis) 5000 M (killed in extremis)	Morgan et al. 1982
4	Mouse (B6C3F1)	6 hr				2200 M (LC_{50})	Chellman et al. 1986b
5	Mouse	2 wk 5 d/wk 6 hr/d				1500 M (5/45 died on first day, no subsequent deaths)	Chellman et al. 1986b
6	Mouse (B6C3F1)	6 hr				2500 M (14/15 died)	Chellman et al. 1986b
7	Mouse (C57BL/6)	2 wk 5 d/wk 6 hr/d				1500 (2/10 died)	Jiang et al. 1985
8	Mouse (C57BL/6)	11 d 5.5 hr/d				2400 F (killed in extremis)	Landry et al. 1985
9	Mouse (C57BL/6)	11 d 22 hr/d				150 F (killed in extremis)	Landry et al. 1985
10	Mouse (C3H) (C57Bl/6) (B6C3F1)	12 d 6 hr/d				1000 M (1/5 died by day 11) 2000 F (all died by day 5)	Morgan et al. 1982
11	Mouse (B6C3F1)	12 d 6 hr/d Gd 6-17				1492 F (all animals terminated early; 2 died prior to necropsy)	Wolkowski-Tyl et al. 1983a

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
12	Mouse (57BL/6)	12 d 6 hr/d Gd 6-17				750 F (6 died, 1 moribund of 75 dams)	Wolkowski-Tyl et al. 1983b
	Systemic						
13	Human	4hr	Gastro		29000M (nausea, vomiting)		Battigelli and Perini 1955
14	Human	1 d	Gastro		39000M (nausea, vomiting)		Jones 1942
15	Human	1-2 wk 2-5 d/wk 1, 3 or 7.5 hr/d	Resp	150			Stewart et al. 1980
			Cardio	150			
			Hemato	150			
16	Rat (Sprague-Dawley)	2 or 3 d 24 hr/d	Resp	2000			Burek et al. 1981
			Hemato	2000			
			Hepatic	500	1000 (fatty infiltration of liver)		
			Renal	500		1000 (increased BUN, tubular cell necrosis)	
			Bd Wt	200	500 (9-15% decrease that was regained by 12 days postexposure)	1000 (29-30% decrease, persistent in males)	
17	Rat (Fischer- 344)	12 d 4-5 d/wk 6 hr/d	Hepatic		3500M (decreased liver non-protein sulfhydryl content)		Chapin et al. 1984

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
18	Rat (Fischer- 344)	5 d 6 hr/d	Hepatic		5000M (cloudy swelling of hepatocytes, obliteration of sinusoids)		Chellman et al. 1986a
			Renal			5000 M (necrosis of proximal convoluted tubules)	
			Endocr		5000M (vacuolation of cell cytoplasm in the adrenal cortex)		
			Bd Wt			5000 M (20% loss of body weight)	
19	Rat	5 d 6 hr/d	Bd Wt	3056			Chellman et al. 1987
20	Rat (Fischer- 344)	9 days 6 hr/d	Gastro		5000 (diarrhea)		Morgan et al. 1982
			Hepatic		2000 F 3500 M (minimal hepatocyte degeneration)		
			Renal			2000 M 3500 F (degeneration and necrosis of proximal convoluted tubules)	
			Endocr	2000	3500 (fatty degeneration of adrenals)		
21	Rat (Fischer- 344)	13 d 6 hr/d Gd 7-19	Bd Wt	1492 F			Wolkowski-Tyl et al. 1983a
22	Rat (Fischer- 344)	5 d 6 hr/d	Bd Wt	1000 M	3000M (16% decr. body weight)		Working et al. 1985a
23	Mouse (B6C3F1)	6 hr	Hepatic		1500M (50 fold increase in ALT)		Chellman et al. 1986b
24	Mouse (NS)	2 wk 5 d/wk 6 hr/d	Renal		1500 (cell regeneration as indicated by 3 fold increased thymidine incorporation)		Chellman et al. 1986b

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
25	Mouse (C57BL/6)	2 wk 5 d/wk 6 hr/d	Renal		1500F (slight degeneration of proximal tubules)		Jiang et al. 1985
26	Mouse (C57BL/6)	11 d 5.5 hr/d	Hemato	1600 F		2400 F (hemoglobinuria; enlarged spleen, low packed cell volume)	Landry et al. 1985
			Hepatic	800 F		1600 F (23% decr. rel. liver weight)	
			Renal	1600 F	2400F (slight multifocal degeneration and regeneration of tubules; increased relative kidney weight)		
			Bd Wt	1600 F	2400F (16% decr. body weight)		
			Other	800 F	1600F (decreased food consumption indicated by decreased ingesta at necropsy)		
27	Mouse (C57BL/6)	11 d 22 hr/d	Hepatic	50 F	100F (decreased hepatocyte size; glycogen depletion)	150 F (necrosis)	Landry et al. 1985
			Renal	150 F			
			Bd Wt	100 F	150F (12% decr. body weight)	200 F (32% decr. body weight)	
			Other		150F (decreased food consumption indicated by diminished amount of feces)		
28	Mouse (C3H) (C57Bl/6) (B6C3F1)	12 d 6 hr/d	Hepatic	1000 M 2000 F		2000 M (degeneration, necrosis)	Morgan et al. 1982
			Renal	500		1000 M (tubular basophilia; hematuria)	

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
29	Mouse (57BL/6)	12 d 6 hr/d Gd 6-17	Hepatic	250 F	500F (increased absolute and maternal liver weight)		Wolkowski-Tyl et al. 1983b
			Bd Wt	250 F		750 F (41% decrease in maternal total weight gain)	
30	Dog (Beagle)	3 d 23.5 hr/d	Resp	500 M			McKenna et al. 1981a
			Cardio	500 M			
			Gastro	500 M			
			Hemato	500 M			
			Musc/skel	500 M			
			Hepatic	500 M			
			Renal	500 M			
			Endocr	500 M			
			Dermal	500 M			
			Ocular	500 M			
			Bd Wt	500 M			
31	Cat (NS)	3 d 23.5 hr/d	Resp	500 M			McKenna et al. 1981a
			Cardio	500 M			
			Gastro	500 M			
			Hemato	500 M			
			Musc/skel	500 M			
			Hepatic	500 M			
			Renal	500 M			
			Endocr	500 M			
			Dermal	500 M			
			Ocular	500 M			
	Neurological						
32	Human	4 hr				29000 M (vertigo, tremors, weakness)	Battigelli and Perini 1955
33	Human	1 d				39000 (ataxia, headache, convulsions)	Jones 1942

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
34	Human	3 hr			200 (4% decrement in performance)		Putz-Anderson et al. 1981a
35	Human	1-2 wk 2-5 d/wk 1, 3 or 7.5 hr/d		150			Stewart et al. 1980
36	Rat (Sprague-Dawley)	2 or 3 d 24 hr/d		500		1000 (lethargy)	Burek et al. 1981
37	Rat (Fischer- 344)	5 d 6 hr/d				5000 M (tremors, ataxia, forelimb/hindlimb paralysis, degeneration of cerebellar granule cells)	Chellman et al. 1986a
38	Rat (Fischer- 344)	9 d 6 hr/d				5000 (hindlimb paralysis, forelimb incoordination, cerebellar lesions)	Morgan et al. 1982
39	Mouse	2 wk 5 d/wk 6 hr/d				1500 M (multiple degenerative and necrotic foci in cerebellar granular cell layer)	Chellman et al. 1986b
40	Mouse (B6C3F1)	6 hr				2500 M (cerebellar damage indicated by tremors, ataxia, and forelimb/hindlimb paralysis)	Chellman et al. 1986b
41	Mouse (C57BL/6)	2 wk 5 d/wk 6 hr/d				1500 F (motor incoordination, coagulative necrosis and edema in cerebellar granule cells)	Jiang et al. 1985
42	Mouse (C57BL/6)	11 d 5.5 hr/d		150 F	400F (slight cerebellar granule cell degeneration)	800 F (poor motor coordination)	Landry et al. 1985
43	Mouse (C57BL/6)	11 d 22 hr/d		50[b] F		100 F (cerebellar granule cell degeneration	Landry et al. 1985

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
44	Mouse (C3H) (C57Bl/6) (B6C3F1)	12 d 6 hr/d		500		1000 (moderate cerebellar degeneration, ataxia)	Morgan et al. 1982
45	Mouse (B6C3F1)	12 d 6 hr/d Gd 6-17		479 F		1492 F (tremors, difficulty righting, degradation and selective necrosis of cerebellar granular cells)	Wolkowski-Tyl et al. 1983a
46	Mouse (57BL/6)	12 d 6 hr/d Gd 6-17		250 F	500F (ataxia)	750 F (tremors, convulsions, hyperactivity, ataxia, and piloerection)	Wolkowski-Tyl et al. 1983b
47	Dog (Beagle)	3 d 23.5 hr/d		200 M		500 M (slight, multifocal lesions in brain and spinal cord; vacuolization, swollen axons, loss of axons)	McKenna et al. 1981a
48	Cat (NS)	3 d 23.5 hr/d		500 M			McKenna et al. 1981a
	Reproductive						
49	Rat (Sprague-Dawley)	2 or 3 d 24 hr/d		200 M		500 M (sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous obstruction of lumen)	Burek et al. 1981
50	Rat (Fischer-344)	12 d 4-5 d/wk 6 hr/d				3500 M (delayed spermiation, seminiferous epithelium vacuolation, and bilateral epididymal granulomas)	Chapin et al. 1984
51	Rat (Fischer-344)	2-5 d 6 hr/d				5000 M (exfoliation of pachytene spermatocytes & early stage spermatids; granuloma in epididymis)	Chellman et al. 1986a

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
52	Rat (Fischer-344)	5 d 6 hr/d				3009 M (preimplantation loss due to testicular toxicity)	Chellman et al. 1986c
53	Rat	5 d 6 hr/d				3056 M (decr. testes weight; delayed spermiation; decreased sperm production; incr. in abnormal sperm; decr. in % motile and % intact sperm)	Chellman et al. 1987
54	Rat (Fischer-344)	9 days 6 hr/d				2000 M (reduction in spermatids, separation of spermatocytes)	Morgan et al. 1982
55	Rat (Fischer-344)	13 d 6 hr/d Gd 7-19		1492 F			Wolkowski-Tyl et al. 1983a
56	Rat (Fischer-344)	5 d 6 hr/d			1000M (decreased fertility)	3000 M (severely reduced fertility)	Working and Bus 1986
57	Rat (Fischer-344)	5 d 6 hr/d		1000 M		3000 M (postimplantation loss in mates, and persistent decreased fertility)	Working et al. 1985a
58	Rat (Fischer-344)	5 d 6 hr/d		1000 M	3000M (reversible disruption of spermatogenesis)		Working et al. 1985b
59	Mouse (B6C3F1)	12 d 6 hr/d Gd 6-17		479 F			Wolkowski-Tyl et al. 1983a
60	Mouse (57BL/6)	12 d 6 hr/d Gd 6-17		500 F			Wolkowski-Tyl et al. 1983b
61	Dog (Beagle)	3 d 23.5 hr/d		500 M			McKenna et al. 1981a
62	Cat (NS)	3 d 23.5 hr/d		500 M			McKenna et al. 1981a

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
63	Rat (Fischer-344)	13 d 6 hr/d Gd 7-19		479		1492 (retarded skeletal development; decreased fetal body weight and crown-rump length in females)	Wolkowski-Tyl et al. 1983a
64	Mouse (B6C3F1)	12 d 6 hr/d Gd 6-17		102		479 (heart defects in fetuses)	Wolkowski-Tyl et al. 1983a
65	Mouse (B6C3F1)	12 d 6 hr/d Gd 6-17		250		500 (heart defect in fetuses)	Wolkowski-Tyl et al. 1983b
INTERMEDIATE EXPOSURE							
Death							
66	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d				997 F (increased mortality)	CIIT 1981
Systemic							
67	Rat (Fischer-344)	6 mo 5 d/wk 6 hr/d	Resp	224 F	997 F (incr. rel. lung wt. from interstitial pneumonia) 51 M (incr. rel. lung wt. from interstitial pneumonia)		CIIT 1981
			Cardio	997			
			Gastro	997			
			Hemato	997			
			Musc/skel	997			
			Hepatic	224 M 997 F	997M (incr. rel. liver weight)		
			Renal	997			
			Endocr	997			
			Bd Wt	224	997 (10-11% decreased body weight)		

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
68	Rat (Fischer- 344)	12 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	997			
			Gastro	997			
			Hemato	997			
			Musc/skel	997			
			Hepatic	224 M 997 F	997M (increased ALT levels)		
			Renal	997			
			Endocr	997			
			Bd Wt	224	997M (18% decreased body weight gain)		
69	Rat (Fischer- 344)	20 wk 5-7 d/wk 6 hr/d	Bd Wt	472	1502F (10-19% decreased body weight gain)	1502 M (20% decreased body weight gain)	Hamm et al. 1985
70	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp	400			McKenna et al. 1981b
			Cardio	400			
			Gastro	400			
			Hemato	400			
			Musc/skel	400			
			Hepatic	400			
			Renal	400			
			Dermal	400			

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
71	Rat (Fischer-344)	90 d 5 d/wk 6 hr/d	Resp	1473			Mitchell et al. 1979
			Cardio	1473			
			Hemato	1473			
			Hepatic	1473 M 741 F	1473F (incr. rel. liver weight)		
			Renal	741 M 1473 F	1473M (incr. rel. kidney weight)		
			Dermal	1473			
			Bd Wt	368 M 741 F	741 M (11% decr. body weight) 1473 F (13% decr. body weight)		
72	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	224 F 997 M	997F (incr. rel. heart weight)		
			Hemato	997			
			Musc/skel	997			
			Hepatic	224	997F (incr. rel. liver weight)	997 M (incr. ALT, necrosis, cytomegaly, karyomegaly, polykaryocytes)	
			Renal	225 M 997 F	997M (renal tubuloepithelial hyperplasia; decreased absolute weight)		
			Endocr	997			
			Bd Wt	224	997 (decreased body weight in the 7-15% range)		

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
73	Mouse (B6C3F1)	6 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	997			
			Hemato	997			
			Musc/skel	997			
			Hepatic	224 F	997 F (incr. rel. liver weight) 51[c] M (incr. ALT, no histological changes)	997 M (incr. ALT, necrosis, karyomegaly, polykaryocytes)	
			Renal	224	997 M (decr. abs. kidney wt) 997 F (incr. rel. kidney wt)		
			Endocr	997			
			Bd Wt	224 M	997 M (10% decr. body weight)		
74	Mouse (CD-1)	90 d 5 d/wk 6 hr/d	Resp	400			McKenna et al. 1981b
			Cardio	400			
			Gastro	400			
			Hemato	400			
			Musc/skel	400			
			Hepatic	150	400 (incr. rel. liver weight)		
			Renal	400			
			Dermal	400			
75	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	1473			Mitchell et al. 1979
			Cardio	1473			
			Hemato	1473			
			Musc/skel	1473			
			Hepatic	741	1473 (increased ALT)		
			Renal	1473			
			Ocular			368 (mucopurulent conjunctivitis)	
			Bd Wt	1473			

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
76	Dog (Beagle)	90 d 5 d/wk 6 hr/d	Resp	400 M			McKenna et al. 1981b
			Cardio	400 M			
			Gastro	400 M			
			Hemato	400 M			
			Musc/skel	400 M			
			Hepatic		50M (swollen hepatocytes)		
			Renal	400 M			
			Dermal	400 M			
			Ocular	400 M			
Immunological/Lymphoreticular							
77	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d		997			CIIT 1981
78	Rat (Fischer- 344)	12 mo 5 d/wk 6 hr/d		997			CIIT 1981
79	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
80	Mouse (B6C3F1)	6 mo 5 d/wk 6 hr/d		224	997 (lymphoid depletion of spleen; thymic lymphoid necrosis)		CIIT 1981
81	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d		997			CIIT 198m1
82	Mouse (CD-1)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
83	Dog (Beagle)	90 d 5 d/wk 6 hr/d		400 M			McKenna et al. 1981b

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Neurological							
84	Human	2-3 wk or more 5 d/wk 8-16 hr/d				265 (impairment of memory, gait, balance, speech, and vision)	Schamweber et al. 1974
85	Rat (Fischer- 344)	12 mo 5 d/wk 6 hr/d		997			CIIT 1981
86	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d		997			CIIT 1981
87	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
88	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		1473			Mitchell et al. 1979
89	Mouse (CD-1)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
90	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		1473			Mitchell et al. 1979
91	Dog (Beagle)	90 d 5 d/wk 6 hr/d		400 M			McKenna et al. 1981b
Reproductive							
92	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d		224		997 M (degeneration & atrophy of seminiferous tubules; sperm granulomas)	CIIT 1981

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
93	Rat (Fischer-344)	12 mo 5 d/wk 6 hr/d		224		997 M (degeneration & atrophy of seminiferous tubules; sperm granulomas)	CIIT 1981
94	Rat (Fischer-344)	20 wk 5-7 d/wk 6 hr/d		150	475M (decreased male fertility, litters per copulation plug)	1500 M (sterility, atrophy of the seminiferous tubules, epididymal granulomas)	Hamm et al. 1985
95	Rat (Fischer-344)	10 wk 5-7 d/wk 6 hr/d		150	475 (decreased F1 generation male fertility and number of litters in F1 females)		Hamm et al. 1985
96	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
97	Rat (Fischer-344)	90 d 5 d/wk 6 hr/d		1473			Mitchell et al. 1979
98	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d		997			CIIT 1981
99	Mouse (CD-1)	90 d 5 d/wk 6 hr/d		400			McKenna et al. 1981b
100	Dog (Beagle)	90 d 5 d/wk 6 hr/d		400 M			McKenna et al. 1981b
	Developmental						
101	Rat (Fischer-344)	20 wk 5-7 d/wk 6 hr/d		1502			Hamm et al. 1985

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
CHRONIC EXPOSURE							
Death							
102	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d				997 (increased mortality)	CIIT 1981
103	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d				997 (increased mortality)	CIIT 1981
Systemic							
104	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	997			
			Gastro	997			
			Hemato	997			
			Musc/skel	997			
			Hepatic	224 M 997 F	997M (increased relative liver weight)		
			Renal	997			
			Endocr	997			
			Bd Wt	224	997 (14-15% decreased body weight gain)		
105	Rat (Fischer- 344)	18 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	997			
			Gastro	997			
			Hemato	997			
			Musc/skel	997			
			Hepatic	997			
			Renal	997			
			Endocr	997			
			Bd Wt	224 M 997 F	997M (10% decreased body weight gain)		

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
106	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	224 F 997 M	997F (incr. rel. heart weight)		
			Hemato	997			
			Musc/skel	997			
			Hepatic	224	997F (incr. rel. liver weight)	997 M (incr. ALT, centrilobular degeneration, karyomegaly, cytomegaly)	
			Renal	224 M 997 F	997M (renal hyperplasia)		
			Endocr	997			
			Bd Wt	224	997 (12-19% decreased body weight)		
107	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d	Resp	997			CIIT 1981
			Cardio	51 F 997 M	224F (incr. rel. heart weight)		
			Hemato	997			
			Musc/skel	997			
			Hepatic	51 M 224 F	224M (increased ALT)	997 (necrosis, cytomegaly, karyomegaly, polykaryocytes)	
			Renal	224	997 (renal hyperplasia)		
			Endocr	997			
			Bd Wt	224	997 (15-19% decreased body weight)		
Immunological/Lymphoreticular							
108	Rat (Fischer-344)	24 mo 5 d/wk 6 hr/d		997			CIIT 1981

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
109	Rat (Fischer- 344)	18 mo 5 d/wk 6 hr/d		997					CIIT 1981
110	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d		224	997	(splenic lymphoid depletion)			CIIT 1981
111	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		224			997	(splenic atrophy and lymphoid depletion)	CIIT 1981
Neurological									
112	Rat (Fischer- 344)	18 mo 5 d/wk 6 hr/d		997					CIIT 1981
113	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		997					CIIT 1981
114	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d			51	(swelling and degeneration of axons in spinal cord)	997	(tremor, paralysis, hindlimb rigidity, cerebellar granular cell atrophy)	CIIT 1981
115	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d			51[d]	(axonal swelling and slight degeneration of axons in spinal cord)	997	(tremor, paralysis; mild reduction in number of cerebellar neurons in the granular cell layer)	CIIT 1981
Reproductive									
116	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		224 M			997 M	(degeneration and atrophy of seminiferous tubules; sperm granulomas)	CIIT 1981
117	Rat (Fischer- 344)	18 mo 5 d/wk 6 hr/d		224 M			997 M	(degeneration and atrophy of seminiferous tubules; sperm granulomas)	CIIT 1981

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
119	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d		224 M		997 M (testicular degeneration and atrophy)	CIIT 1981
118	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		224 M		997 M (testicular degeneration and atrophy)	CIIT 1981
Cancer							
120	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d				997 M (CEL: renal cortex adenomas and adenocarcinomas, papillary cystadenomas, and papillary cystadenocarcinomas)	CIIT 1981
121	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d				997 M (CEL: renal cortex adenoma)	CIIT 1981

Table 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
122	Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d				997 M (CEL: renal cortical adenoma)	CIIT 1981

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

[b]Used to derive an acute inhalation minimal risk level (MRL). No adjustment was made for continuous exposure and a human equivalent concentration was derived. Uncertainty factor of 100 (10 for intraspecies variability, 10 for interspecies variability) applied resulting in an MRL of 0.5 ppm.

[c]Used to derive an intermediate inhalation MRL. No adjustment was made for continuous exposure and a human equivalent concentration was derived. Uncertainty factor of 300 (3 for a minimal LOAEL to NOAEL, 10 for intraspecies variability, 10 for interspecies variability) applied resulting in an MRL of 0.2 ppm (rounded to one significant figure from 0.17 ppm).

[d]Used to derive a chronic inhalation MRL. No adjustment was made for continuous exposure and a human equivalent concentration was derived. Uncertainty factor of 1000 (10 for LOAEL to NOAEL, 10 for intraspecies variability, 10 for interspecies variability) applied resulting in an MRL of 0.05 ppm (rounded to one significant figure from 0.051 ppm).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr. = decreased; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); incr. = increased; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell; rel. = relative; Resp = respiratory; WBC = white blood cell; wk = week(s)

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

Acute (≤14 days)

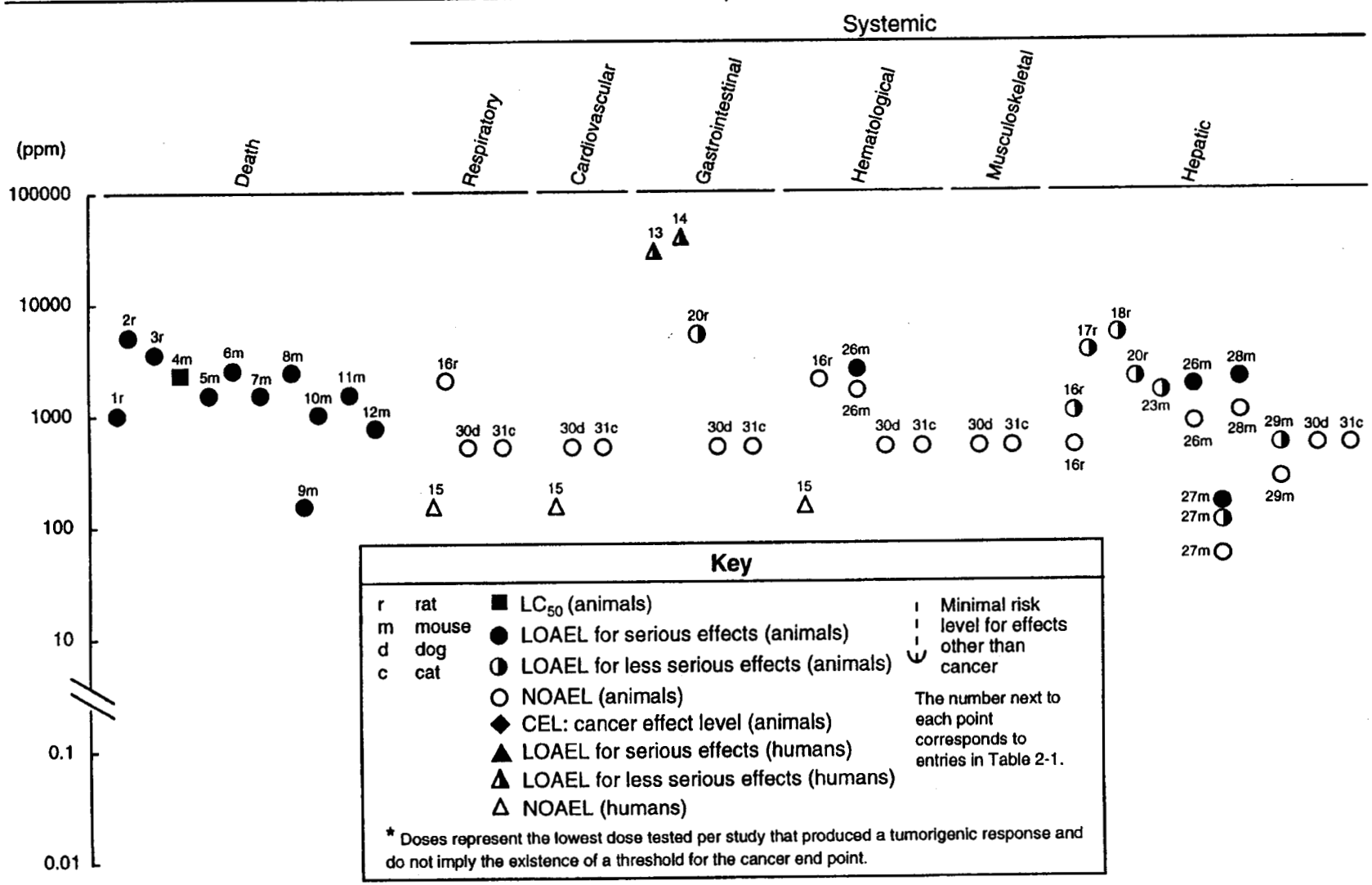


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Acute (≤14 days)

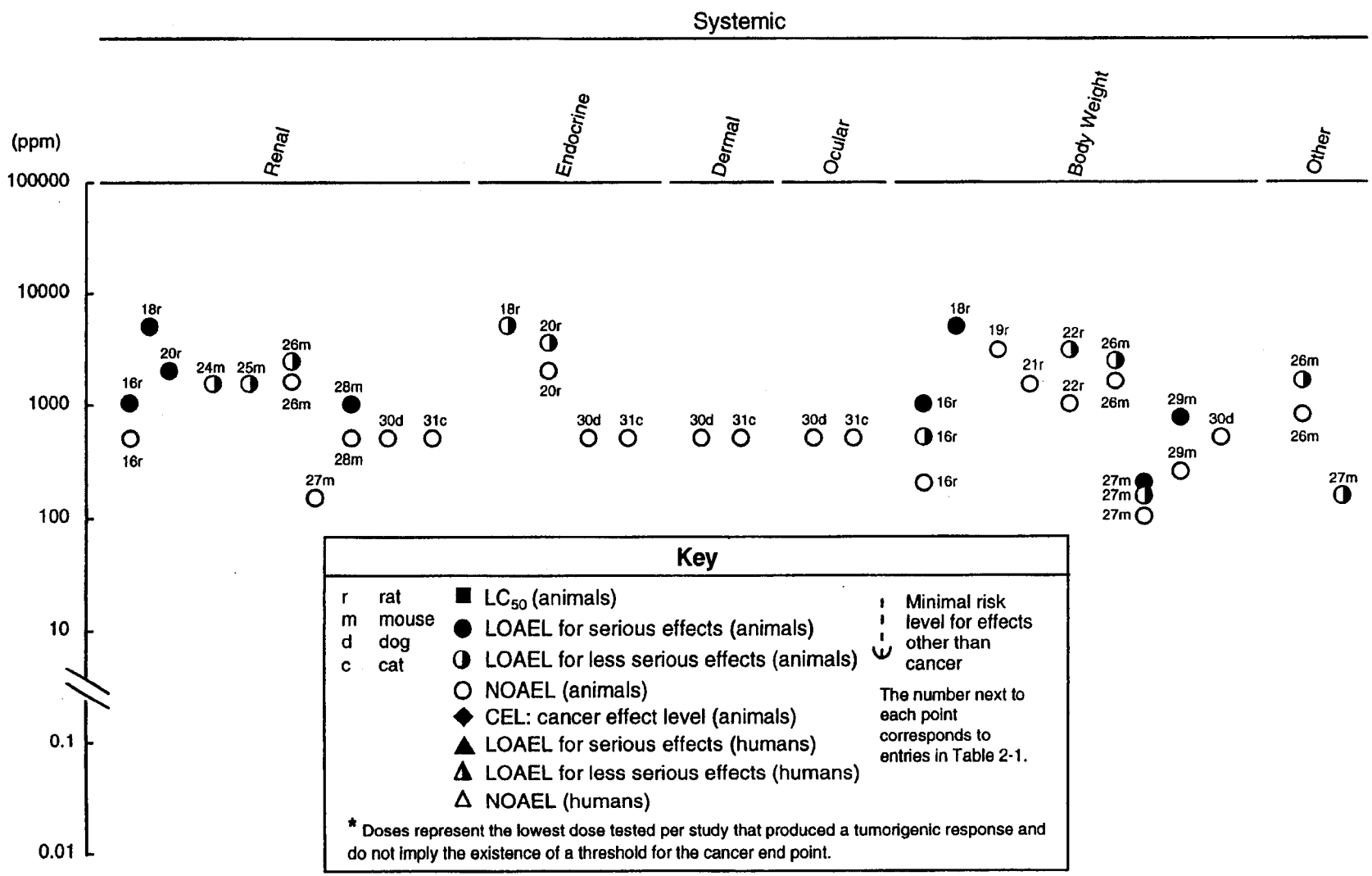


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Acute (≤14 days)

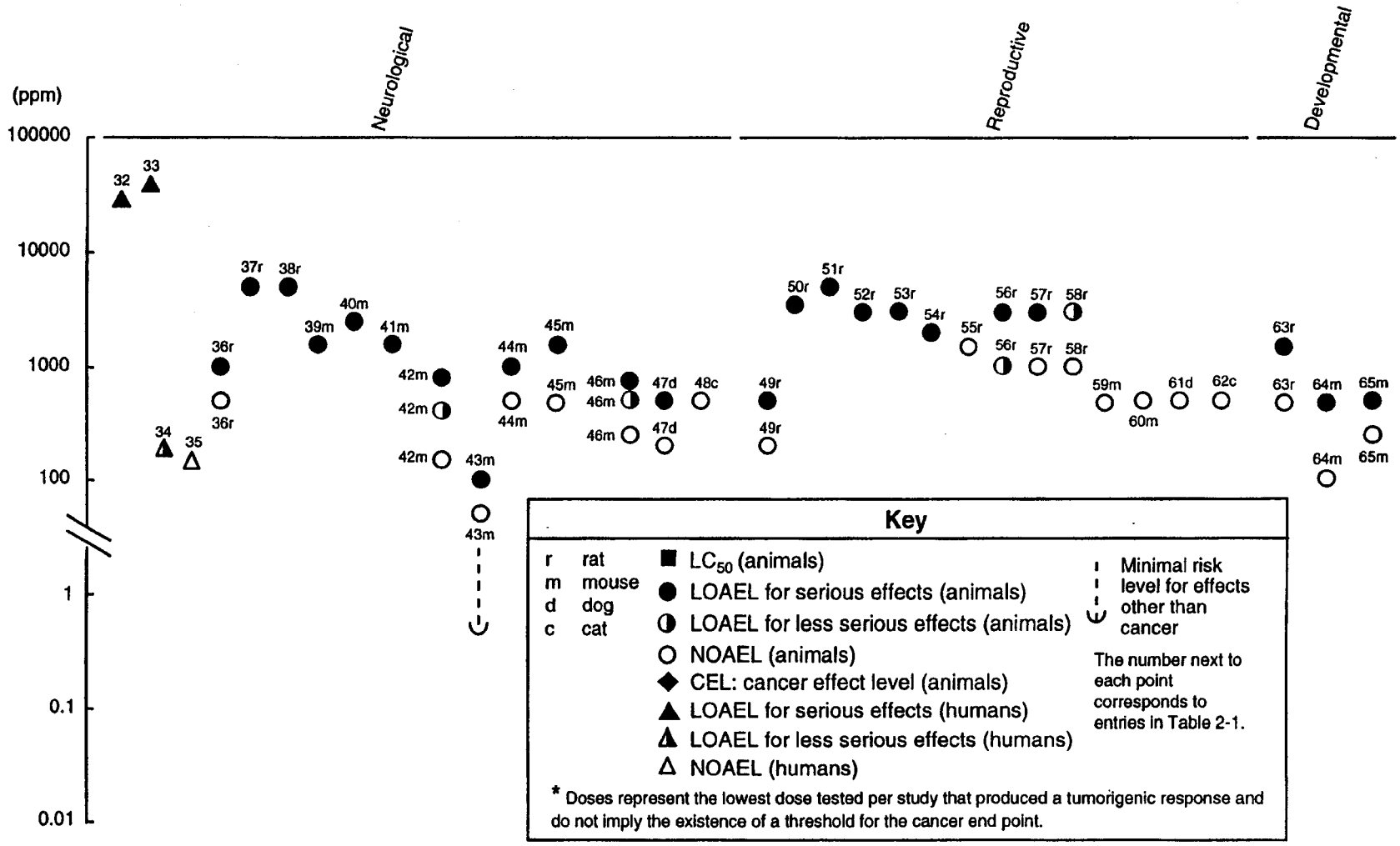


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Intermediate (15-364 days)

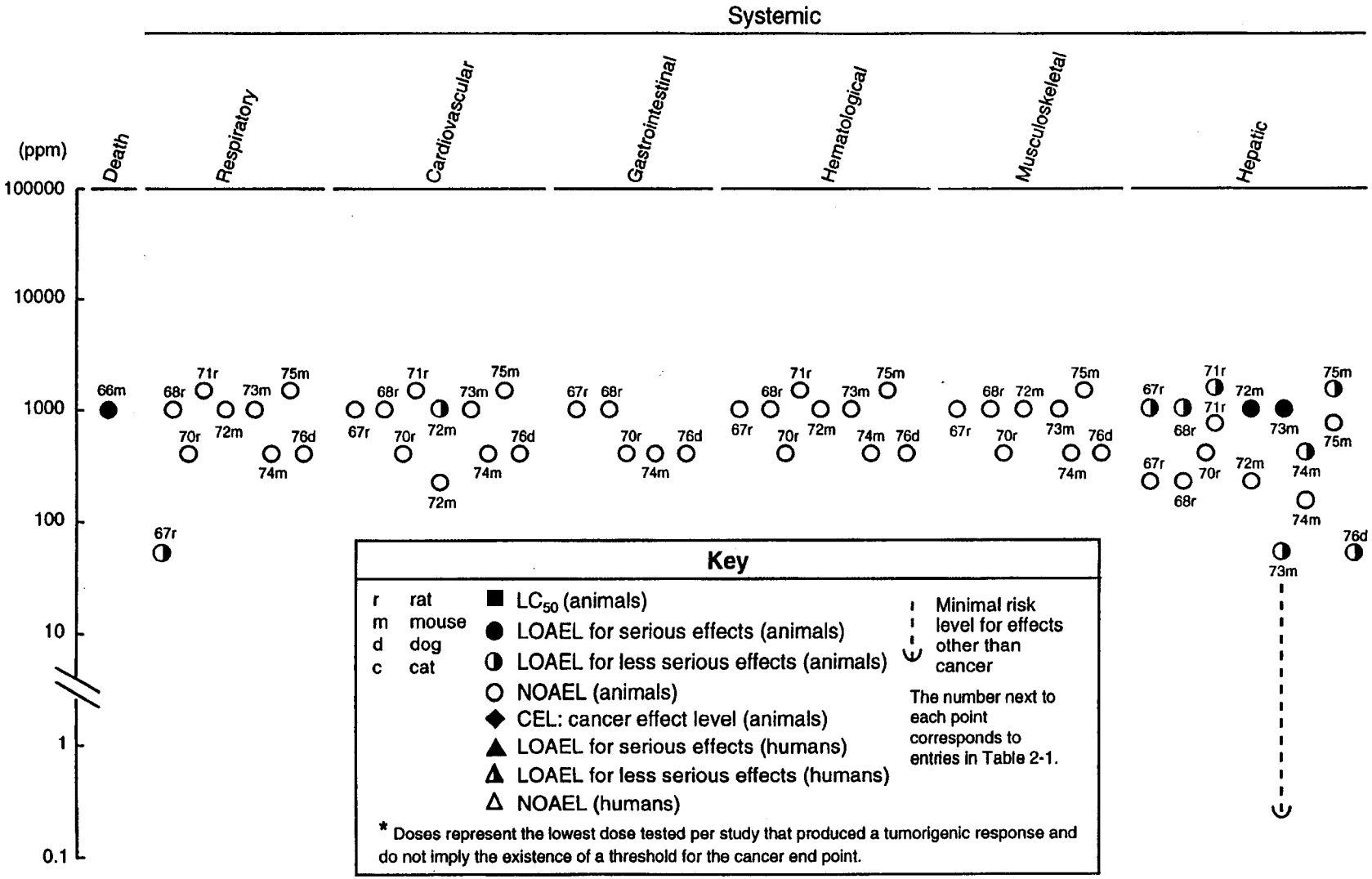


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Intermediate (15-364 days)

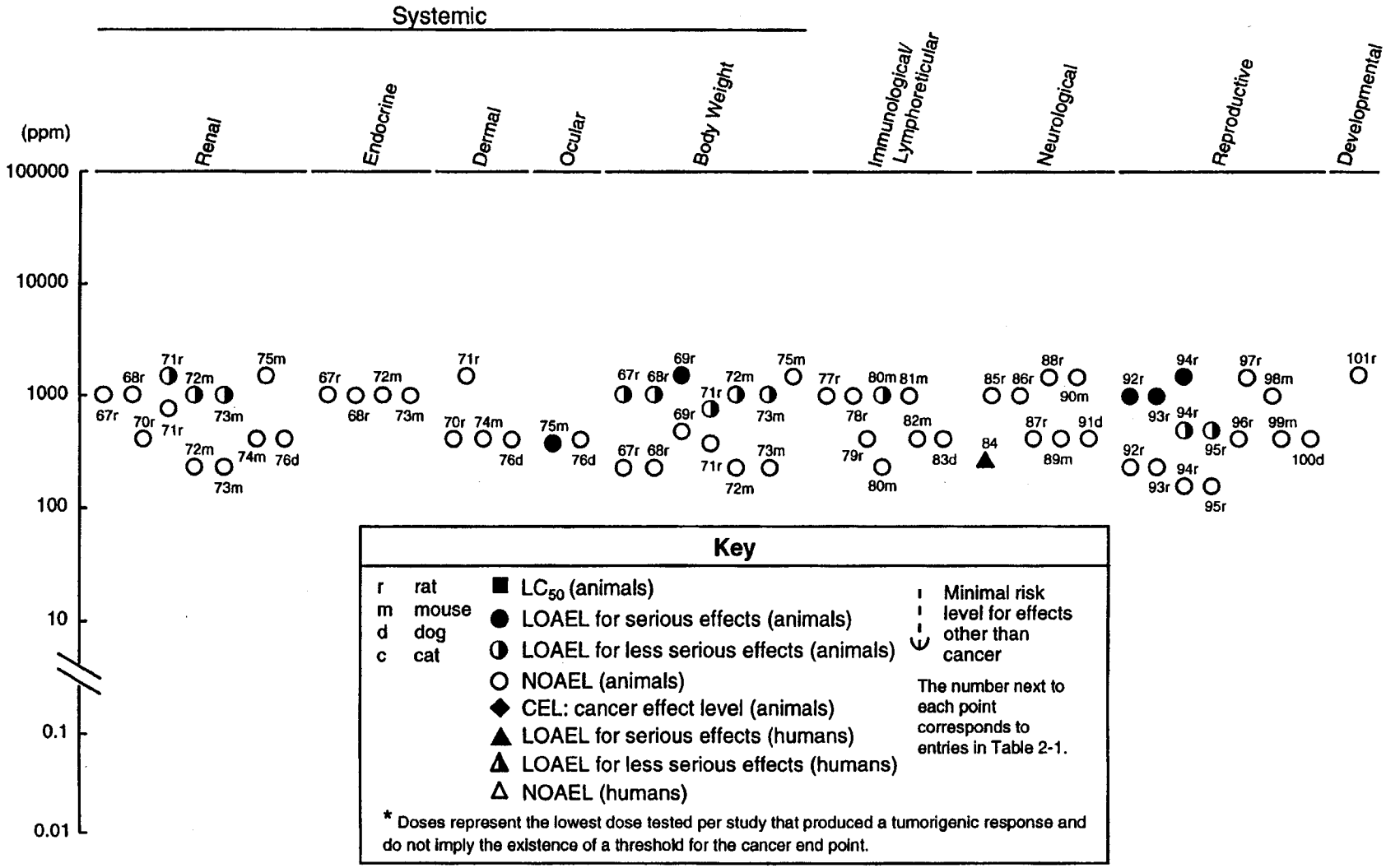


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Chronic (≥365 days)

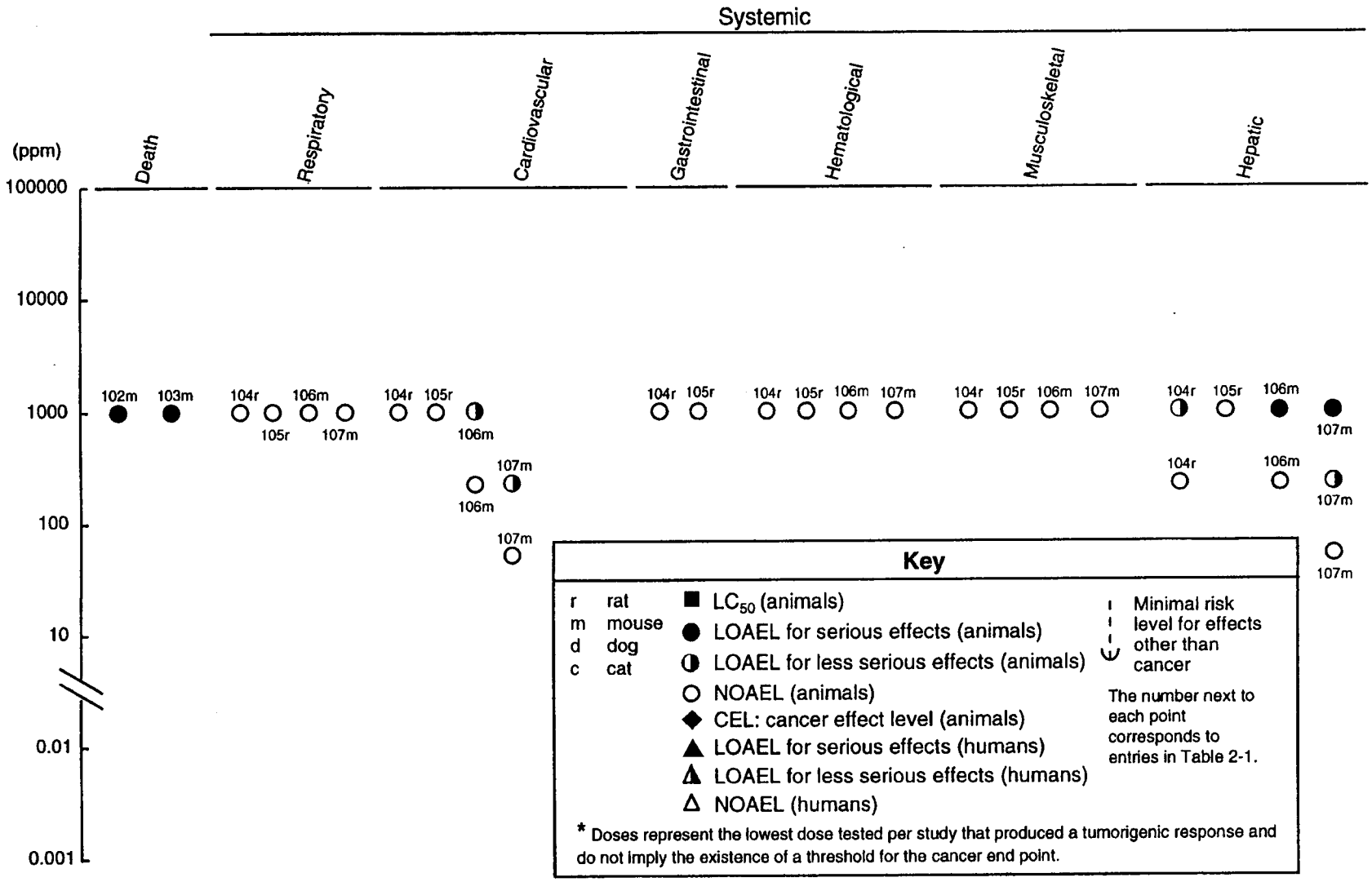
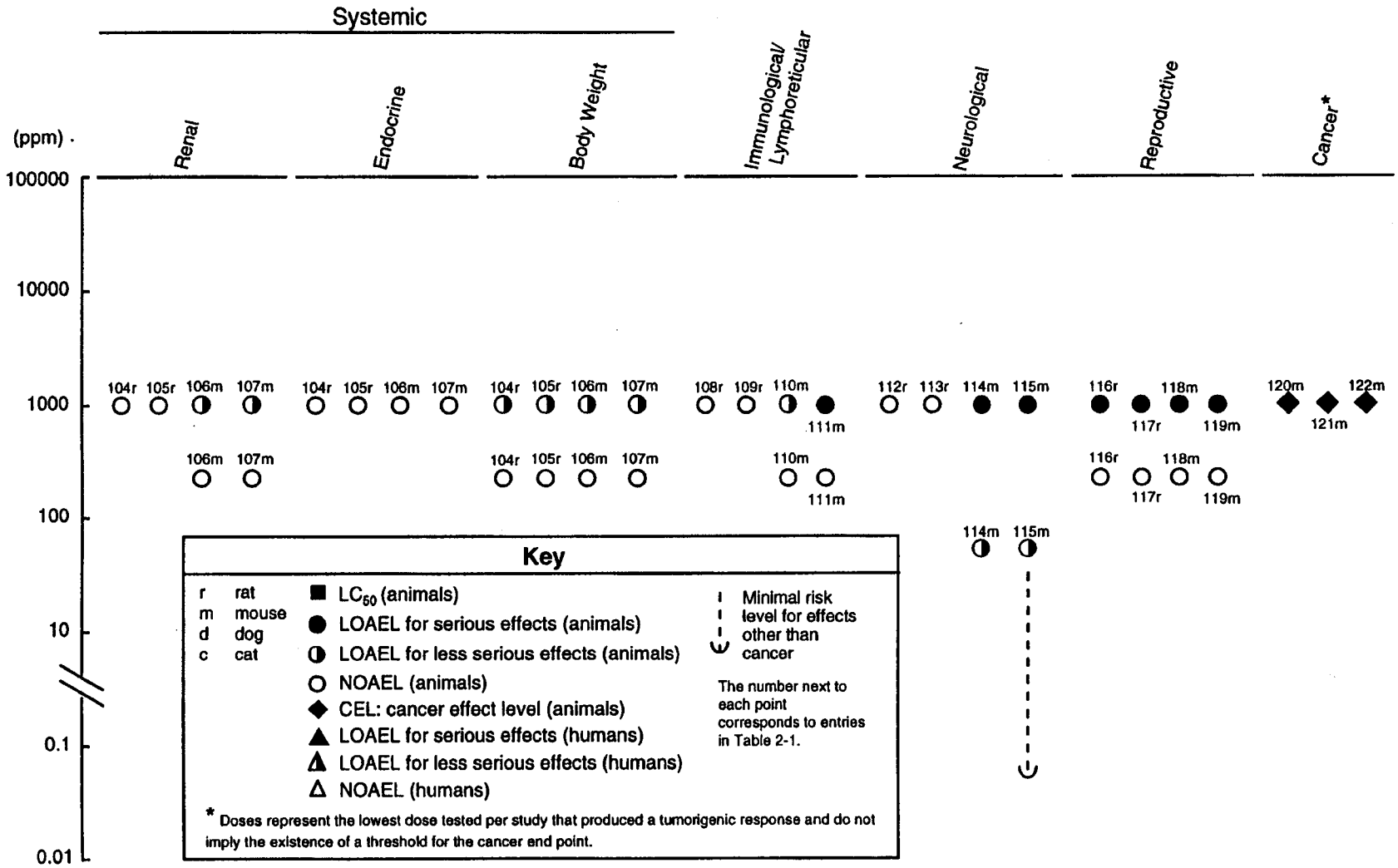


Figure 2-1. Levels of Significant Exposure to Chloromethane - Inhalation (cont.)

Chronic (≥365 days)



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. More recent studies using very pure chloromethane (99.5-99.9%) failed to find any exposure-related histopathological lesions in the lungs of dogs and cats exposed acutely to 500 ppm chloromethane (McKenna et al. 1981a), rats exposed acutely to 2,000 ppm (Burek et al. 1981), male dogs exposed to 400 ppm, and rats and mice exposed to up to 1,500 ppm chloromethane for intermediate durations (McKenna et al. 1981b; Mitchell et al. 1979).

Dodd et al. (1982) examined the effects of an inhalation exposure to chloromethane on tissue nonprotein sulfhydryl (NPSH) content in male Fischer 344 rats. Groups of four animals each were exposed to chloromethane at concentrations of 0, 100, 500, or 1,500 ppm for 6 hours. Additional groups of four were exposed to 500 ppm chloromethane for periods of 1, 2, or 4 hours. Other groups of four were pretreated with Aroclor-1254 (metabolic inducer) or SKF-525A (metabolic inhibitor) prior to exposure to 500 ppm chloromethane [duration not noted]. The animals were sacrificed at various time points (0-18 hours) after exposure, at which time blood, liver, lung, and one kidney were collected for subsequent NPSH determinations. NPSH content of liver, kidney, and lung were decreased in a concentration-related manner. At 1,500 ppm, NPSH levels were 30% of control values in lungs immediately following exposure. At 500 ppm, levels were 55% of control values. No differences in NPSH content of the organs were observed after exposure to 100 ppm chloromethane compared with control. Lung NPSH levels returned to control values within 18 hours of exposure. A duration-related decrease was observed when rats were exposed to 500 ppm chloromethane for 1, 2, 4, or 6 hours. Pretreatment with Aroclor 1254 (inducer of microsomal enzymes) did not alter the decreases in tissue NPSH seen after exposure to chloromethane alone. Pretreatment with SKF-525A (inhibitor of microsomal enzymes) may have interfered with the ability of chloromethane to decrease NPSH in some tissues. Treatment with chloromethane significantly increased the activity of glutathione-S-alkyltransferase, and pretreatment with Aroclor 1254 did not alter the increase. The toxicological significance of this effect is not clear.

Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day,

5 days/week. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure. At 6 months, relative lung weight was significantly increased at 50, 225, and 1,000 ppm in male rats and at 1,000 ppm in female rats. One male and 4 female rats at 1,000 ppm, 1 female at 225 ppm, and 2 males and 1 female at 50 ppm had minimal to moderate interstitial pneumonia with lymphocytic peribronchiolitis and perivasculitis. The interstitial lesions consisted of macrophage and lymphocytic infiltration. Also present were alveolar cell hyperplasia and mild alveolar luminal infiltrates consisting of large macrophages, lymphocytes, and in some areas, a few neutrophils. Five females at 1,000 ppm had areas of minimal subacute tracheitis (this lesion also occurred in 1 control male rat). At 12, 18, or 24 months, no chloromethane-related lung effects were observed. No effects on lungs were observed at any time point in mice. These respiratory effects were transitory, and the authors did not consider the effects to be associated with exposure to chloromethane (CIIT 1981).

Cardiovascular Effects. Cardiovascular effects of chloromethane have been described in case reports of humans exposed 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).

The long-term cardiotoxic effects from an acute exposure to chloromethane were also studied by Rafnsson and Gudmundsson (1997) who found an excess mortality rate from cardiovascular disease. Seventeen crew members (males) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (exposure levels were not reported). The refrigerator was located under the sleeping quarters of the crew. This study followed a cohort of 24 men on board the vessel (6 officers and 18 deckhands) at 32 years postexposure. The reference group was selected from three registries of seamen. The Icelandic registries for seamen are some of the most comprehensive and complete available. The reference group contained five times as many individuals as the study group, and was controlled for age, occupation, and social class. The authors assumed simultaneous control for lifestyle factors including smoking habits and diet. The authors report excess mortality from all causes of death associated with acute

exposure to chloromethane (Mantel-Haenszel point estimate=2.2, 95%; CI=1.3-3.1), and a clear excess mortality from cardiovascular disease (M-H=2.1, 95%; CI= 1.2-3.8). This excess was more prominent among the deckhands who had received the highest exposure to chloromethane from the leaking refrigerator. The Risk ratios were elevated for all causes of death (RR=2.5, 95%; CI=1.0-5.7) as well as for cardiovascular disease (RR=3.9, 95%; CI=1.0-14.4). The study is weakened by the assumption of a simultaneous control for lifestyle factors including smoking habits and diet, and by the relatively small numbers of individuals with significant exposure. The authors also do not discuss the potential influence of the documented neurological deficits in this cohort on cardiovascular function (Gudmundsson 1977), and no definite mechanism of action was found in the literature. The authors suggest, however, that additional study on chloromethane's potential cardiovascular toxicity is warranted (Rafnsson and Gudmundsson 1997).

Scharnweber et al. (1974) presented 6 case studies of workers who were exposed to relatively low levels (200-400 ppm) of chloromethane for at least 2-3 weeks before onset of symptoms. Two cases occurred after "prolonged" (not otherwise specified) exposure to 8 hour time-weighted average (TWA) levels up to 300 ppm. Four cases occurred after work exposure on the order of 265 ppm (g-hour TWA) after 2-3 weeks of 12-16 hour days. One of the workers having prolonged exposure to 8-hour TWA levels up to 300 ppm experienced moderate hypertension (160/120 mm Hg).

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 1,500 ppm chloromethane (McKenna et al. 1981b; Mitchell et al. 1979).

Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure. No cardiovascular effects were observed in male or female rats at any time point. No cardiovascular effects were observed in male mice. At 12 and 18 months, 1000 ppm female mice had increased relative heart

weight, and at 24 months, 225 ppm female mice had increased relative heart weight. These effects were considered to be chloromethane-related, but no associated histopathological lesions were observed (CIIT 1981).

Gastrointestinal Effects. Numerous case reports of humans exposed to chloromethane 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; 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; Jones 1942) provided exposure concentration data.

Morgan et al. (1982) investigated the lesions induced by an inhalation exposure to chloromethane in C3H, C57BL/6, and B6C3F$_1$ mice and in Fischer 344 rats. Ten rats per sex were exposed to chloromethane for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure. Rats were exposed to 0, 2,000, 3,500, or 5,000 ppm. Five mice per sex were exposed to chloromethane for 12 days, 6 hours/day. Mice were exposed to 0, 500, 1,000, or 2,000 ppm. Animals were sacrificed 18 hours after the last exposure or immediately after exposure if found to be moribund. Within 2 days of treatment, male and female rats in the 5,000 ppm group developed foul-smelling diarrhea. Gastrointestinal effects were not observed in mice.

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, 1981b).

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.

No long-term effect on the hematological system from an acute exposure was reported by Gudmundsson (1977). Seventeen crew members (males) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (no estimates of exposure levels were reported).

The refrigerator was located under the sleeping quarters of the crew. Thirteen years later (i.e., in 1976) 10 of the 11 survivors were examined (one lived in a foreign country and could not be located). All 10 were employed; 8 were employed at sea. The mean age of the 10 patients examined was 38.3 years (range 30-50 years). All 10 patients had normal hemoglobin, white cell count, differential leukocyte count, erythrocyte sedimentation rate, and serum creatinine.

Spleen enlargement, suggestive of extramedullary hematopoiesis, and hemoglobinuria, suggestive of intravascular hemolysis, were found in mice exposed intermittently to a high concentration (2,400 ppm) of chloromethane for 11 days (Landry et al. 1985). These effects were not seen when 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 2,000 ppm (Burek et al. 1981). In addition, male dogs exposed to 400 ppm, rats and mice exposed to 1,500 ppm for 90 days (McKenna et al. 198 lb; Mitchell et al. 1979), and rats and mice exposed for 6, 12, 18, or 24 months to up to 1,000 ppm (CIIT 1981) did not have hematological effects.

Musculoskeletal Effects. Case reports generally have not described muscular or skeletal effects in humans exposed to chloromethane.

No adverse muscular or skeletal effects related to chloromethane exposure were observed in dogs and cats exposed acutely to 500 ppm chloromethane (McKenna et al. 1981 a), male dogs exposed to 400 ppm, and rats and mice exposed to 21,500 ppm chloromethane for intermediate durations (McKenna et al. 1981 b; Mitchell et al. 1979) or rats and mice exposed to up to 1,00 ppm chloromethane for chronic durations (CIIT 1981).

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 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 1,000-1,500 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 serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bilirubin (Burek et al. 1981; CIIT 1981; Mitchell et al. 1979; Morgan et al. 1982). No necrosis was seen. Acute, intermediate, or chronic exposure of mice to 1,000-1,500 ppm generally resulted in necrosis and degeneration (CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan et al. 1982). Although no significant liver effects were observed in male dogs and cats (McKenna et al. 1981 a, 1981 b), the exposure concentrations (400 or 500 ppm) may not have been high enough to produce liver toxicity in these species.

Chapin et al. (1984) investigated the cellular targets and the mechanism of reproductive tract lesions induced by inhaled chloromethane in male Fischer 344 rats. The animals were exposed to 3500 ppm chloromethane or air (controls) for 5 days, 6 hours/day, were subsequently not exposed for 3 days, and then exposed again for 4 days. Rats were killed on days 5, 7, 9, 11, 13, 15, 19, and 70 after starting exposure. To test for the effects of lower feed consumption in exposed rats, four weight-matched naive animals for each time interval were pair-fed identical amounts of feed to that consumed by the exposed animals and killed in the same manner. Tissue non-protein sulfhydryl (NPSH) content was measured in testes, caput and caudal epididymides, liver and heart blood. Liver NPSH content was significantly depleted within 1 hour of exposure (1.33 versus 5.44 μmol/g tissue; $p<0.05$).

Chellman et al. (1986a) studied the effects of 3-amino-l-[m-(trifluoromethyl)phenyl]-2-pyrazoline (BW755C), a potent anti-inflammatory agent, on chloromethane-induced lethality and reproductive toxicity in male Fischer 344 rats. Rats were exposed to 5,000 ppm chloromethane for 5 days, 6 hours/day, with or without treatment with BW755C (10 mg/kg, intraperitoneally 1 hour pre- and postexposure). Rats exposed to 5,000 ppm chloromethane, 6 hours/day for 5 days exhibited cloudy swelling of hepatocytes in the liver with subsequent obliteration of the sinusoids. Rats exposed to both chloromethane and BW755C had only very subtle, if any, lesions. The results are surprising because the liver lesions were not inflammatory in nature. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution or excretion of ^{14}C-chloromethane and administration of BW755C did not decrease hepatic glutathione content. The protection afforded by BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis.

Dodd et al. (1982) examined the effects of an inhalation exposure to chloromethane on tissue nonprotein sulfhydryl (NPSH) content in male Fischer 344 rats. Groups of four animals each were exposed to chloromethane at concentrations of 0, 100, 500, or 1,500 ppm for 6 hours. Additional groups of four were exposed to 500 ppm chloromethane for periods of 1, 2, or 4 hours. Other groups of four were pretreated with Aroclor-1254 (metabolic inducer) or SKF-525A (metabolic inhibitor) prior to exposure to 500 ppm chloromethane (duration not noted). The animals were sacrificed at various time points (0 to 18 hours) after exposure, at which time blood, liver, lung, and one kidney were collected for subsequent NPSH determinations. NPSH content of liver was decreased in a concentration-related manner. At 1,500 ppm, NPSH levels were 17% of control values immediately following exposure. At 500 ppm, NPSH levels were 41% of control values. No differences in NPSH content were observed after exposure to 100 ppm chloromethane compared with control. Liver NPSH levels returned to control values within 8 hours of treatment. Pretreatment with Aroclor 1254 (inducer of microsomal enzymes) did not alter the decreases in liver NPSH seen after exposure to chloromethane alone. Pretreatment with SKF-525A (inhibitor of microsomal enzymes) may have interfered with the ability of chloromethane to decrease NPSH in some tissues. Treatment with chloromethane significantly increased the activity of glutathione-S-alkyltransferase, and pretreatment with Aroclor 1254 did not alter the increase. The toxicological significance of this effect is not clear.

Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver, kidney and brain of male $B6C3F_1$ mice. Animals were exposed for 6 hours to 1,500 ppm chloromethane, with and without pretreatment with buthionine-S,R-sulfoximine (BSO), diethyl maleate (DEM), or fasting to deplete glutathione (GSH). The mice were sacrificed 18 hours after completion of exposures, blood samples were collected, and the serum was analyzed for alanine aminotransferase (ALT) to measure liver toxicity. There was a 50-fold increase in ALT activity in exposed mice without pretreatment. Fasting or pretreatment with BSO or DEM resulted in ALT values which were similar to those of controls. Therefore, depletion of GSH protected mice from hepatic toxicity of chloromethane.

Jager et al. (1988) investigated the effects of an inhalation chloromethane exposure on tissue levels of glutathione-S-transferase (GST) and formaldehyde dehydrogenase (FDH) in male and female Fischer 344 rats and $B6C3F_1$ mice. Activities of GST were 2-3 times higher in livers of male $B6C3F_1$ mice, compared with those of female mice, and with rats of both sexes. In kidneys, GST activities of male mice were about 7 times lower than those found in the liver. The activity of FDH was higher in mouse liver (both sexes)

than in rat liver. More formaldehyde was produced in the liver of male, as compared to those of female mice. After a single, g-hour exposure to 1,000 ppm chloromethane in males or female mice, formaldehyde levels were not observed to increase in livers or kidneys (ex vivo). Lipid peroxidation was significantly and markedly increased in the liver of male and female mice, and to a lesser extent in the kidney, from the single exposure to chloromethane.

Landry et al. (1985) observed mild hepatic effects in mice intermittently exposed to 400 to 2,400 ppm (glycogen depletion, no hepatic degeneration or necrosis). Only the 1,600 ppm mice had significantly increased liver absolute (22%) and relative (23%) weight. Mice continuously exposed to 400 ppm died or were sacrificed by day 4, and by day 5 for a 200 ppm group, due to severe toxicity. Mice continuously exposed to 150 ppm were sacrificed in moribund condition by day 10.5. Decreased food consumption was indicated by diminished amount of feces and scratched food under the cages of the 150 or 200 ppm groups. The 150 ppm exposure resulted in a significant decrease in absolute liver weight (13%), but not relative weight. Mice had a decreased hepatocyte size (due to glycogen depletion) at 100 ppm with focal necrosis at 150 ppm and greater.

Morgan et al. (1982) investigated the lesions induced by an inhalation exposure to chloromethane in C3H, C57BL/6, and B6C3F$_1$ mice and in Fischer 344 rats. Ten rats per sex were exposed to chloromethane for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure. Rats were exposed to 0, 2,000, 3,500, or 5,000 ppm. Animals were sacrificed 18 hours after the last exposure or immediately after exposure if found to be moribund. All exposed groups except 2,000 ppm males had high incidences (8/10 to 10/10) of minimal hepatocellular lesions, consisting of loss of normal area of cytoplasmic basophilia. Five mice per sex were exposed to chloromethane for 12 days, 6 hours/day at levels of 0, 500, 1,000, or 2,000 ppm. Animals were sacrificed 18 hours after the last exposure or immediately after exposure if found to be moribund. Hepatocellular degeneration consisting of necrosis, hyaline accumulation in bile ducts, vacuolization, and glycogen depletion was observed. The lesions resembled those usually described for carbon tetrachloride and chloroform. Necrosis was confined to male C57BL/6 and B6C3F$_1$ mice exposed to 2,000 ppm. The other lesions occurred to varying degrees in other groups and were of minimal severity. No liver lesions were observed in controls.

Wolkowski-Tyl et al. (1983b) assessed the reproductive and developmental effects of an inhalation exposure to chloromethane in C57BL/6 females mated to C3H males to produce B6C3F$_1$ offspring. After mating, 74-77 females were exposed to chloromethane at concentrations of 0, 250, 500, or 750 ppm on

Gd 6-17. Surviving dams were weighed and sacrificed on gestation day 18. A significant increase in maternal absolute liver weight (9%) and relative liver weight (6%) was observed in the 500 ppm mice. A nonsignificant decrease was observed in the 750 ppm dams.

Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week (CIIT 1981). Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure. Increased ALT associated with exposure-related liver lesions was seen in male mice exposed to 1,000 ppm chloromethane at all time points. The lesions were centrilobular and characterized by mild to moderate hepatocellular degeneration often associated with vacuolization of most of the cytoplasm, individual hepatocellular necrosis, cytomegaly and karyomegaly, and numerous hepatocytes containing eosinophilic, intranuclear inclusion material. Increased ALT was also seen in 50 and 225 ppm males but no histopatholgical changes to the liver were observed at these exposure levels. Increased ALT in female mice exposed to 50, 225, and 1,000 ppm at 6 and 12 months was observed, but no histopathological changes were observed in females at any of the dose levels. ALT levels returned to normal at 18 and 24 months in female mice. Females that became moribund or that were exposed to 1,000 ppm for the longer 18- and 24-month exposure periods had liver lesions similar to those found in the males, but with less frequency and severity. Statistically significant increases in relative liver weight were observed in both male and female mice at 1,000 ppm. Male and female rats did not have the histopathological liver lesions seen in mice. Male rats did generally have increased relative liver weights at 1,000 ppm. No effect on ALT levels was observed in rats.

McKenna et al. (1981b) exposed CD-l mice to 99.9% pure chloromethane. Complete histological examination performed on the control and 400 ppm groups. In the liver, there was a significant increase in relative liver weight in 400 ppm females and a trend in 400 ppm males and 150 ppm males and females. The increase was accompanied by equivocal lesions (change in tinctorial properties of liver cells, possibly due to decrease vacuolization). The lesions were subtle and reversible and not considered adverse. McKenna et al. (1981b) also exposed Beagle dogs to 99.9% pure chloromethane. There were no effects on ALT or AST, but hepatocytes were swollen in 2 of 4 dogs at 400 ppm, 1 of 4 dogs at 150 ppm, 2 of 4 dogs at 50 ppm, and 0 of 4 controls. No other liver effects were observed, and the toxicological significance of these effects are unclear.

The lowest concentration for dose-related hepatic effects is the LOAEL of 51 ppm for increased ALT in male mice (CIIT 1981). This LOAEL is used as the basis for an intermediate inhalation MRL of 0.2 ppm, calculated as described in the footnote to Table 2-1 and in Appendix A. This MRL is presented 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 occurred are not known.

Sprague-Dawley rats exposed to chloromethane at 1,000 ppm for 72 hours had slightly increased blood urea nitrogen (BUN), but this effect only occurred significantly in females. Abnormal urinalysis parameters indicative of renal failure occurred in both sexes of rats exposed to 1,000 or 2,000 ppm for 48 or 72 hours. Histological examination revealed renal tubular cell necrosis, increased lipid accumulation in tubule cells at 1,000 ppm for both exposure periods, and evidence of regeneration after the recovery period. Greatly increased (statistically significant) BUN in 2,000 ppm male and female rats sacrificed at 48 hours indicated kidney failure (Burek et al. 1981).

Chellman et al. (1986a) exposed male Fischer 344 rats to 5,000 ppm chloromethane for 5 days, 6 hours/day resulting in necrosis of the proximal convoluted tubules. Dodd et al. (1982) exposed male Fischer 344 rats to chloromethane at 0, 100, 500, or 1,500 ppm for 6 hours. Nonprotein sulfhydryl (NPSH) content of kidney was decreased in a concentration-related manner. Kidney NPSH levels returned to control values within 8 hours of treatment. The toxicological significance of this effect is not clear.

Morgan et al. (1982) investigated the lesions induced by an inhalation exposure to chloromethane in C3H, C57BL/6, and B6C3F$_1$ mice and in Fischer 344 rats. Rats were exposed to 0, 2,000, 3,500, or 5,000 ppm for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure. Mice were exposed to 0, 500, 1,000, or 2,000 ppm for 12 days, 6 hours/day. Two types of kidney lesions were seen, basophilia of renal tubules and degeneration and necrosis of renal proximal convoluted tubules. The degeneration was found mainly in the 2,000 ppm groups in both males and females of all strains. The basophilia, presumed to be regeneration, was found mainly in the 1,000 ppm group. Hematuria occurred in mice exposed to 1,000 and 2,000 ppm, but it was not clear whether it was due to renal damage or lesions elsewhere in the urogenital tract. In the rat kidneys, there was a dose-related increased incidence and

severity of degeneration of proximal tubules. No basophilia in renal tubules occurred in rats as was seen in mice. The authors speculated that the basophilia in mice is a proliferative response related to the induction of kidney tumors seen in mice and not rats.

Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the liver, kidney and brain of male $B6C3F_1$ mice. Mice exposed to 1,500 ppm chloromethane 6 hours/day, 5 days/week for 2 weeks had no significant changes in kidney weight, glomerular filtration rate, urinary excretion of glucose and protein, or urinary concentrating ability. Histologically, the only effect of chloromethane exposure was a slight increase in the number of basophilic cortical tubules. Incorporation of tritiated thymidine into deoxyribonucleic acid (DNA) was 3-fold greater in kidneys of chloromethane exposed male mice than controls. Incorporation of tritiated thymidine was not significantly elevated in mice exposed and pretreated with BSO. BSO alone had no effect on DNA synthesis. In female mice, incorporation of tritiated thymidine into DNA was S-fold greater in kidneys of chloromethaneexposed versus controls. Therefore, depletion of GSH protected mice from increased DNA synthesis induced by chloromethane. The increased DNA synthesis may result from a compensatory proliferation in response to cell death. Although cell death was not observed in kidneys histologically, basophilic foci are consistent with regenerative cellular response following cell death.

Jager et al. (1988) investigated the effects of a chloromethane inhalation exposure on tissue levels of glutathione-S-transferase (GST) and formaldehyde dehydrogenase (FDH) in male and female Fischer 344 rats and $B6C3F_1$ mice. Activities of GST in kidneys of male mice were about 7 times lower than those found in the liver. About 50% more formaldehyde was produced in the male mouse kidney, compared to the female kidney (indicative of higher levels of P-450 in the male kidney). No DNA-protein crosslinks in the kidney and only some evidence of single-strand breaks was observed in male $B6C3F_1$ mice exposed to 1,000 ppm chloromethane for 4 days, 6 hours/day. After a single, 8 hour exposure to 1,000 ppm chloromethane in male or female mice, formaldehyde levels were not observed to increase in livers or kidneys (ex vivo). Lipid peroxidation was significantly and markedly increased in the liver of male and female mice, and to a lesser extent in the kidney, from the single exposure to chloromethane.

Female C57BL/6 mice exposed to 1,500 ppm chloromethane for 2 weeks, 5 days/week, 6 hours/day showed a slight degeneration of proximal convoluted tubules and proteinaceous material in tubular lumen. The renal and brain lesions in the study were unrelated in terms of severity; therefore, the authors

concluded that the brain lesions seen after exposure to chloromethane were probably not a direct consequence of renal lesions (Jiang et al. 1985).

Landry et al. (1985) evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice. Mice were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. Kidney effects were only observed in the intermittently exposed mice at 2,400 ppm. The effects consisted of a slight multifocal degeneration and regeneration of tubules, and an eosinophilic staining cast within the tubules. The 2,400 ppm mice had a nonsignificant increase in relative kidney weight. No histopathological lesions were observed in the kidney, thus the increased weight does not appear to represent an adverse effect.

Beagle dogs and cats exposed to 200 or 500 ppm chloromethane for 23.5 hours/days for 3 days had no significant differences in clinical chemistry or urinalysis parameters. A comprehensive histological examination revealed no exposure-related lesions in any system other than neurological. This was a good comprehensive study, but is limited by the number of animals (3) per group (McKenna et al. 1981a). Beagle dogs were also exposed to 0, 50, 150, and 400 ppm for 6 hours/day, 5 days/week for 90 days. There were no exposure-related gross or histopathological lesions in the kidneys and no effect on BUN (McKenna et al. 1981b). This was a comprehensive study, but is limited by the number of animals (4) per group.

Sprague-Dawley rats were exposed to 0, 50, 150, or 400 ppm chloromethane 6 hours/day, 5 days/week, for 90 days. There was no effect on BUN, but urinary specific gravity was decreased in males at 400 ppm and females at 150 ppm. This decrease was not associated with gross histologic pathology, and therefore, the toxicological significance of this effect is unclear. CD-l mice were exposed to the same regimen with no apparent effects on the kidneys (McKenna et al. 1981b).

Fischer 344 rats exposed to 0, 375, 750, and 1,500 ppm for 6 hours/day, 5 days/week, for 13 weeks developed a significant increase in relative left kidney weight for the 1,500 ppm males. There were no clinically significant hematological, clinical chemistry, or urinalysis abnormalities so the significance of this effect is unclear (Mitchell et al. 1979).

B6C3F$_1$ mice were exposed to 0, 375, 7.50, and 1,500 ppm for 6 hours/day, 5 days/week, for 13 weeks. No exposure-related histopathological lesions of the kidneys, and no clinically significant effects on hematological and urinalysis indices were observed. Relative kidney weight was increased in 1,500 ppm males, but no histopathological lesions were associated with the increase (Mitchell et al. 1979).

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure. Increased relative kidney weights were noted in female mice at 1,000 ppm, while decreased absolute kidney weights were seen in males at 1,000 ppm; there was no apparent reason for the sex difference. The authors interpreted the decrease in absolute kidney weight in male mice as biologically significant. Males exposed to 1,000 ppm developed renal tubuloepithelial hyperplasia and karyomegaly that became progressively worse, followed by the development of renal adenomas and adenocarcinomas. Females did not develop these lesions until after 18 months and to a much lesser extent. Male and female rats had varying levels of increased relative kidney weights throughout the study, but these were not associated with clinical, gross, or histopathological findings; thus, the toxicological significance of these effects is unclear (CIIT 1981).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to chloromethane.

Some effects have been observed in high-level, acute exposure animal studies. Male Fischer 344 rats exposed to 5,000 ppm chloromethane for 5 days, 6 hours/day developed vacuolar degeneration in the cell cytoplasm of the adrenal cortex in the outer region of the zona fasciculata (Chellman et al. 1986a). Fatty droplets were seen in the epithelial cells of the zona fasciculata in the adrenals of Fischer 344 rats exposed to 3,500 and 5,000 ppm chloromethane for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure; the severity of this lesion increased with dose (Morgan et al. 1982).

Results are generally negative with lower level or longer duration exposures. No chloromethane-related effects on the endocrine organs were observed from acute exposures up to 500 ppm in Beagle dogs or cats (McKenna et al. 198 la), or from intermediate and chronic exposures up to 1,000 ppm in mice or rats (CIIT 1981).

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to chloromethane.

No dermal effects were observed from acute chloromethane exposures up to 500 ppm in Beagle dogs or cats (McKenna et al. 1981a), or from intermediate exposures up to 400 ppm in Sprague-Dawley rats or CD-l mice (McKenna et al. 1981b), up to 1,500 ppm in Fischer 344 rats.(Mitchell et al. 1979), or up to 400 ppm in Beagle dogs (McKenna et al. 1981b).

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 Beagle dogs exposed to 500 ppm continuously for 3 days (McKenna et al. 1981a), dogs exposed to 400 ppm for 90 days (McKenna et al. 1981b), or of rats and mice exposed to 1,000 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 6 hours/day, 5 days/week, 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.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to chloromethane.

A 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). Landry et al. (1985) evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice. Groups of 12 mice each were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. The 400 ppm exposed mice died or were sacrificed by day 4, and

the 200 ppm group by day 5, due to severe toxicity. Mice exposed to 150 ppm were sacrificed in moribund condition by day 10.5. Continuous exposure to chloromethane resulted in significantly decreased body weight in the 200 ppm group (33%) by day 4 compared to the controls, and in the 150 ppm group by day 4 (16%) persisting to the sacrifice at day 10.5 (12%). A nonsignificant decrease was seen in the 100 ppm group and no effects on body weight were seen at 50 ppm.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to chloromethane.

The only other systemic effect reported in animal studies was a decrease in food consumption in the Landry et al. (1985) study. This study evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice exposed to chloromethane in whole body inhalation chambers for 11 days either continuously (C) for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently (I) for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. There was a significant degree of inanition in the 200-C and 400-C ppm mice prior to necropsy with decreased carcass size, amount of abdominal fat, amount of ingesta in the gastrointestinal tract, and small, pale livers.

2.2.1.3 Immunological and Lymphoreticular Effects

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

In animals, lymphoid depletion of the spleen and splenic atrophy were observed in mice exposed to 1,000 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 the most reliable 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 immunologically-related 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.

Landry et al. (1985) exposed female C57BL/6 mice to chloromethane for 11 days either continuously for 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently for 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2400 ppm. The absolute and relative weight of the thymus was significantly decreased at the 1,600 ppm (40% and 39%, respectively) and 2,400 ppm intermittent exposures (89% and 87%, respectively). There was no exposure-related histopathology in the thymus, but the decreased relative thymus weight is generally considered to be evidence of possible immunotoxicity. There was decreased absolute and relative thymus weight at 15 (23% and 22%, respectively), 50 (21% and 21%), 150 ppm (71% and 69%) continuous exposures, but not at 100 ppm. The decrease at 150 ppm was considered to be exposure-related, but the decreases at 15 and 50 ppm were not because they were within normal historical range.

In contrast to the results of the Landry et al. (1985) study, exposure to chloromethane at levels up to 400 ppm for 6 hours/day, 5 days/week for 90 days resulted in no observed exposure-related adverse effects to the organs and tissues of the immune system of Sprague-Dawley rats, CD-1 mice, or male Beagle dogs (McKenna et al. 1981b). Thus, the potential for chloromethane-induced immunotoxicity remains unresolved.

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; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). 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. In some cases, complete recovery eventually occurs. In other cases of more severe poisoning, convulsion, coma, and death may ensue; or neurological effects may persist. Microscopic examination of the brain of an individual who died following chloromethane exposure 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).

Battigelli and Perini (1955) report two cases of workers in a cooling plant who were exposed to a leak of chloromethane while repairing refrigeration system with an estimated exposure of >29,000 ppm. Both workers developed symptoms of vertigo, tremors, dulled senses, nausea, vomiting, and abdominal pain. The symptoms appeared 3-4 hours after the inhalation exposure. Disturbances began to recede about 6 hours postexposure and disappeared completely by 1 day postexposure.

A case was reported by Lanham (1982) of a man and wife who developed symptoms of blurred vision, fatigue, vertigo, tremor, and abnormal gait several days after storing insulating boards made of Styrofoam in the basement of their house. Air levels of chloromethane measured by 3 different devices were above 200 ppm.

Seven men had acute exposures to chloromethane while repairing refrigeration systems. Four of the cases provided sufficient information to estimate an exposure level of 39,000, 50,000,440,000, and 600,000 ppm, respectively. Common symptoms were ataxia, staggering, headache, drowsiness, anorexia, blurred and double vision, convulsions, nausea, and vomiting (Jones 1942).

Putz-Anderson et al. (1981b) assessed the behavioral effects of inhaled chloromethane when administered alone at 0 or 200 ppm, or in combination with alcohol or caffeine. Chloromethane exposures in volunteers lasted 3.5 hours. Patients were subjected to three performance tests (visualvigilance, dual task, and time discrimination (designed to test human attention or alertness) prior to and during the treatment period. Venous blood and alveolar air concentrations of chloromethane were obtained prior to and 90 minutes after beginning chloromethane exposures. Chloromethane alone had no effect. Alcohol caused a significant impairment in performance, but there was no difference in alcohol-induced impairment when chloromethane was given with alcohol. Caffeine alone improved performance, but there was no effect on improvement when chloromethane was given with caffeine. There was much variation in alveolar air and blood levels of chloromethane.

Putz-Anderson et al. (198 la) assessed the behavioral effects of inhaled chloromethane, alone or in combination with oral diazepam (a central nervous system depressant), in 56 men and women. Chloromethane was administered alone at concentrations of 0, 100, or 200 ppm, or in combination with

10 mg orally administered diazepam. Chloromethane exposures lasted 3 hours. Patients were subjected to three performance tests (visual vigilance, dual task, and time discrimination; designed to test human attention or alertness) prior to and during the treatment period. Venous blood and alveolar air concentrations of chloromethane were obtained prior to and 90 minutes after beginning chloromethane exposures. Due to a limited number of patients, data from the 100 ppm chloromethane group was excluded from the analysis. For all tests, the control group (no chloromethane or diazepam) had a 2.73% decline in performance between the precontrol and control test (i.e., a control for the fatigue effect). The net impairment resulting from exposure to 200 ppm chloromethane was a marginally significant 4% (total impairment 6.7% minus the 2.73% negative control). The net impairment of diazepam alone was 10.1%. The net impairment of the combined chloromethane and diazepam was 13.5%. The authors concluded that the effects of chloromethane exposure were minimal and were not potentiated by concomitant diazepam exposure.

Spevak et al. (1976) describe a case of chloromethane poisoning among four family members (one brother [age 64] and three sisters [ages 50, 52, and 60]). All were exposed to fluid and vapors leaking from a refrigerator for approximately 1 hour while cleaning the spill. Approximately 4 hours after their exposure, all four subjects felt weak and had abdominal pains, vomiting, hiccups, and severe headaches; which they thought was due to food poisoning. All subjects lost consciousness until the next day. Neighbors told the subjects that a doctor visited them and administered some medication, but the identity of the medication was unknown. By 2 days after the exposure, the symptoms had not disappeared, and all four were admitted to the hospital with clinical signs of drunkenness, confusion, somnolence, ataxia, and dysarthria. Nervous system damage progressed with cerebellar symptoms of nystagmus in all four patients, and adiadochokinesis developing in one of the women. All subjects had disturbances of the cranial nerves (optic, oculomotor, and facial), as well as speech disturbances, tremors, and elevated reflexes. Tachycardia, faint heart sounds and slightly elevated blood pressure were also noted. The most severely affected subject (one of the sisters who also had the longest exposure) suffered from jaundice, conjunctival hemorrhages, and epigastric tenderness; however, her liver and spleen were not enlarged. The brother had the shortest exposure and had a normal skin color. Biochemical analysis of blood and urine revealed increases in indirect bilirubin in all three sisters and serum creatinine for all four patients. Blood urea was increased only for the most severely affected sister. All other hematology and blood chemistry data were normal including number of red and white blood cells, platelets, and reticulocytes; red cell osmotic fragility test; coagulation factors; serum electrophoresis, cholesterol, alkaline phosphatase, ALT, AST, and fibrinogen; and blood glucose, blood ammonia, bone marrow smears, blood pH, and blood gases.

Electroencephalograms were also normal. The three sisters received symptomatic treatment with isotonic glucose, B complex vitamin, and oxygen. The treatment resulted in a disappearance of all symptoms of intoxication except ataxia. The brother refused treatment. Symptoms of kidney damage disappeared after two weeks, and the outcome of the intoxication was, in the words of the physicians, good in all cases (Spevak et al. 1976).

Stewart et al. (1980) found no exposure-related neurological abnormalities, abnormal EEG, effect on cognitive test, or significant subjective response from acute exposures up to 150 ppm in volunteers. This study, however, had several limitations such as small sample size, multiple dosing schemes, and a confusing protocol. Specifically, groups of two to four men and two to four women were exposed to 10, 100, or 150 ppm or to concentrations that were increased from 50-1.50 ppm in the same group for 1, 3, or 7.5 hours per day over 2-5 days per 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. The same subjects were also included in different protocols during different weeks of the study.

Gudmundsson (1977) reports on a 20-month and 13-year follow-up after an acute high level exposure to chloromethane. Seventeen crew members (males) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (no estimates of exposure levels were reported). The refrigerator was located under the sleeping quarters of the crew. This case history describes both the acute phase of the illness and a follow-up of the survivors at 20 months and 13 years postexposure. Fifteen of the seventeen crew members exposed to chloromethane showed signs of intoxication.
In the acute phase of the illness, nine patients exhibited abnormal neurological signs. Four died, one within 24 hours of the exposure. Two patients developed severe depression and committed suicide 11 and 18 months later, respectively. The fourth patient was assessed as 75% disabled due to severe neurological and psychiatric disturbances, and died 10 years postexposure at the age of 34. Autopsy revealed recent coronary occlusion (not necessarily connected with the primary illness). At 20 months postexposure, 7 patients had neurological symptoms (not specified), and 8 had psychiatric complaints primarily psychoneurosis and depression. Five survivors stated they had a reduced tolerance to alcohol. Thirteen years later (i.e., in 1976) 10 of the 11 survivors were examined (one lived in a foreign country and could not be located). The mean age of the 10 survivors examined was 38.3 years (range 30-50 years). All 10 were employed; 8 were employed at sea. Neurological deficits included fine tremor of the hands in three survivors, paralysis of accommodation in two, and signs of peripheral neuropathy in two. Five survivors had no abnormal neurological signs. Six survivors had marked neurotic and depressive symptoms. Two

complained of decreased libido and two complained of severe headache. Alcohol may be a confounding factor. Nine survivors complained of a markedly reduced tolerance for alcohol, and the same number complained of early fatigue and decreased stamina. Excessive alcohol consumption was admitted by four survivors. Alcohol may contribute to the peripheral neuropathy. Regarding the progress or reversibility of the symptoms, one patient who had considerable muscle atrophy and fasiculations 20 months after the accident had improved by 13 years postexposure, but still exhibited signs of anterior horn damage. In two survivors, the paralysis of accommodation remained unchanged, but in one there was a complete regression. In conclusion, all survivors of the acute chloromethane exposure suffered from mild to permanent neurological and/or psychiatric sequelae directly attributable to chloromethane neurotoxicity.

Some information on longer term exposures is available. MacDonald (1964) presented eight case reports of chloromethane poisoning in a polymer plant. Symptoms of blurring vision, mental confusion, headache, loss of coordination, and dizziness were common. More severely intoxicated individuals experienced nausea and vomiting. Personality changes, depression and irritability were reported by many of the cases. The symptoms persisted for months. It was not possible to determine the LOAEL.

Schamweber et al. (1974) presented 6 case studies of workers who were exposed to relatively low levels (200-400 ppm) of chloromethane for at least 2-3 weeks before onset of symptoms. Two cases occurred after "prolonged" (not otherwise specified) exposure to S-hour TWA levels up to 300 ppm. Four cases occurred after work exposure on the order of 265 ppm (S-hour TWA) after 2-3 weeks of 12-16 hour days. A 54-year-old worker initially suffered from confusion, blurry vision, erratic driving, difficulty in eating and swallowing, headache, and disturbance of balance. Three weeks after hospitalization, the patient still complained about headache and had a staggered gait. Memory difficulties persisted for 2 months. Patient improved at three months, but still had tremors and nervousness. A second B-year-old worker had delirium, confusion, disorientation, and combativeness. Two months after hospitalization, the patient still had poor memory and nervousness. Three months later, the patient was well enough to return to work. A 33-year-old foam worker had blurred vision, increased tiredness, nervousness, and stuttering that resolved after a 6-week recovery period. Other foam workers developed similar symptoms with impairment in memory, gait, and speech (tongue swelling, slurring) and vision (diplopia, blurred), slight to moderate increase in blood pressure, and an EEG with a predominance of slow waves in the beta range that resolved from 1 to 3 months after removal from exposure. The authors concluded that an 8-hour TWA of 200 ppm or greater is necessary for development of chronic chloromethane intoxication based on these and other industrial experiences.

Repko et al. (1977) performed a study on the effects of chloromethane from exposures to workers. Seventy-three behavioral measures of task performance, four indices of exposure, eight indicators of neurological function, and a clinical EEG were obtained. The exposed population was derived from several fabricating plants. Ambient air concentrations of chloromethane ranged from 7.4 to 70 ppm, with means from each plant ranging from 8.46 to 58.72 ppm. The overall mean was 33.57 ppm. Mean concentration of chloromethane in breath ranged from 2.67 to 24.19 ppm, with a mean of 13.32 ppm. Correlations were found between the duration of exposure and breath concentration, duration and ambient concentration, concentration in air and concentration in breath, chloromethane in air and hematocrit, urine pH and hematocrit, and duration and hematocrit. There were no significant differences in neurological tests or EEGs. In the behavioral battery, effects on cognitive time-sharing and finger tremor were found, but correlation coefficients indicated that chloromethane in breath is not a sensitive indicator of performance deficit. Workers showed a general tendency toward poorer performance as chloromethane levels in air increased. The authors concluded that occupational exposure to chloromethane below 100 ppm produces subtle, quantifiable behavioral effects, but that data on the threshold at which chloromethane begins to produce these changes in functional capacity are not currently available. A limitation of this study was the inability to achieve perfect matching as to sex, race, age, and level of education.

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, 1947b). As discussed in Section 2.2.1.1, these studies have several limitations that preclude determination of concentration-duration-response relationships, but the results do demonstrate the universal response of animals to the neurotoxic effects of chloromethane.

More recent animal studies support the neurotoxic potential of chloromethane, with sufficiently high levels of acute inhalation exposure leading to ataxia, tremors, limb paralysis and incoordination, and cerebellar lesions consisting of degeneration of the granular layer. Mice appear to be more sensitive than rats, with similar but more severe responses at lower exposure concentrations.

After 48 continuous hours of chloromethane exposure at 1,000 ppm, Sprague-Dawley rats were lethargic compared to the controls, and their condition worsened to sick or moribund by the end of a 72-hour exposure. The 2,000 ppm exposure eventually led to death. There were no effects on brain weight, and no

exposure-related gross or histopathological lesions in the brain. No effects were seen at 500 ppm for up to 72 hours of exposure (Burek et al. 1981).

Male Fischer 344 rats exposed to 5,000 ppm chloromethane alone for 5 days, 6 hours/day had more pronounced signs of central nervous system toxicity (tremors, ataxia, forelimb/hindlimb paralysis) than those receiving chloromethane plus pre-and post-treatment with the potent anti-inflammatory agent, BW755C (10 mg/kg, intraperitoneally 1 hour pre- and postexposure). Chloromethane alone caused a degeneration of cerebellar granule cells, while rats exposed to chloromethane and BW755C did not exhibit this effect. The result was surprising because this brain lesion is not usually associated with inflammation. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution or excretion of ^{14}C-chloromethane, and administration of BW755C did not decrease hepatic glutathione content. The protection of BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis (Chellman et al. 1986a).

Fischer 344 rats were exposed to 0, 2,000, 3,500, or 5,000 ppm chloromethane for 6 hours/day, 5 days/week, for 2 weeks. On day 5, hind limb paralysis was observed in two males and one female in the 5,000 ppm group. After the fifth day, 13 animals were killed in extremis (5,000 ppm:6 males, 5 females; 3,500 ppm:2 females). By the second week, the rats appeared to tolerate the exposures much better, but one 5,000 ppm female had convulsive seizures during the last exposure. Histological examination of the brain and thoracic spinal cord revealed minimal to moderate degeneration of cerebellar internal granular layer in two females and three males exposed to 5,000 ppm. The lesions were identical to those seen in mice. There were no lesions in the spinal cord. The authors concluded that this study confirmed the existence of species, sex, and strain differences in susceptibility to chloromethane-induced toxicity. No neurological or histopathological lesions were reported for the 3,500 ppm group. The 3,500 ppm dose is not designated a NOAEL due to the absence in the report of an explicit statement that no neurotoxicity occurred at 3,500 ppm and the severity of this effect reported for the 5,000 ppm mice. C3H, C57BL/6, or B6C3F$_1$ mice were exposed to chloromethane for 12 days, 6 hours/day. Mice were exposed to 0,500, 1,000, or 2,000 ppm. Some of the mice that died had moderate to severe ataxia. Histologically, there were no brain lesions at 500 ppm in any strain. Cerebellar degeneration was seen as follows: C3H mice (none); C57BL/6 mice, 3 of 5 males and 5 of 5 females exposed to 1,000 ppm and 0 of 5 males and 4 of 4 females exposed to 2,000 ppm; B6C3F$_1$ mice, 2 of 5 females exposed to 2,000 ppm. The lesions were most severe in 2,000 ppm C57BL/6 females, followed by 1,000 ppm C57BL/6 males. The cerebellar lesions consisted

of focal degeneration of the granular layer, which affect posture and coordination. The authors concluded that this study confirmed the existence of species, sex, and strain differences in susceptibility to chloromethane-induced neurotoxicity (Morgan et al. 1982).

Chellman et al. (1988a) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the brain of male $B6C3F_1$ mice. Mice exposed to 1,500 ppm chloromethane for 6 hours/day, 5 days/week, for 2 weeks developed multiple degenerative, necrotic foci in the internal granule cell layer of the cerebellum; in some areas the foci involved the whole thickness of the granular cell layer. Cerebellar degeneration consisted of granule cells with pyknotic nuclei and clear, swollen perikarya. Tremors, ataxia, and forelimb/hindlimb paralysis were seen in chloromethane-exposed mice prior to death, and were associated with cerebellar damage. Cerebellar damage was not observed in chloromethane-exposed mice pretreated with a glutathione depleter. The authors concluded that the depletion of GSH protected mice from cerebellar damage due to exposure to chloromethane. Based on this result, the mechanism of neurotoxicity may involve conjugation of chloromethane with glutathione in the liver, followed by biliary excretion and enterohepatic circulation of the glutathione conjugate, or possibly a cysteine conjugate, and further metabolism by kidney and/or gut flora beta-lyase to methanethiol. Methanethiol produces similar central nervous system symptoms (tremors, convulsion, coma) as seen in animals or humans acutely intoxicated with chloromethane (Chellman et al. 1986b).

Jiang et al. (1985) characterized the cerebellar lesions resulting from an acute inhalation exposure of 1,500 ppm chloromethane to female C57BL/6 mice for 2 weeks, 5 days/week, 6 hours/day. Two mice died, and several had motor incoordination. All exposed mice had varying degrees of cerebellar degeneration located mainly in the ventral paraflocculus, but also occurring in dorsal paraflocculus. Granule cells were mainly affected, with two distinct types of lesions: (1) nuclear and cytoplasmic condensation of scattered granule cells with slight hydropic swelling of astrocytes (also seen to a lesser extent in controls); and (2) focal malacia with varying degrees of watery swelling of groups or extensive areas of granule cells, nuclear condensation, karyorrhexis, and necrosis. The second type of lesion was more prevalent. Purkinje cells were largely unaffected by the malacic process, and the inflammatory response was minimal. Electron microscopy showed that the damage in the areas of malacia (the type 2 lesion above) ranged in severity from edema of granule cell perikarya to severe edema and almost complete destruction of all tissue components. Involvement of cell types other than granule cells occurred only in the most severely affected areas (i.e., Purkinje cells were well preserved while astrocytes adjacent to Purkinje cells [the Bergmann's glia] showed moderate to severe cytoplasmic distention by translucent edema fluid).

The biochemical mechanism for the induced defects in granule cell fluid/electrolyte balance is unknown. Only one exposure concentration was used, but the study was designed to examine the neurological and kidney effects specifically, and therefore, used an exposure regimen known to produce these effects. Based on the severity of the kidney effects, the authors concluded that the observed brain lesions were probably not a direct consequence of renal lesions; rather, the mechanism may be associated with metabolic changes in granule cells.

Landry et al. (1985) observed decreased performance on the rotating rod at an 800 ppm and greater intermittent exposure (5.5 hours/day for 11 days) when tested at 4 days, but persisting to day 8 only in the 2,400 ppm mice (with considerably greater deficit in this group). Histological lesions consisted of slight cerebellar granule cell degeneration in some of the mice exposed to 400, 800, or 1,600 ppm. In the 2,400 ppm group, all of the mice were affected to a slight degree. Mice exposed continuously for 22 hours/day for 11 days had similar effects at exposure levels of 100 ppm. The apparent greater sensitivity to continuous exposure may be related to the conversion of chloromethane to an active metabolite, decreased respiration at concentrations that are intolerable when exposure is continuous, and/or diurnal susceptibility. Diurnal susceptibility (i.e., in this case lower sensitivity during the daytime intermittent exposure) could result from the lower activity of mice during the daytime and the lower respiratory minute volume.

Pregnant $B6C3F_1$ mice exposed to 1,500 ppm chloromethane in whole-body exposure chambers, 6 hours/day on Gd 6-17 developed tremors, hunched appearance, difficulty righting, disheveled fur, bloody urine, and granular cell degradation in cerebellum with selective necrosis of neurons in the internal granular layer. All females in this group were sacrificed on Gd 11-14 prior to the completion of exposure to Gd 17; two females died prior to necropsy (as early as Gd 9, after only 4 days of exposure). These effects were not seen in the 479 ppm or lower exposure (Wolkowski-Tyl et al. 1983a).

C57BL/6 females were mated to C3H males to produce $B6C3F_1$ offspring. After mating, 74-77 females were exposed to chloromethane at concentrations of 0, 250, 500, or 750 ppm on Gd 6-17. Exposure to 500 ppm chloromethane resulted in ataxia in 6 of 74 females by Gd 18; exposure to 750 ppm resulted in hyperactivity, ataxia, piloerection, tremors and convulsions. The authors concluded that inhalation exposure to chloromethane during Gd 6-17 resulted in maternal toxicity at 750 ppm; teratogenic effects were seen at 500 and 750 ppm. Exposure of pregnant mice to 250 ppm chloromethane produced neither maternal nor fetal toxicity nor teratogenicity (Wolkowski-Tyl et al. 1983b).

Beagle dogs (n=3) exposed to 500 ppm chloromethane for 23.5 hours/days for 3 days had moderate to severe limb stiffness, tremors, salivation, and incoordination. These effects became less severe but persisted during a 4-week recovery. All 500 ppm dogs had neurological deficiencies based on clinical testing at 4 days after exposure, but nearly complete recovery on day 26 after exposure. Histological examination revealed brain and spinal cord lesions in all 3 dogs consisting of vacuolization, swollen eosinophilic axons, loss of axons, demyelinization and gitter cells. These changes were very slight and multifocal in the brain stem (medulla, pons, or both) and slight and multifocal in the lateral and ventral funiculi of the spinal cord. No lesions were observed in the cerebrum or cerebellum nor in the dorsal funiculi or grey matter of the spinal cord (McKenna et al. 1981a).

Cats (n=3) exposed to 500 ppm chloromethane for 23.5 hours/days for 3 days were less active than controls after 24 hours of exposure, but had no clinical signs after exposure. Cats did not undergo neurological tests. Histological lesions in cats were seen in 1/3 control, 1/3 at 200 ppm, and 3/3 at 500 ppm; and consisted of lesions in the brain occurring in a multifocal or random pattern in the white matter of the cerebrum, cerebellum and midbrain. In the spinal cord they primarily occurred in the lateral and ventral funiculi. The authors did not believe that these were treatment related but were instead consistent with infection or post-vaccinal reaction (cats were vaccinated for panleukopenia by supplier). The authors stated that exposure to 500 ppm may have resulted in an exacerbation of a viral-induced, spontaneously occurring disease process in the central nervous system of the cats. (McKenna et al. 1981a).

Intermittent exposures for longer durations also resulted in less severe neurotoxicity. $B6C3F_1$ mice or Fischer 344 rats exposed to 0, 375, 750, and 1,500 ppm for 6 hours/day, 5 days/week, for 13 weeks showed no exposure-related histopathological lesions of brain and spinal cord and no effect on brain weight (Mitchell et al. 1979). Beagle dogs, CD-1 mice, or Sprague-Dawley rats exposed to as high as 400 ppm chloromethane for 6 hours/day, 5 days/week for 90 days showed no apparent neurological effects (McKenna et al. 1981b).

Longer-term higher-level exposures have, however, resulted in neurotoxicity in mice even if only for 6 hours/day. Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to 24 months. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure. As early as 6 months, the absolute brain weight was reduced in male and female mice exposed to 1,000 ppm chloromethane; however, relative brain weights were not affected by chloromethane

exposure. Clinical signs of neurotoxicity (tremor, paralysis) were observed in both sexes (exposure level not specified, but most likely 1,000 ppm). By 18 months, decreased absolute brain weights were noted in females exposed to 1,000 ppm chloromethane. Clinical signs of neurotoxicity (tremor, paralysis) were seen in both sexes, along with abnormal functional test neurological results (restricted use of rear legs, abnormal gait, poor extensor thrust, leg rigidity), and cerebellar lesions (minimal to mild reduction in the number of neurons in the granular cell layer, most prominently in the sulci). Axonal swelling and degenerative changes of minimal severity were observed in the spinal nerves and cauda equina in the lumbar spinal cord of 3 of 7 male mice (1,000 ppm), 5 of 5 male and 10 of 10 female mice (225 ppm), 4 of 5 male and 10 of 10 female mice (50 ppm), and 1 of 5 male and 2 of 10 female mice (control). The neurotoxic lesions progressed in frequency and severity in mice to the end of the exposure period. In contrast to its effects in mice, chloromethane did not produce neurotoxicity in rats (i.e., negative clinical, pathological, and functional tests) at levels up to 1,000 ppm for 6 to 24 months in duration (CIIT 1981). The mechanisms underlying this dramatic difference in species susceptibility are not understood.

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 acutely (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 0.5 ppm was calculated as described in the footnote to Table 2-1 and in Appendix A. The 51 ppm concentration in mice exposed chronically to chloromethane (CIIT 1981) is the lowest LOAEL (axonal swelling and slight degeneration of axons in the spinal cord). Based on this LOAEL, a chronic inhalation MRL of 0.05 ppm was calculated as described in the footnote to Table 2-1 and in Appendix A. These MRLs are presented in Figure 2-1.

2.2.1.5 Reproductive Effects

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

Chloromethane has been shown to be a reproductive toxicant in a variety of animal studies. Sprague-Dawley rats exposed to 500 ppm for 48 hours had increased proteinaceous and cellular aggregates in the epididymis with interstitial edema (2/5 rats) and focal suppurative inflammation (1/5) immediately after the exposure. By 12 days postexposure, the lesions had increased in severity with the formation of sperm granulomas, decreased sperm in the tubule lumen, interstitial edema, coagulated proteinaceous

debris or inflammation leading to obstructive changes causing at least partial occlusion of the affected lumen, and unilateral testicular atrophy. The lesions were more severe in rats exposed to higher concentrations and/or for the longer duration. Mean absolute and relative testicular weight was decreased to 50% in rats exposed to 1,000 ppm for 72 hours; this effect was thought to be secondary to a severely obstructed epididymis. The decreased testes weight was not observed in 1,000 ppm rats exposed for 48 hours or in males exposed to 200 or 500 ppm for either duration (Burek et al. 1981).

Male Fisher 344 rats were exposed to 3,500 ppm chloromethane for 6 hours/day for 5 days, then a stop in exposure for 3 days, and then a restarting of the exposure for another 4 days. This regimen resulted in several testicular and epididymal lesions and interference with neuroendocrine control of spermatogenesis. The initial testicular effects were directed at either the late stage spermatids or the Sertoli cells with a resultant delay in spermiation. No testicular abnormalities were found at 5 days, but at 7 days one rat had scattered foci of disruption of seminiferous epithelium, and exfoliation of germinal cells. By day 9 all exposed rats had disruption of spermatogenesis, and by day 13 all had disruption and disorganization of seminiferous epithelium and epithelial vacuolation. At 70 days, 70-90% of seminiferous tubules were shrunken, contained whorls of Schiff's reagent-positive material, and had Sertoli cell nuclei near the basement membrane. The remainder showed varying degrees of recovery. All animals killed after 19 days displayed bilateral epididymal granulomas in regions 5 or 6 of the cauda epididymis. The nature and distribution of the inflammatory cells indicated that the primary neutrophilic response may have been against the tubular epithelium and not extravasated sperm. Serum testosterone showed a time dependent decrease during the 5 consecutive days of exposure (not seen in the pair-fed controls). Leydig cell and gonadotropin function was normal when challenged with hCG and LHRH; thus, the authors propose that chloromethane lowers circulating testosterone by acting in the brain to decrease circulating levels of gonadotrophic hormones. NPSH content was depleted in testis, caput and caudal epididymides samples, but not in heart blood. This effect is thus probably the result of enzyme-mediated conjugation of glutathione with chloromethane, and not a consequence of direct alkylation. The authors speculate that chloromethane conjugation with testicular and epididymal glutathione may result in depletion of glutathione, which serves in a variety of protective cellular functions (Chapin et al. 1984).

Rats exposed to 7,500 ppm chloromethane 6 hours/day for 2 days developed epididymal granulomas within 3 weeks after exposure (Chellman et al. 1986a). Effects of 7,500 ppm chloromethane on testes were not reported. Rats exposed to 5,000 ppm, 6 hours/day for 5 days developed sperm granulomas in the epididymides, and testicular lesions (exfoliation of pachytene spermatocytes and early stage spermatids).

No granulomas were found in rats treated concurrently with chloromethane and the anti-inflammatory agent, amino-l-[m-(trifluoromethyl)-phenyl]-2-pyrazoline (BW755C). There was also no evidence of epididymal or testicular lesions in rats treated with both 5,000 ppm chloromethane and BW755C. BW755C, therefore, protected rats against chloromethane toxicity. The authors concluded that protection from chloromethane-induced injury by BW755C was not simply the result of altered metabolism because BW755C had no effect on tissue distribution or excretion of ^{14}C-chloromethane, and administration of BW755C did not decrease hepatic glutathione content. The protection of BW755C may have been related to an inhibition of leukotriene and prostaglandin synthesis.

Chellman et al. (1986c) investigated the relationship between chloromethane-induced epididymal inflammation and the occurrence of dominant lethal mutations in male Fischer 344 rats. Chloromethane exposure at 3,009 ppm for 6 hours/day for 5 days resulted in a significant increase in pre-implantation loss in females mated with exposed males at weeks 2 and 3 postexposure, and BW755C did not protect against this effect. The authors concluded that pre-implantation losses were due to the cytotoxic effect of chloromethane on the testes. A subsequent study by the authors (see Chellman et al. 1987) showed reduced numbers and abnormal sperm from chloromethane induced testicular toxicity in male rats, leading to a failure to fertilize.

Chellman et al. (1987) also investigated the role of chloromethane-induced testicular and epididymal inflammation in the induction of sperm cytotoxicity and preimplantation loss in male Fischer 344 rats. Rats exposed to 3,056 ppm chloromethane 6 hours/day for 5 consecutive days had significantly decreased relative weight of seminal vesicles at week 1, epididymis at weeks 2 and 3, and testes at week 3; disruption of spermatogenesis (delayed spermiation, disorganization of seminiferous epithelium, and decreased number of mid- and late spermatids); and decreased sperm production per day at weeks 1, 2, and 3 postexposure. Epididymal examination revealed visible sperm granulomas and inflammation; a large amount of PAS-positive material in epididymis associated with greatly decreased number of sperm, increased number of abnormal sperm and cellular debris of testicular origin; reduced number of sperm, decreased percent motile sperm and percent intact sperm, and increased abnormal sperm in the vas deferens by week 3. Concurrent treatment with BW755C did not protect the rats from these testicular effects, but did protect the rats from the formation of sperm granulomas and inflammation in the epididymides. The authors concluded that chloromethane-induced sperm toxicity was due to toxicity to the testes, rather than the result of inflammation and granuloma formation in the epididymis. This testicular toxicity and

movement of damaged sperm out of the testes into the epididymis and vas deferens was probably responsible for fertilization failures and preimplantation losses seen by Working and Bus (1986).

Male Fischer 344 rats were exposed to chloromethane at 0, 2,000, 3,500, or 5,000 ppm for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure. Histological examination of the testes and epididymides revealed testicular degeneration in all males of all exposed groups with a clear dose-related increase in severity. The testicular lesions consisted of a reduction in or lack of late stage spermatids, separation of spermatocytes, and early stage spermatids. The lumen of epididymal tubules contained greatly reduced numbers of sperm. There was a dose-related increase in eosinophilic, hyaline droplets and degenerating cells of unknown type (Morgan et al. 1982).

Pregnant Fischer 344 rats exposed to 1,492 ppm chloromethane 6 hours/day on Gd 7-19 had significantly depressed maternal food consumption and weight gain during exposure, but there were no statistically significant differences among the treatment groups for number of litters, percent litters with live fetuses, the number of corpora lutea, number of implantations, number or percent resorptions, number of live fetuses per litter, or fetal sex ratio. $B6C3F_1$ mice exposed to 1,492 ppm chloromethane for 6 hours/day on Gd 6-17 developed severe maternal toxicity resulting in tremors, hunched appearance, difficulty righting, disheveled fur, bloody urine, and granular cell degradation in cerebellum with selective necrosis of neurons in the internal granular layer. All females in this group were sacrificed on Gd 11-14 prior to the completion of exposure to Gd 17; two females died prior to necropsy (as early as Gd 9, after only 4 days of exposure). These effects were not seen in the 479 ppm group. There were no significant differences for exposures of 479 ppm or less for the number of litters, percent litters with live fetuses, the number of corpora lutea, number of implantations, number or percent resorptions, number of live fetuses per litter, or fetal sex ratio (Wolkowski-Tyl et al. 1983a).

Working and Bus (1986) assessed the effects of inhalation exposure to chloromethane on preimplantation loss to distinguish between cytotoxicity (i.e., fertilization rate) and genotoxicity in rats. Male Fischer 344 rats exposed to chloromethane at 3,000 ppm for 5 days, 6 hours/day were bred to no more than 2 females weekly during weeks l-4 and week 8 post-exposure. Males in the 1,000 ppm group were bred to no more than 2 females during week 3 post-exposure. Females were sacrificed lo-12 hours postmating, and embryos and ova were scored as fertilized or unfertilized. In an *in vitro* experiment, fertilized ova were examined in culture for cleavage. The combined fertilization rate in all females bred to control males was 88%. In females bred to the 1,000 ppm males, 80% of ova were fertilized. In females bred to the

3,000 ppm males, fertilization of ova was 39% at week 1 of mating, 3.4% at week 2, 22.1% at week 3, 41% at week 4, and 72% at week 8. There were no significant differences in the cleavage rates of ova from females bred to controls (96.5%) or to males exposed to 1,000 or 3,000 ppm chloromethane (92.4-93.8%). The authors concluded that all preimplantation losses observed in previous studies (Working et al. 1985a) could be explained by a cytotoxic effect resulting in failure of fertilization and not a genotoxic effect resulting in early embryonic death (Working and Bus 1986).

Working et al. (1985a) studied the effects of inhalation exposure to chloromethane on germ cell viability in male Fischer 344 rats. At 17 weeks after exposure to 3,000 ppm chloromethane for 6 hours/day for 5 days, 30% of the males had sperm granulomas in one or both epididymides; none were noted in the 1,000 ppm or control groups. Exposure to 3,000 ppm chloromethane also resulted in a slight increase (9.5%) in postimplantation loss only at week 1 postexposure (sperm exposed in epididymis or vas deferens), but increased preimplantation losses at week 1 (31.4%), peaking at week 2 (93.6%) then declining to 14.1% by week 8 postexposure. Fertility in males exposed to 3,000 ppm chloromethane was significantly decreased by postexposure week 2 and remained depressed throughout the study period. The authors concluded that a cytotoxic rather than genotoxic mechanism may play a role in the observed preimplantation losses. They further speculated that inflammation-derived reactive metabolites (e.g., superoxide anion) could damage DNA or sperm in epididymis (Working et al. 1985a).

Fischer 344 rats exposed to 3,000 ppm chloromethane at 6 hours/day for 5 days had decreased testicular weight from the third post-exposure week with a steady decline to 50% by week 8, and a recovery by week 16. Histologically, sperm granulomas in epididymides were observed in 50% of the exposed rats. Disruption of spermatogenesis in testes, decreased number of sperm, increased number of abnormal sperm, and decreased sperm motility were also observed. Recovery was nearly complete by week 16. The authors concluded that inhalation of high concentrations of chloromethane produce a prolonged cytotoxicity in testes leading to oligospermia due initially to depletion of postmitotic stages of spermatogenic cells, and ultimately to the killing of spermatogonial stem cells. The resultant decreased fertility was not permanent. The inflammation of the epididymis may account for depressed motility and increased numbers of abnormal sperm, but a genotoxic effect could not be ruled out on the basis of this study (Working et al. 1985b).

Exposure to chloromethane up to 750 ppm had no effect on reproductive parameters in C57BL/6 females mated to C3H males to produce $B6C3F_1$ offspring, such as the percentage of pregnant females, the number of implantations/litter, number of resorptions/litter, or the number of dead/litter. The authors concluded

that inhalation exposure to chloromethane during Gd 6-17 resulted in maternal toxicity only at 750 ppm and teratogenic effects at 500 and 750 ppm. Exposure of pregnant mice to 250 ppm chloromethane produced neither maternal nor fetal toxicity nor teratogenicity (Wolkowski-Tyl et al. 1983b).

Beagle dogs or cats exposed to 500 ppm chloromethane for 23.5 hours/days for 3 days and observed for 4 weeks (dogs) or two weeks (cats) postexposure showed no changes in weights of testes or development of histopathological lesions in the testes (McKenna et al. 1981a). No exposure-related gross or histopathological lesions in reproductive organs and no changes in testes weight occurred from exposures up to 400 ppm for 6 hours/day 5 days/week for 90 days in CD-l mice, Beagle dog, or Sprague-Dawley rat (McKenna et al. 1981b) or up to 1,473 ppm in Fisher 344 rats (Mitchell et al. 1979).

Han-n-n et al. (1985) examined whether an inhalation exposure to chloromethane affected the reproductive status of Fischer 344 rats exposed to 1,500 ppm chloromethane 6 hours/day, 5 days/week for 10 weeks premating, and then for 7 days/week during a 2-week mating period. Male rats exhibited seminiferous tubule atrophy (lo/lo) and granulomas in the epididymis (3/10) following exposure. No treatment effects were noted for litter size, sex ratio, pup viability, pup survival, or pup growth, and there was no significant difference in fertility between exposed and nonexposed females. In the F_0 recovery study, males exposed to 1,500 ppm chloromethane experienced a partial recovery of fertility, while males exposed to 475 ppm chloromethane experienced a full recovery. There were no F_1 litters from the 1,500 ppm group. Chloromethane had no statistically significant effect on fertility in the second generation (F_1 for 151 and 472 ppm exposures), but there was a dose related trend towards fewer litters and fewer males proven fertile in the 475 ppm group. Litters in the 475 ppm group had a significantly decreased percentage of males and significantly less male and female F_2 pup growth only during postnatal days 14 to 21. The significance of these affects are unknown (Han-m et al. 1985). The study did not mate unexposed males with exposed females. Such a mating with females exposed to 1,500 ppm would be necessary to rule out an effect on female fertility. Reduced fertility may be due to a cytotoxic effect on the testes (Working et al. 1985a, 1985b).

Male and female Fischer 344 rats and B6C3F_1 mice were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for 6, 12, 18, or 24. At 12 months, there were no exposure-related lesions in reproductive organs of mice exposed to chloromethane at concentrations up to 1,000 ppm., but lesions developed in the later months. Seven of 43 males exposed to 1,000 ppm, and that died or were sacrificed between 18 and

21 months, had testicular germinal cell degeneration, giant cell formation, and tubular atrophy, compared with 1/20 controls sacrificed at 24 months. Lesions developed earlier in the rat. By 6 months of exposure in rats, one male rat from the 1,000 ppm group had bilateral, diffuse degeneration and atrophy of the seminiferous tubules. This lesion significantly increased in this group at later sacrifices. At 12 months, gross and histological examination of testes and epididymides of males revealed germinal epithelial degeneration and atrophy of seminiferous tubules (4/10 males exposed to 1,000 ppm chloromethane). Chloromethane exposure had no effect on testis or ovary weights. At 18 months, gross and histological examination of testes and epididymides of male rats exposed to 1,000 ppm revealed germinal epithelial degeneration and atrophy of seminiferous tubules. Exposure to chloromethane had no effect on testes or ovary weights. Sperm granulomas were seen in two 1,000 ppm male rats at the 6-month sacrifice, in one male each at 50 and 225 ppm at 18 month, and in one male at 1,000 ppm at 24 months. None were seen at 12 months. The authors stated that it is possible that the sperm granulomas were induced early but resolved at later times, or that the lesion was spontaneous, but it is not possible to definitively attribute the lesions to chloromethane exposure on the basis of the results of this study. By 24 months, all male rats, including controls, had interstitial cell hyperplasia or adenomas associated with aging, which precluded detection of further exposure-related seminiferous tubule degeneration and atrophy. Absolute and relative testes weights were decreased in the 1,000 ppm group. There was a concentration-related decrease in bilateral compressive degeneration and atrophy and increase in unilateral compressive degeneration and atrophy (caused by testicular tumors), which correlated with decreased interstitial cell tumor size. This observation was supported by the testicular weight decreases observed in 1,000 ppm exposed male rats (CIIT 1981).

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

2.2.1.6 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 1,500 ppm chloromethane for 6 hours per day during gestational days (Gd) 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 hindlimbs.

Wolkowski-Tyl et al. (1983a) also found increased incidences of heart malformations in the fetuses of mouse dams exposed by inhalation to 480 ppm chloromethane during Gd 6-17. The heart malformations consisted of absence or reduction of atrioventricular valves, chordae tendineae, and papillary muscles. Heart malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during Gd 11.5-125, which they considered to be the critical period for development of the embryonal heart (John-Greene et al. 1985). John-Greene et al. (1985) suggested that the heart anomaly reported by Wolkowski-Tyl et al. (1983) may have been an artifact of the sectioning technique, due to the examination of the fixed as opposed to unfixed fetal tissue, or a misdiagnosis. They also found much inter-animal variability in the appearance of the papillary muscles in control mice. 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. The developmental toxicity of chloromethane in mice is, therefore, controversial; it is not known whether chloromethane could produce developmental effects in humans.

The highest NOAEL and all reliable LOAEL values for developmental effects in mice and rats 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 (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 3,500 ppm, 6 hours per 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).

Jager et al. (1988) have shown that the formation of formaldehyde (via P-450 activity) was 10 times higher in male mouse liver than in male kidney. Male mouse liver also produced formaldehyde at about twice the amount produced by female liver, and male kidney about 50% more than female kidney. This led to the hypothesis that male mice renal tumors resulted from increased production of formaldehyde and increased numbers of formaldehyde-induced DNA lesions. Glutathione depletion also removes the cofactor for formaldehyde dehydrogenase (FDH), the enzyme that inactivates formaldehyde. Jager et al. (1988), however, did not observe increased formaldehyde levels in mouse liver or kidney after a single 8-hour exposure to 1,000 ppm chloromethane, or an increase in DNA protein cross links (DPC), a typical formaldehyde-induced lesion, after exposure to 1,000 ppm for 6 hours per day for 4 days. Ristau et al. (1989), however, did observe an increase in DPC in the renal tissue of male but not female $B6C3F_1$ mice exposed to chloromethane at 1,000 ppm for 8 hours. DNA-protein crosslinks were not observed in liver. In a follow-up study, Ristau et al. (1990) showed a rapid removal of DPC whereas single strand breaks appeared to accumulate. Both types of lesions were ascribed to the action of formaldehyde. Ristau et al. (1989) assayed for DPC immediately after a single 8-hour exposure, whereas Jager et al. (1988) dosed over a 4-day period. Delays from exposure to assays that allow rapid repair of formaldehyde-induced DPCs could possibly explain why Jager et al. (1988) did not observe an increase. Both the DPCs and the incomplete and delayed repair of chloromethane-induced DNA lesions may contribute to the formation of renal tumors. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A retrospective epidemiology study of male workers exposed to chloromethane in a butyl rubber manufacturing plant produced no statistical evidence that the rates of death due to cancer at any site were increased in the exposed population when compared with U.S. mortality rates (Holmes et al. 1986). No specific exposure levels were given in this study.

Rafnsson and Gudmundsson (1997) report on excess mortality from cancer in a long-term follow-up after an acute high-level exposure. Seventeen crew members (males) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (no estimates of exposure levels were reported). The refrigerator was located under the sleeping quarters of the crew. Gudmundsson (1977) reported mild to permanent neurological and/or psychiatric sequelae at 20 months and 13 years postexposure. This study evaluated a cohort of 24 men on board the vessel at 32 years postexposure (6 officers and 18 deckhands including the surviving crew members who had the highest

exposure). The reference group was selected from three registries of seamen. The Icelandic registries for seamen are some of the most comprehensive and complete available. The reference group contained five times as many individuals as the study group, and was controlled for age, occupation, and social class. The authors report an excess mortality from all causes associated with chloromethane exposure (Mantel-Haenszel point estimate=2.2, 95%; CI=1.3-3.1). An elevated mortality from all cancers was also reported (M-H=15, 95%; CI=0.3-5.6) and for lung cancer (M-H=2.7, 95%; CI=0.1-52.6). Because the reference group matched for age, occupation, and social class, the authors assumed simultaneous control for lifestyle factors including smoking habits and diet. Conclusions from this study are limited because of this assumption. Indirect effects of the neurological deficits in this cohort on cancer susceptibility or lifestyle factors were also not discussed.

A high incidence of renal tumors was found in male mice that were exposed to 1,000 ppm chloromethane and died or were killed at 12 months or later in a 2-year oncogenicity study (CIIT 1981). Tumors consisted of renal cortex adenomas and adenocarcinomas, papillary cystadenomas, tubular cystadenomas, and papillary cystadenocarcinomas. No evidence of carcinogenicity was found in female mice or in male or female rats exposed to concentration of 1,000 ppm or less in this study. The cancer effect levels from this study are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

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

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, endocrine, dermal, ocular, or body weight effects in humans or animals after oral exposure to chloromethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to chloromethane.

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 mgkg. 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. The NOAEL from this study is recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding the following health effects in humans or animals after oral exposure to chloromethane:

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals following oral exposure to chloromethane.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

Table 2-2. Levels of Significant Exposure to Chloromethane - Oral

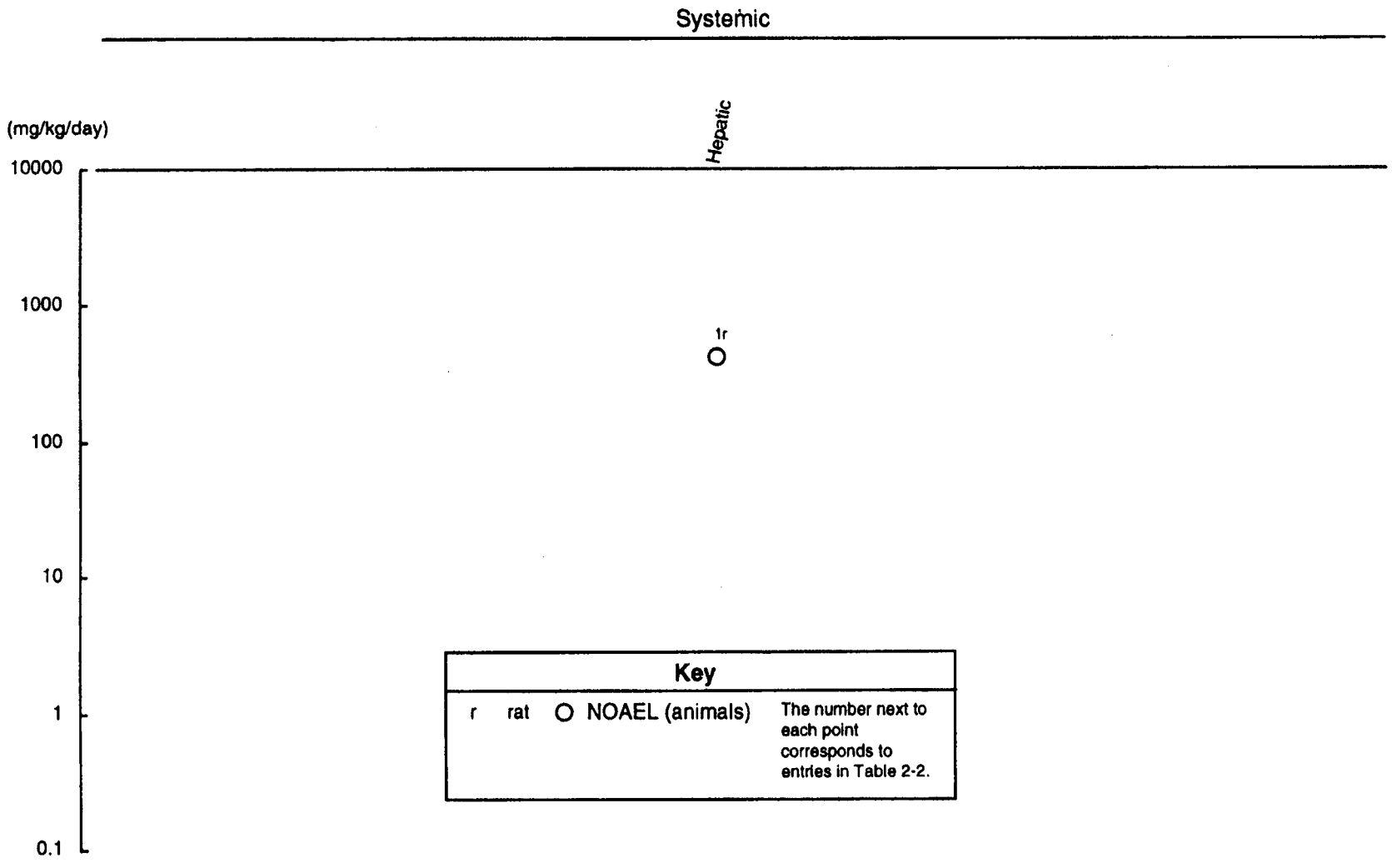
Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Charles River)	once (GO)	Hepatic	420			Reynolds and Yee 1967

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

(GO) = gavage in oil; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

Figure 2-2. Levels of Significant Exposure to Chloromethane - Oral

Acute (≤14 days)



2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, or body weight effects in humans or animals after dermal exposure to chloromethane.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to chloromethane.

A limited number of animal studies report ocular effects, but the results are mixed. Beagle dogs and cats were exposed by inhalation to 0, 200, or 500 ppm chloromethane 23.5 hours/day for 3 days, and were observed for 4 weeks (dogs) or 2 weeks (cats) postexposure before sacrifice. No ocular effects were observed in dogs from direct contact with chloromethane gas. On postexposure day 13, examination of the cat eye revealed focal opacity of the cornea consistent with a temporally persistent papillary membrane in the left eye of a control cat and a 200 ppm cat. These lesions were not considered to be treatment related (McKenna et al. 1981a).

Mitchell et al. (1979) reported mucopurulent conjunctivitis with total destruction of the eye in $B6C3F_1$ mice exposed to 375, 750, or 1,500 ppm for 6 hours/day, 5 days/week, for 13 weeks. No eye lesions were observed in controls. These lesions were attributed to exposure because no lesions were found in controls; however, the failure of longer-term studies to detect comparable eye lesions at higher concentrations makes the findings of Mitchell et al. (1979) questionable.

Beagle dogs exposed to 400 ppm chloromethane for 6 hours/day, 5 days/week for 90 days had no exposure-related gross or histopathological lesions in the eyes from direct contact with chloromethane gas (McKenna et al. 1981b).

Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to chloromethane at target concentrations of 0, 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Ophthalmic exams were performed at baseline and at sacrifice. At 6 months, corneal cloudiness or opacity without conjunctivitis was noted in control rats (2 of 10 male rats and 1 of 10 females), at 50 ppm (1 of 10 males at 12 months), and at 225 ppm (1 of 10 females at 18 months). The significance of this lesion is not clear because there was no dose-related incidence pattern at later sacrifices. At 12 months, a corneal lesion described as a haze

elliptically patterned over a central portion of the eye was seen in control rats (1 of 10 males and l/ of 10 females), at 50 ppm (8 of 10 males and 6 of 10 females), at 225 ppm (9 of 10 males and 7 of 10 females), and at 1,000 ppm group (9 of 10 males and 9 of 10 females). This lesion was only seen at 12 months and was distinctly different from the corneal cloudiness or opacity seen at 6 or 18 months. This corneal haze may have been the result of chemical effects upon the eyes in which the lacrimal function was compromised by intercurrent disease (an outbreak of sialodacryo-adenitis [SDA] was histopathologically diagnosed at 12 months). At 18 months in rats, the incidence of corneal cloudiness in exposed male rats was similar to that of control males. In females, the incidence of corneal cloudiness increased with dose: controls (2/20), at 50 ppm (4/20), at 225 ppm (12/20), and at 1,000 ppm (12/20). No significant difference in ocular lesions were observed in rats at 24 months. In mice, at 6 months, an acute, focal scleritis was observed in 3 of 10 males and 1 of 10 females in the 1,000 ppm group. This lesion was always associated with a neutrophilic inflammatory infiltrate which was present at the corneoscleral junction. At 12, 18, and 24 months, there were no statistically significant ocular lesions observed in mice (CIIT 1981).

The highest NOAEL and all reliable LOAEL values for ocular effects in mice and rats are recorded in Table 2-3.

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

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5

Table 2-3. Levels of Significant Exposure to Chloromethane - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Systemic						
Dog (Beagle)	3 d 23.5 hr/d	Ocular	500M ppm			McKenna et al. 1981a
Cat (NS)	3 d 23.5 hr/d	Ocular	500M ppm			McKenna et al. 1981a
INTERMEDIATE EXPOSURE						
Systemic						
Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Ocular	997 ppm			CIIT 1981
Rat (Fischer- 344)	12 mo 5 d/wk 6 hr/d	Ocular		51 ppm (corneal haze)		CIIT 1981
Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d	Ocular	997 ppm			CIIT 1981
Mouse (B6C3F1)	6 mo 5 d/wk 6 hr/d	Ocular	224 ppm		997 ppm (acute focal scleritis)	CIIT 1981
Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Ocular			368 ppm (mucopurulent conjunctivitis)	Mitchell et al. 1979
Dog (Beagle)	90 d 5 d/wk 6 hr/d	Ocular	400M ppm			McKenna et al. 1981b

Table 2-3. Levels of Significant Exposure to Chloromethane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
CHRONIC EXPOSURE						
Systemic						
Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Ocular	997 ppm			CIIT 1981
Rat (Fischer- 344)	18 mo 5 d/wk 6 hr/d	Ocular	51 M ppm 997 F ppm	224 F ppm (corneal cloudiness)		CIIT 1981
Mouse (B6C3F1)	18 mo 5 d/wk 6 hr/d	Ocular	997 ppm			CIIT 1981
Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d	Ocular	997 ppm			CIIT 1981

d = day(s); F = female; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s)

2.2.3.8 Cancer

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

2 . 3 TOXICOKINETICS

Chloromethane is readily absorbed from the lungs and rapidly reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations. At high concentrations, kinetic processes like metabolism or excretion may become saturated, limiting the rate of uptake. Differences in these processes may account for some of the observed differences in species uptake and distribution. It is not known what levels, if any, of chloromethane or its metabolites cross the placenta or enter the milk. There is also no information on differences between adults and children for the toxicokinetics of chloromethane.

Animal studies demonstrate that chloromethane absorbed from the lungs is extensively distributed throughout the body with relatively little variation in the pattern of distribution with respect to dose. Chloromethane is metabolized by conjugation with glutathione to yield S-methylglutathione, S-methyl-cysteine, and other sulfur-containing compounds. These compounds are excreted in the urine or can be further metabolized to methanethiol. Cytochrome P-450 dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms are then available to the one-carbon pool for incorporation into macromolecules or for formation of CO_2. Alternatively, formaldehyde may be directly produced from chloromethane via a P-450 oxidative dechlorination.

The conjugation of chloromethane with glutathione is primarily enzyme catalyzed. In contrast to all other animal species investigated (rats, mice, bovine, pigs, sheep, and rhesus monkeys), human erythrocytes contain a glutathione transferase isoenzyme that catalyzes the conjugation of glutathione with chloromethane. There are two distinct human subpopulations based on the amount or forms of this transferase. They are, for practical purposes, known as fast metabolizers (i.e., lower body burdens and higher excretion rates) and slow metabolizers (i.e., higher body burdens and lower excretion rates). These two subpopulations are also called conjugators and nonconjugators. Determination of the relative proportion of these subpopulations to the whole has just begun, but early results indicate considerable variation among different ethnic groups. There is considerable interest in further evaluating the relationship between endogenous levels of glutathione transferase and susceptibility of subpopulations to

chloromethane-induced toxicity. There is no information available on differences in isoforms or levels of glutathione transferase or P-450 in children (i.e., a different metabolic profile) that would result in a significantly increased or decreased susceptibility to chloromethane toxicity compared to that observed in adults. Research that addresses this issue is needed.

Little is known about the toxicokinetics of chloromethane from the oral or dermal routes of exposure.

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 3.5hour exposure of men and women (Putz-Anderson et al. 1981a, 1981b). Mean f 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 indicate that uptake was roughly proportional to exposure concentration, but individual levels were quite variable. A high correlation between alveolar air and blood levels ($r=0.85$, $p<0.01$) was found.

Blood and alveolar air levels of chloromethane also reached equilibrium during the first hour of exposure in 6 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 50-1,000 ppm for 3-6 hours (Landry et al. 1983a, 1983b). Absorbed doses were calculated as 67 mg/kg for rats exposed to 1,000 ppm and 3.8 mg/kg for rats exposed to 50 ppm (i.e., a ratio of 17.6 compared to a predicted ratio of 20 based on absorption being directly proportional to exposure concentration). The rate of uptake was 0.167 mg/min/kg for 1,000 ppm and 0.01 mg/min/kg for 50 ppm (ratio of 16.7). 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 a lower respiratory minute volume in the rats exposed to 1,000 ppm or to different amounts remaining in the body at the end of exposure and how much is metabolized. Blood chloromethane concentrations reached equilibrium within 1 hour and were proportional to exposure concentration for dogs exposed to 50 or 1,000 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, kinetic processes like metabolism or excretion may become 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 1,500 ppm as compared with 500 ppm. Upon acid precipitation of protein, 80% of the radioactivity present In liver

and testes was found in the acid soluble (unbound) fraction. The remainder was found to have been metabolically incorporated into lipid, ribonucleic acid (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 6 workers exposed to TWA 8-hour workroom concentrations of 30-90 ppm, the urinary excretion of S-methylcysteine showed wide variations, with little correlation to exposure levels (van Doorn et al. 1980). S-methylcysteine is formed from conjugation of chloromethane with glutathione (Kornbrust and Bus 1983). 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. There are two distinct subpopulations of individuals: 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 tissue glutathione levels and differences in biliary excretion and fecal elimination of thiolated conjugates. As a working hypothesis, however, the two distinct subpopulations are referred to as fast and slow eliminators. Two distinct subpopulations 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, and was not significantly different in pre-

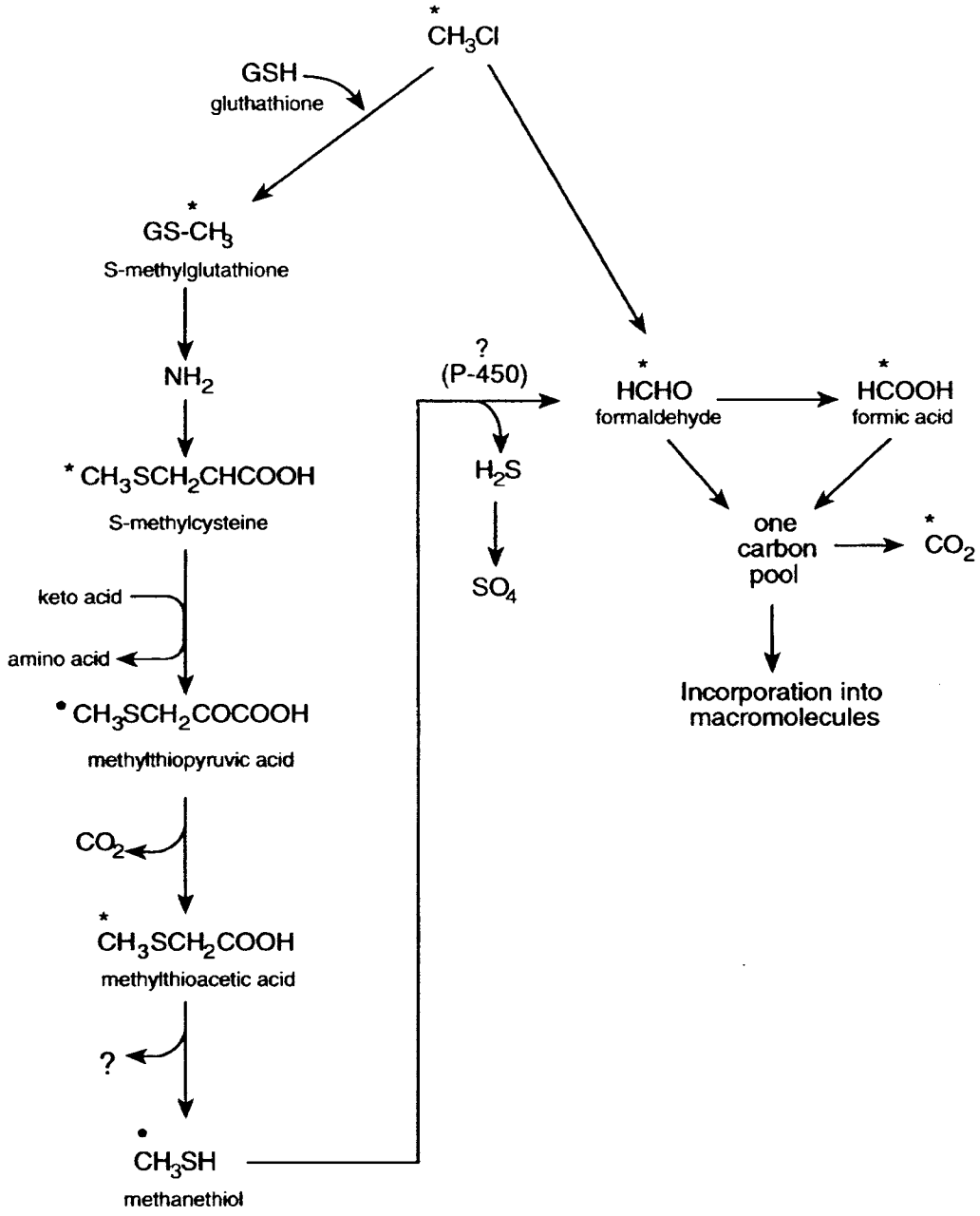
and postexposure levels. No change was detected in the S-methylcysteine concentration or in the total sulfhydryl concentration in the urine of 4 workers before and after a 7-hour shift in a styrene production plant by DeKok and Antheunius (1981) who concluded that S-methylcysteine is not a human metabolite of chloromethane. It is possible, however, that the workers examined by DeKok and Antheunius (1981) were slow eliminators.

Peter et al. (1989a, 1989b) assayed erythrocyte cytoplasm of humans with chloromethane and monitored the decline of chloromethane and the production of S-methylglutathione. About 60% of the human blood samples showed a significant metabolic elimination of the substance (conjugators), whereas 40% did not (nonconjugators). The results suggested that a minor form of human erythrocyte glutathione S-transferase is responsible for the unique metabolism of methyl chloride in human erythrocytes. Hallier et al. (1990) demonstrated that other monohalogenated methanes (methyl iodide and methyl bromide) could undergo enzymatic conjugation with glutathione, but that in contrast to chloromethane, methyl iodide and methyl bromide also showed significant non-enzymatic conjugation with glutathione.

Warholm et al. (1994) studied the polymorphic distribution of the erythrocyte glutathione transferases in a Swedish population and found three distinct sub-groups:11.1% lacked activity, 46.2% had intermediate activity, and 42.8% had high activity. The authors calculated two allelic frequencies, one for a functional allele with a gene frequency of 0.659 and one for a defect allele with a frequency of 0.341. This two allele hypothesis is compatible with the observed distribution of the three phenotypes. A follow-up study on genotype indicated that approximately 10% of the Swedish population lacked the glutathione transferase isoenzyme (Warholm et al. 1995). This 10% number is considerably smaller than a previously proposed proportion of nonconjugators of 30-40% reported for a German population (Peter et al. 1989a). A different study by Kempkes et al. (1996) found a frequency of 15% for nonconjugators in a German cohort of 40 people. Whether this lack of activity poses an increased risk of developing disease such as cancer is not known. Warholm et al. (1995) suggest that additional ethnic groups be evaluated for percentage of non-conjugators.

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 2-3 was proposed (Kornbrust and Bus 1983). According to the proposed pathways, chloromethane 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, 1983b; Redford-Ellis and Gowenlock 1971a,

Figure 2-3. Proposed Scheme for the Metabolism of Chloromethane



*Indicates the position of the radioactive label

Source: Kornbrust and Bus 1983

1971b). These compounds can be excreted in the urine (Landry et al. 1983a), or S-methylglutathione may be further metabolized to methanethiol. Cytochrome P-450 dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms are then available to the one-carbon pool for incorporation into macromolecules or for formation of CO_2 (Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983; Kornbrust et al. 1982). 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 (Kornbrust and Bus 1983, 1984; Jager et al. 1988). Dekant et al. (1995) demonstrated oxidation of chloromethane to formaldehyde by cytochrome P-450 (2El) in male mouse kidney microsomes, and that the amount of formaldehyde formed was dependent upon the hormonal status of the animal. Female mouse kidney microsomes produced considerably less formaldehyde than male kidney microsomes. Liver microsomal activity from both sexes was 2-fold higher than in kidney microsomes from the male. In contrast, rat kidney microsomes did not catalyze formaldehyde formation from chloromethane.

Peter et al. (1989a) assayed erythrocyte cytoplasm of a variety of test animals with chloromethane and monitored the decline of chloromethane and the production of S-methylglutathione. Rats, mice, bovine, pigs, sheep, and rhesus monkeys showed no conversion of chloromethane in erythrocyte cytoplasm.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Very little unchanged chloromethane is excreted in the urine. In volunteers exposed to chloromethane, Stewart et al. (1980) found no chloromethane in the urine, 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). Based upon data presented in the report, the half-life for the β-phase was estimated at 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 1,000 ppm, blood levels rose rapidly and reached equilibrium 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 a-phase were 4 minutes in rats, and 8 minutes 'in 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 cysteine conjugate by one-carbon metabolic pathways leads to incorporation of the carbon atom into macromolecules, and the production of carbon dioxide.

2.3.4.2 Oral Exposure

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

2.3.4.3 Dermal Exposure

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

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

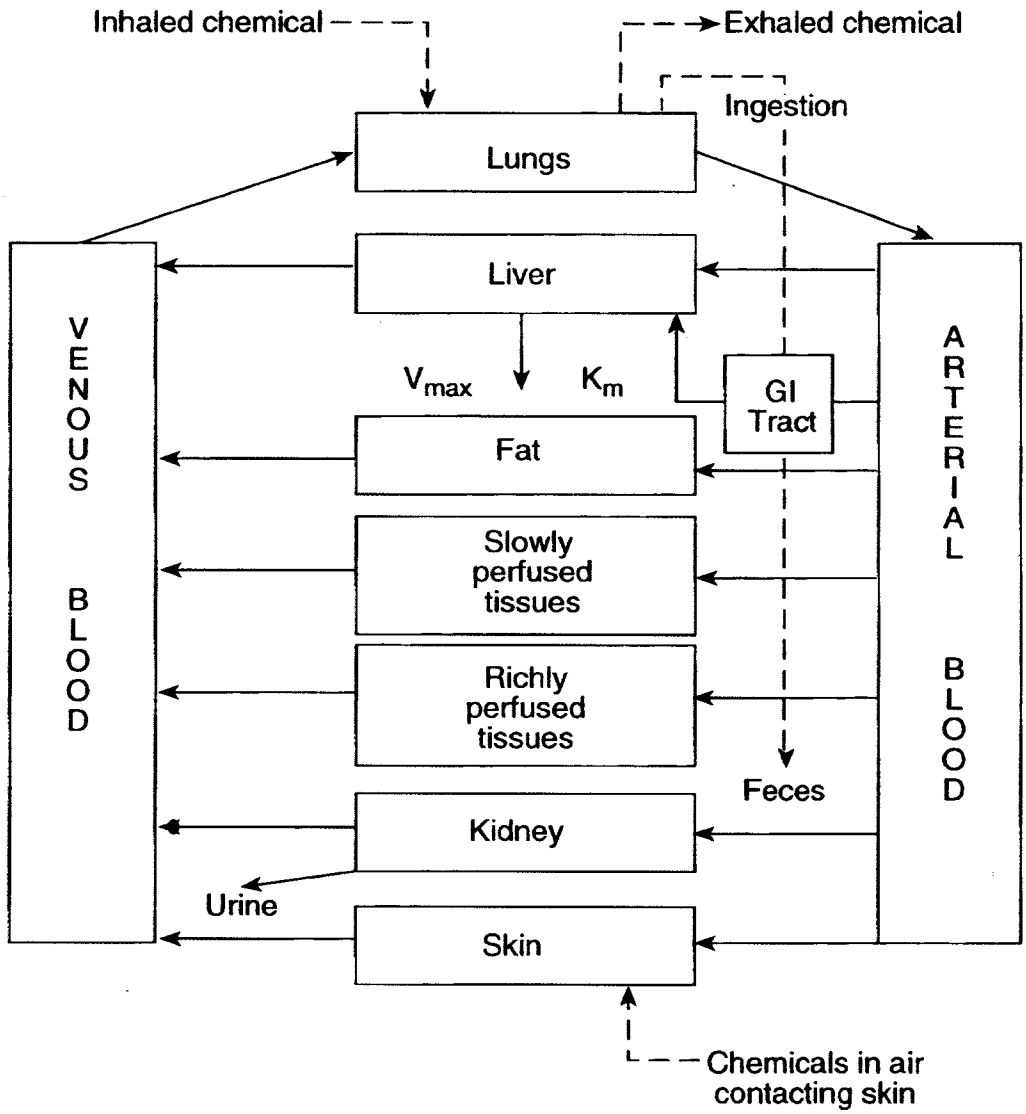
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

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

No PBPK models for adults, children, or test animal models were located for chloromethane.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

As presented in Section 2.3.3, metabolism of chloromethane 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, 1983b; Redford-Ellis and Gowenlock 1971a, 1971b). 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 can then enter the one-carbon pool for incorporation into macromolecules or formation of CO_2 (Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983). Guengerich and Shimada (1991) suggest that the human cytochrome P-450 enzyme 2El is a major catalyst in the oxidation of chloromethane. Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination. Methanethiol and formaldehyde, and lipid peroxidation due to glutathione depletion have been suggested as the toxic intermediates and mechanism responsible for the toxicity of chloromethane (Dekant et al. 1995; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Ristau et al. 1989, 1990). There is no information available on differences in isoforms or levels of glutathione transferase or P-450 in children that would result in significantly different metabolic rates (i.e., increased or decreased susceptibility to chloromethane toxicity) than those observed in adults.

2.4.2 Mechanisms of Toxicity

Hepatic effects: While the exact mechanism for the hepatotoxic effects of chloromethane is unclear, chloromethane can elicit lipid peroxidation as a secondary consequence of glutathione depletion (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. Further evidence that the mechanism of

hepatotoxicity may involve lipid peroxidation comes from the finding that mice exposed to 2,500 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.

Dodd et al. (1982) examined the effects of an inhalation exposure to chloromethane on tissue nonprotein sulfhydryl (NPSH) content in male Fischer 344 rats. NPSH content of liver, kidney, and lung were decreased in a chloromethane concentration-related manner. Pretreatment with Aroclor 1254 (an inducer of microsomal enzymes) did not alter the decreases in tissue NPSH seen after exposure to chloromethane alone. Pretreatment with SKF-525A (an inhibitor of microsomal enzymes) may have interfered with the ability of chloromethane to decrease NPSH in some tissues. Treatment with chloromethane significantly increased the activity of glutathione-S-alkyltransferase, and pretreatment with Aroclor 1254 did not alter the increase. The toxicological significance of this effect is not clear. These results support the hypothesis that chloromethane reacts enzymatically with glutathione (GSH), which is the most abundant NPSH, and the hypothesis that the reaction is not dependent upon the formation of a reactive intermediate by microsomal enzymes. Possible mechanisms for the toxicity of chloromethane related to glutathione depletion include: enhancement of the toxicity of chemicals that are detoxified via conjugation with GSH; prevention of GSH from acting as a cellular reducing agent, thereby interfering with a variety of physiological functions; or an increase in chloromethane-glutathione conjugates that are then further metabolized to putative toxic metabolite (e.g., formaldehyde or methanethiol).

Neurological effects: Chellman et al. (1986b) investigated the role of glutathione in the mediation of chloromethane-induced toxicity in the brain of male $B6C3F_1$ mice. Mice exposed to 1,500 ppm chloromethane for 6 hours/day, 5 days/week for 2 weeks, developed multiple degenerative, necrotic foci in the internal granule cell layer of the cerebellum; in some areas the foci involved the whole thickness of the granular cell layer. Cerebellar degeneration consisted of granule cells with pyknotic nuclei and clear, swollen perikarya. Tremors, ataxia, and forelimb/hindlimb paralysis were seen in chloromethane-induced lethality and were associated with chloromethane-induced cerebellar damage. Cerebellar damage was not observed in chloromethane-exposed mice pretreated with BSO, a glutathione depleter. The authors concluded that the depletion of GSH protected mice from cerebellar damage due to exposure to chloromethane. The mechanism may involve conjugation of chloromethane with glutathione in the liver, followed by biliary excretion and enterohepatic circulation of the glutathione conjugate or possibly a cysteine conjugate and further metabolism by kidney and/or gut flora beta-lyase to methanethiol.

Methanethiol produces similar central nervous system symptoms (tremors, convulsion, coma) as seen in animals or humans acutely intoxicated with chloromethane (Chellman et al. 1986b).

In the metabolic scheme proposed by Kornbrust and Bus (1983), chloromethane reacts with glutathione to form S-methylglutathione. Subsequent metabolism of S-methylglutathione produces methanethiol as an intermediate. Jiang et al. (1985) discuss the possibility of a relationship between degenerative effects in the kidney and granular layer lesions in the brain, which were also observed in mice. Granular cell necrosis is often seen in people who die of renal insufficiency (i.e., not due to chloromethane exposure). In the Jiang et al. (1985) mouse study, however, the severity of the brain and kidney lesions were unrelated, and the authors conclude that the brain lesions were probably not a direct consequence of the chloromethaneinduced kidney lesions.

Reproductive effects: Studies on the mechanism of chloromethane-induced testicular effects suggest that preimplantation loss is due to chloromethane cytotoxicity to the sperm in the testes at the time of exposure rather than genotoxic effects on the sperm (Chellman et al. 1986a, 1986c, 1987; Working and Bus 1986; Working and Chellman 1989; Working et al. 1985a, 1985b). Working et al. (1985a) previously had provided results indicating that chloromethane-induced postimplantation loss results from an inflammatory response in the epididymis that indirectly produces genetic damage to the sperm rather than from a direct genotoxic effect of chloromethane. Inhibition of the chloromethane-induced epididymal inflammatory response with anti-inflammatory agent BW755C (Chellman et al. 1986c) was subsequently shown to reduce the amount of postimplantation loss (Chellman et al. 1986c).

Genotoxicity: Chloromethane exposure consistently produced dominant lethal mutations in the sperm of rats, as measured by postimplantation loss in females mated to exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Because of the known transit times for sperm in the epididymis and the resulting observed times of the postimplantation losses, Working et al. (1985a) observed that the timing of the genetic damage to the sperm coincided with their location in the chloromethane induced inflammation of the epididymis. Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, greatly reduced the amount of postimplantation loss, the dominant lethal mutations probably resulted secondary to the epididymal inflammatory response (Chellman et al. 1986c; Working and Chellman 1989). The activation of phagocytic cells during the inflammatory process may result in the production of potentially genotoxic chemical species including the superoxide anion radical,

hydrogen peroxide, and lipid peroxide decomposition products (Fridovich 1978; Goldstein et al. 1979, 1981; Working et al. 1985a).

Renal tumors: Some proposed mechanisms for the carcinogenic effect (renal tumors) detected in male mice include glutathione depletion in the target tissue, increased lipid peroxidation, and formation of formaldehyde-induced DNA lesions (Bolt and Ganswendt 1993). Chloromethane can be metabolized to formaldehyde (Kornbrust and Bus 1982). Exposure to 1,000 ppm chloromethane depletes glutathione in the kidney to ≈5% of the pre-exposure levels (Bolt et al. 1986; Hallier et al. 1990), effectively removing the cofactor for the glutathione-dependent primary metabolic pathway for chloromethane. The alternate oxidative pathway leads directly to the formation of formaldehyde via cytochrome P-450. Jager et al. (1988) have shown that the formation of formaldehyde (via P-450 activity) was 10 times higher in male mouse liver than in male kidney. Male mouse liver also produced formaldehyde at about two times the amount of female liver, and male kidney about 50% more than female kidney. This led to the hypothesis that male mice tumors resulted from increased production of formaldehyde and increased numbers of formaldehyde-induced DNA lesions. Glutathione depletion also removes the cofactor for formaldehyde dehydrogenase (FDH), the enzyme that inactivates formaldehyde. Jager et al. (1988), however, did not observe increased formaldehyde levels in mouse liver or kidney after a single, 8-hour exposure to 1,000 ppm chloromethane, or an increase in DNA protein cross links (DPC), a typical formaldehydeinduced lesion, after exposure to 1,000 ppm for 6 hours per day for 4 days. Ristau et al. (1989), however, did observe an increase in DPC in the renal tissue of male but not female mice. In a follow-up study, Ristau et al. (1990) showed a rapid removal of DPC whereas single strand breaks appeared to accumulate. Both types of lesions were ascribed to the action of formaldehyde. Ristau et al. (1989) assayed for DPC immediately after a single 8-hour exposure, whereas Jager et al. (1988) dosed over a 4-day period. Delays from exposure to assay that allow rapid repair of formaldehyde-induced DPCs could possibly explain why Jager et al. (1988) did not observe an increase. Both the DPCs and the incomplete and delayed repair of chloromethane-induced DNA lesions may contribute to the formation of renal tumors. Morgan et al. (1982) also noted a proliferative response in male and female mouse proximal tubules following exposure to 1,000 ppm of chloromethane. This proliferative response could also contribute to the tumorigenicity of chloromethane in the males.

2.4.3 Animal-to-Human Extrapolations

Acute and chronic inhalation studies indicate that mice are more sensitive than rats to the lethal effects of chloromethane (Chellman et al. 1986a, 1986b; CIIT 1981). The greater susceptibility of mice may be due to different metabolic rates involving glutathione or different oxidative rates for the production of formaldehyde. Chloromethane conjugates with glutathione to much greater extent in mouse liver, kidney, and brain compared with rats (Kornbrust and Bus 1984). Pretreatment of mice with buthionine-S,R-sulfoxime (BSO), a glutathione depleter, protected mice from the chloromethane-induced lethal effects (Chellman et al. 1986b). Thus, the reaction of chloromethane with glutathione to produce S-methylglutathione appears to be a toxifying rather than a detoxifying reaction (Chellman et al. 1986b).
Alternatively, chloromethane can elicit lipid peroxidation as a consequence of depletion of glutathione (Kornbrust and Bus 1984).

In humans, S-methylcysteine appears as a metabolite of chloromethane (see Section 2.3.3), so conjugation with glutathione probably also occurs in humans.

Different P-450 activities between species, sexes, and tissues within the body (i.e., liver versus kidney) affect the dehalogenation of chloromethane to formaldehyde, and can thus influence the level of formaldehyde-induced DNA or tissue damage (Dekant et al. 1995; Jager et al. 1988; Ristau et al. 1989, 1990).

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Information regarding health effects of chloromethane in humans and animals is available primarily 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 rapidly moves from water or soil to the air (see Chapter 5). Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

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 target organs for chloromethane toxicity in humans and animals from acute or longer-term exposure. Toxic manifestations seen in humans, but generally not in animals, include cardiovascular and gastrointestinal effects. These may be secondary to the neurotoxicity. Effects that have been observed in animals, but not reported in humans, include epididymal occlusion, testicular atrophy, infertility, sterility in males, carcinogenicity (e.g., kidney tumors in male mice), and possibly developmental effects (e.g., heart defects) in mice.

Species differences in susceptibility to chloromethane toxicity have been observed. Different P-450 activities between species, sexes, and tissues within the body affect the dehalogenation of chloromethane to formaldehyde, and can thus influence the level of formaldehyde-induced DNA or tissue damage. Rates of conjugation with glutathione differ and lead to differing levels of toxic metabolites. In animal studies, mice have been shown to be more sensitive than rats to the lethal effects of chloromethane, probably due to the higher rate of formation of the toxic metabolite, S-methylglutathione. S-methylcysteine appears as a metabolite of chloromethane in humans, so conjugation with glutathione probably also occurs in humans. There is no information available on differences in isoforms or levels of glutathione transferase or P-450 in children that would result in significantly different metabolic rates (i.e., increased or decreased susceptibility to chloromethane toxicity) than those observed in adults.

Minimal Risk Levels for Chloromethane.

Inhalation MRLs.

- An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure (14 days or less) to chloromethane.

An acute MRL of 0.5 ppm was derived from a NOAEL of 50 ppm for no effect on motor coordination or damage to the cerebellar granule cells in a study by Landry et al. (1985). This study evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice. The results support a good dose-response effect for cerebellar damage and motor incoordination. The NOAEL of 50 ppm was converted to a human equivalent dose by multiplying with the ratio of the blood:gas (air) partition coefficient for the mouse to the human value. The default value of 1.0 was used because the

coefficients are not known (see formula 4-48a, EPA 1994b). The resulting $NOAEL_{[HEC]}$ of 50 ppm was then divided by an uncertainty factor of 100 (10 for interspecies variability and 10 for human variability). The obtained MRL value is 0.5 ppm (see Appendix A).

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; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Raalte and van Velzen 1945; Rafnsson and Gudmundsson 1997; 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. In some cases, mild to permanent neurological and/or psychiatric deficits have been reported 13 years after an acute high level exposure (Gudmundsson 1977).

Severe neurological signs (ataxia, tremors, limb paralysis, incoordination, convulsions) have also 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, 1986b; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice are more susceptible than rats (CIIT 1981; Morgan et al. 1982), and 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 makes the mouse a good model for the neurotoxicological effects seen in humans.

- An MRL of 0.2 ppm has been derived for intermediate-duration inhalation exposure (15 to 364 days) to chloromethane.

An intermediate MRL of 0.2 ppm was derived from a LOAEL of 51 ppm for significantly increased serum alanine amino transferase levels (indicative of hepatotoxicity) in male mice at the 6 month time point in a 2-year study (377 I.U./L ± 124 versus 170 ±49 in controls). This LOAEL is a minimal LOAEL because no histopathological lesions were observed in the low- or mid-dose levels, but were observed at the high dose level. The objective of the study was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and $B6C3F_1$ mice. The dose-response effect for liver toxicity was observed in male mice. Females also had increased ALT, but the increase was not associated

with treatment-related histopathological changes in the liver. Liver necrosis and other pathological changes in the liver of high dose male mice was also observed at 12, 18, and 24 months. No further adjustments in the LOAEL were made for a continuous exposure, and the comparable $LOAEL_{[ADJ]}$ of 51 ppm was then converted to a human equivalent dose by multiplying with the ratio of the blood:gas (air) partition coefficient for the mouse to the human value. The default value of 1.0 was used because the coefficients are not known (see formula 4-48a, EPA 1994b). The resulting $LOAEL_{[HEC]}$ of 51 ppm was then divided by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for interspecies variability, and 10 for human variability) and rounded to one significant figure. The obtained MRL value is 0.2 ppm (see Appendix A).

Case reports of humans exposed to chloromethane vapors have described clinical jaundice and cirrhosis of the liver (Kegel et al. 1929; Ma&e 1961; Weinstein 1937; Wood 1951), but exposure concentrations were not known.

Hepatic effects have been observed in animals exposed by inhalation to chloromethane at concentrations > 1,000 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 ALT and AST with no necrosis). Furthermore, no hepatic lesions were observed in rats over the course of 2 years of inhalation exposure to 1,000 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 toxifying rather than detoxifying (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 (Kombrust 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 finding that mice exposed to 2,500 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.

- An MRL of 0.05 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to chloromethane.

A chronic MRL of 0.05 ppm was derived from a LOAEL of 51 ppm for axonal swelling and degeneration . of axons of the spinal cord in mice after 18 months of exposure (CIIT 1981). This two year study evaluated the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and $B6C3F_1$ mice. There was a consistent dose-response for neurological effects in male and female mice. At the high dose, there was a mild reduction in the number of neurons in the granular cell layer of the cerebellum with decreased width of the granular cell layer. In the high, mid, and low dose groups, axonal swelling and degeneration of minimal severity was observed in the spinal nerves and the cauda equina associated with the lumbar spinal cord. The LOAEL was converted to a human equivalent dose by multiplying the LOAEL with the ratio of the blood:gas (air) partition coefficient for the mouse to the human value. The default value of 1.0 was used because the coefficients are not known (see formula 4-48a, EPA 1994b). The resulting $LOAEL_{[HEC]}$ of 5.1 ppm was then divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for interspecies variability, and 10 for human variability) and rounded to one significant figure. The obtained MRL value is 0.05 ppm (see Appendix A).

As with support for the acute MRL, neurological effects have been described in numerous case reports of humans exposed to chloromethane vapors (Baird 1954; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; MacDonald 1964; McNally 1946; Raalte and van Velzen 1945; Rafnsson and Gudmundsson 1997; Spevak et al. 1976; Wood 1951). Signs and symptoms can range from staggering and blurred vision to coma, convulsions, and death. Severe neurological signs (ataxia, tremors, limb paralysis, incoordination, convulsions) have also 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, 1986b; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982).

Oral MRLs.

No acute, intermediate, or chronic-duration oral MRLs were derived for chloromethane because of lack of appropriate data on effects of oral exposure to chloromethane.

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 19.54; Borovska et al. 1976; Gudmundsson 1977; 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, result in neurological effects (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 containing chloromethane 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, 1986b; 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 is 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-methyl-glutathione 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-methyl-glutathione 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 (Kombrust 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 in humans.

Systemic Effects.

Respiratory Effects. Case reports generally have not described respiratory effects in humans exposed to chloromethane.

In dogs acutely exposed to lethal concentrations there was a marked reduced in respiration prior to death, but this effect was probably secondary to central nervous system depression (von Oettingen et al. 1949, 1950). Pulmonary congestion prior to death was a common finding among a variety of species (rats, mice, guinea pigs, rabbits, dogs, cats, and monkeys), but the study limitations precluded the determination of a good dose-response relationship (Dunn and Smith 1947; Smith and von Oettingen 1947a). More recent studies failed to find exposure-related histopathological lesions in the lungs of dogs and cats exposed acutely to 500 ppm chloromethane (McKenna et al. 198 la), rats exposed acutely to 2,000 ppm (Burek et al. 198 l), male dogs exposed to 400 ppm, and rats and mice exposed to up to 1,500 ppm chloromethane for intermediate durations (CIIT 1981; McKenna et al. 198 lb; Mitchell et al. 1979), or rats and mice exposed chronically to up to 1,000 ppm (CIIT 1981).

Cardiovascular 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; 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.

Rafnsson and Gudmundsson (1997) report a clear excess mortality from cardiovascular disease (Mantel-Haenszel point estimate=2.1, 95%; CI=1.2-3.8) in crew members (males) exposed for 2 days to chloromethane that leaked from a refrigerator on board an Icelandic fishing trawler (no estimates of exposure levels were reported). This excess was more prominent among deckhands who had received the highest exposure to chloromethane. The Risk ratios were elevated for all causes of death (RR=2.5, 95%; CI=l.0-5.7) as well as for cardiovascular disease (RR=3.9, 95%; CI=l.0-14.4). The study is weakened by an assumption of comparable lifestyle factors (including smoking habits and diet) between the cohort and the

reference group and by the relatively small size of the exposed cohort. The authors also do not discuss the potential influence of the documented neurological deficits in this cohort (Gudmundsson 1977) on cardiovascular function. The authors suggest, however, that additional study on chloromethane's potential cardiovascular toxicity is warranted.

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.

Gastrointestinal Effects. Numerous case reports of humans exposed to chloromethane 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; 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.

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, 1981b).

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.

No long-term effect on the hematological system from an acute exposure was reported by Gudmundsson (1977). Seventeen crew members (males) were exposed for 2 days in 1963 to chloromethane that leaked from a refrigerator under the crew sleeping quarters on board an Icelandic fishing trawler (no estimates of exposure levels were reported). Thirteen years later (i.e., in 1976) 10 of the 11 survivors were examined. All 10 were employed; 8 were employed at sea. The mean age of the 10 survivors examined was 38.3 years

(range 30-50 years). All 10 survivors had normal hemoglobin, white cell count, differential leukocyte count, erthrocyte sedimentation rate, and serum creatinine.

No studies were located regarding the hematological effects of chloromethane in humans following oral or dermal exposures.

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.

Musculoskeletd Effects. No studies were located regarding the musculoskeletal effects of chloromethane in humans or animals following inhalation, oral, or dermal exposures.

Hepatic Effects. 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 > 1,000 ppm in acute, intermediate, and chronic duration experiments (Burek et al. 1981; Chellman et al. 1986a; CIIT 1981; Landry et al. 198.5; 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 ALT and AST with no necrosis). Furthermore, no hepatic lesions were observed in rats over the course of 2 years of inhalation exposure to 1,000 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 ratherthan 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 finding that mice exposed to 2,500 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.

Endocrine Effects. No studies were located regarding the endocrine effects of chloromethane in humans following inhalation, oral, or dermal exposures.

Only one animal study reported fatty droplets in the epithelial cells of the zona fasciculata in the adrenals of Fischer 344 rats acutely exposed to 3,500 and 5,000 ppm chloromethane; the severity of the lesion increasing with dose (Morgan et al. 1982). Rats were exposed for 5 days, 6 hours/day with a break in exposure for 2 days, and then a further 4 days of exposure.

Renal Effects. 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 1,000 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) (Chellman et al. 1986a; Morgan et al. 1982). 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 may not involve glutathione-related peroxidase activity (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.

Dermal Effects. No studies were located regarding the dermal effects of chloromethane in humans or animals following inhalation, oral, or dermal exposures.

Ocular Effects. No studies were located regarding the dermal effects of chloromethane in humans following inhalation, oral, or dermal exposures.

Ophthalmological examination of male cats and dogs exposed to 500 ppm continuously for 3 days (McKenna et al. 1981a), dogs exposed to 400 ppm for 90 days (McKenna et al. 1981b), or of rats and mice exposed to 1,000 ppm for up to 24 months (CIIT 1981) failed to reveal eye lesions. 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. The effect was probably due to direct contact of the chloromethane vapor with the eye, rather than a consequence of inhalation.

Body Weight Effects. No studies were located regarding the body weight effects of chloromethane in humans or animals following inhalation, oral, or dermal exposure to chloromethane.

Metabolic Effects. No studies were located regarding the metabolic effects of chloromethane in humans or animals following inhalation, oral, or dermal exposures.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological and/or lymphoreticular effects in humans after inhalation exposure to chloromethane.

The only effects 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; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; 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 years (Gudmundsson 1977), but complete recovery may eventually occur. In cases in which exposure was quantitated, concentrations were generally >29,000 ppm (Battigelli and Perini 1955; 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 couple's home was an order of magnitude lower than the typical rate. In addition, a small statistically nonsignificant 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, 1986b; 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 (CIIT 1981; Morgan et al. 1982), 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 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.

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

Acute-, intermediate-, and chronic-duration 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, decreased fertility at about 500 ppm, and sterility at higher concentrations of 1,000 or 3,000 ppm (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986b, 1987; CIIT 1981; Han-m et al. 1985; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b). 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, 1986c, 1987; Working and Bus 1986; Working et al. 1985a, 1985b).

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.

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

Maternal toxicity, evidenced by decreased body weight gain and retarded development of fetuses, was observed in rats exposed to 1,500 ppm chloromethane for 6 hours per day during gestational days (Gd) 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 hindlimbs. These researchers also reported increased incidences of heart malformations in the fetuses of mouse dams exposed by inhalation to 500 ppm chloromethane during Gd 6-17. The heart malformations consisted of absence or reduction of atrioventricular valves, chordae tendineae, and papillary muscles. Heart malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during Gd 11.5-12.5, which they considered to be the critical period for development of the embryonal heart (John-Greene et al.

1985). John-Greene et al. (1985) suggested that the heart anomaly reported by Wolkowski-Tyl et al. (1983) may have been an artifact of the sectioning technique, due to the examination of the fixed as opposed to unfixed fetal tissue, or a misdiagnosis. They also found much inter-animal variability in the appearance of the papillary muscles in control mice. However, Wolkowski-Tyl(1 985) 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. The developmental toxicity of chloromethane in mice is, therefore, controversial; it is not known whether chloromethane could produce developmental effects in humans.

The investigators also found increased incidences of heart malformations in the fetuses of mouse dams exposed by inhalation to 500 ppm chloromethane during Gd 6-17. Heart malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during Gd 11.5-12.5, which they 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.

Genotoxic Effects. Chloromethane has been tested for genotoxicity in a number of *in vitro* and *in vivo* systems (Tables 2-4 and 2-5). 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); and appears to be a direct-acting genotoxicant *in vitro.* The ability of inflammatory cells (human phagocytes) to produce superoxides capable of genetic damage has been demonstrated (Weitzman and Stossel 1981). 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.

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 postimplantation loss, it was suggested that the dominant lethal

Table 2-4. Genotoxicity of Chloromethane *In Vivo*

Species (test system)	End point	Results	Reference
Rat (inhalation)	Dominant lethal	+	Working et al. 1985a
Rat (inhalation)	Dominant lethal	+	Chellman et al. 1986c
Rat (inhalation)	Dominant lethal	+	Rushbrook 1984
Rat (inhalation)			
hepatocytes	Unscheduled DNA synthesis	(+)	Working et al. 1986
spermatocytes	Unscheduled DNA synthesis	–	Working et al. 1986
tracheal epithelial cells	Unscheduled DNA synthesis	(+/–)	Working et al. 1986

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

Table 2-5. Genotoxicity of Chloromethane *In Vitro*

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

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

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). 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 and carcinogenicity (see Section 2.2.1.8) may be secondary to other toxic effects of chloromethane. Nevertheless, the *in vitro* studies demonstrate the direct genotoxicity of chloromethane.

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).

Cancer. The information regarding carcinogenicity in humans after exposure to chloromethane is limited. An epidemiology study on a cohort of 24 Icelandic fishermen reported a slight increase in excess mortality from all cancers, and more specifically, lung cancer (Rafnsson and Gudmundsson 1997). The study was conducted 32 years after an acute (i.e., 2 days) high level exposure to chloromethane from a leaking refrigerator. Confounding factors for lifestyle and smoking were not explicitly controlled in this study, but assumed to be similar based on controls for age, social class, and occupation. One epidemiology study of butyl rubber workers chronically exposed to chloromethane reported no statistically significant increase in the rate of death due to cancer (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 1,000 ppm-exposed $B6C3F_1$ male mice. Renal hyperplasia was also observed after 12 months of exposure. In an acute study, Chellman et al. (1986b) found significant increases in cell proliferation in the kidneys of male $B6C3F_1$ mice, as measured by incorporation of tritiated thymidine into DNA of the kidneys. 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 (Korubrust et al. 1982; Peter et al. 1985). Female $B6C3F_1$ mice exposed to 1,500 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 those 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 $B6C3F_1$ males than in females of the same strain exposed to 500 and 1,000 ppm chloromethane for 12 days (Morgan et al. 1982). In mice exposed to 2,000 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.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of

their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

In adults, there appear to be two distinct populations with regard to metabolism and elimination of chloromethane. One population has higher amounts of the metabolizing enzyme, glutathione-S-transferase, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with glutathione (Chellman et al. 1986b; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Nolan et al. 1985; Stewart et al. 1980; Warholm et al. 1995). It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis. If a polymorphism is present in children, then some children (i.e., those with higher levels of glutathione-S-transferase) would be more susceptible to the toxic effects of chloromethane.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

There have been no human studies to determine the health effects of exposure to chloromethane in children, or whether children are more or less susceptible to the potential health effects of chloromethane at a given exposure level and duration of exposure. There is no information on whether the effects in children would be similar to those in adults for either accidental short-term exposures or longer-term lower level exposures. It is not known whether chloromethane affects the developing fetus or the development of young children.

There have also been no studies where young animals were exposed to chloromethane. With mid- to high levels of chloromethane administered to female adult rats and mice during pregnancy, the offspring were smaller than normal, with underdeveloped bones, and possibly abnormal hearts (although this latter effect remains uncertain and occoured only in mice).

It is not known whether chloromethane or methanethiol in the body can cross the placenta and enter into the developing young, or if either compound can enter into breast milk. We do know that chloromethane is broken down and eliminated from the body very quickly in adults (Nolan et al. 1985) and animals (Landry et al. 1983a; von Oettingen et al. 1949, 1950). Thus, it is unlikely that chloromethane would be stored in maternal tissues or be mobilized (i.e., released from stores) during pregnancy or lactation.

In adults, there appear to be two distinct populations with regard to metabolism and elimination of chloromethane. One population appears to have higher amounts of the metabolizing enzyme, glutathione-S-transferase, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with glutathione (Chelhnan et al. 1986b; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Nolan et al. 1985; Stewart et al. 1980; Warholm et al. 1995). It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis. If a polymorphism is present in children, then some children (i.e., those with higher levels of glutathione-S-transferase) would be more susceptible to the toxic effects of chloromethane.

Although the breakdown and elimination of chloromethane is expected to be the same in children as in adults, more studies are needed to answer this and other questions concerning the movement of chloromethane into the fetus or breast milk, and what levels might result in harmful effects. There are no PBPK models for children, adults, or test animal models. There are no good biomarkers of exposure for children (or adults), although clinical symptoms of drunkenness or food poisoning, and a sweet odor of the breath may alert a physician. Attempts to use urinary levels of S-methylcysteine as an indicator of chloromethane exposure have not been successful.

Only limited information is available from animal studies on potential effects in the developing young. In one animal study, pregnant rats were exposed to 1,500 ppm chloromethane by inhalation during gestation. Maternal toxicity, evidenced by decreased body weight gain and retarded development of fetuses, was observed in rats exposed to 1,500 ppm chloromethane for 6 hours per day during gestational days (Gd) 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 hindlimbs.

In a mouse study, dams were exposed by inhalation to chloromethane during gestation days 6-17 (Wolkowski-Tyl et al. 1983a). The investigators found increased incidences of heart malformations in the fetuses of mouse dams exposed to 500 ppm chloromethane during Gd 6-17. The heart malformations consisted of absence or reduction of atrioventricular valves, chordae tendineae, and papillary muscles. Heart malformations, however, were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during Gd 11 S-12.5, which they considered to be the critical period for development of the embryonal heart (John-Greene et al. 1985). John-Greene et al. (1985) suggested that the heart anomaly reported by Wolkowski-Tyl et al. (1983) may have been an artifact of the sectioning technique, due to the examination of the fixed as opposed to unfixed fetal tissue, or a misdiagnosis. They also found much inter-animal variability in the appearance of the papillary muscles in control mice. 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. The developmental toxicity of chloromethane in mice is, therefore, controversial; it is not known whether chloromethane could produce developmental effects in humans.

Acute-, intermediate-, and chronic-duration 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, decreased fertility at about 500 ppm, and sterility at higher concentrations of 1,000 or 3,000 ppm (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986b, 1987; CIIT 1981; Hamm et al. 1985; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b). 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, 1986c, 1987; Working and Bus 1986; Working et al. 1985a, 1985b).

Chloromethane exposure consistently produced dominant lethal mutations in the sperm of rats, as measured by postimplantation loss in females mated to exposed males (Chellman et al. 1986c; Rushbrook 1984; Working et al. 1985a). Because of the known transit times for sperm in the epididymis and the resulting observed times of the postimplantation losses, Working et al. (1985a) observed that the timing of the genetic damage to the sperm coincided with their location in the chloromethane-induced inflammation of the

epididymis. Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, greatly reduced the amount of postimplantation loss, the dominant lethal mutations probably resulted secondary to the epididymal inflammatory response (Chellman et al. 1986c; Working and Chellman 1989). The activation of phagocytic cells during the inflammatory process may result in the production of potentially genotoxic chemical species including the superoxide anion radical, hydrogen peroxide, and lipid peroxide decomposition products (Fridovich 1978; Goldstein et al. 1979, 1981; Working et al. 1985a).

Chloromethane has been tested for genotoxicity in a number of *in vitro* and *in vivo* systems (see Tables 2-4 and 2-5). 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); and appears to be a direct-acting genotoxicant *in vitro*. The ability of inflammatory cells (human phagocytes) to produce superoxides capable of genetic damage has been demonstrated (Weitzman and Stossel 1981). 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. No information was available on the distribution of chloromethane or metabolites to parental reproductive organs or germ cells in humans that could lead to genetic or epigenetic damage to germ cells. It is also not known whether chloromethane produces a sublethal level of genetic or epigenetic damage to sperm that would, in turn, be sufficiently viable to form an embryo and subsequently be detrimental (at clinical or subclinical levels) to the developing young.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic

compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time 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 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chloromethane are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 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 6 workers exposed to TWA g-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 6 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.

Xu et al. (1990) evaluated whether covalent binding of chloromethane to hemoglobin would be a viable measure for monitoring exposure. In comparison to the other monohalomethanes tested (methyl bromide and methyl iodide), chloromethane had the lowest reactivity with hemoglobin. The authors support further assay development for methyl bromide, but make no mention of the usefulness of a covalent binding assay for chloromethane, presumably because its reactivity was too low.

2.7.2 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). Although volunteers exposed to 200 ppm chloromethane for 3 hours had a 4% decrement in their performance on behavioral tests, blood and alveolar air levels of chloromethane were too variable to be of practical use (Putz-Anderson et al. 1981a). The decrement in performance was also small and not statistically significant.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.8 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.

Minami et al. (1992) report on a patient in Japan exposed simultaneously to chloromethane and chloramine gas. The exposure resulted from the patient first cleaning a porcelain toilet with sodium hypochlorite (NaOCl) in an alkaline solution then, without first rinsing off the hypochlorite, spraying a hydrochloric acid (HCl) solution to remove hard salt adhesions. The toilet was connected directly to a sewage storage tank. The resulting fumes produced a toxic response in the patient 30 minutes after cleaning. The patient recovered from the acidosis after bicarbonate transfusion, plasmapheresis, and plasma exchange; but permanent blindness ensued 3 days postexposure. In a follow-up study, Minami et al. (1993) demonstrated an increase in formate excretion in mice dosed with chloramine after exposure to chloromethane. The authors ascribe this increase to an inhibitory effect of chloramine on formyl tetrahydrofolate dehydrogenase and formaldehyde dehydrogenase. More recently, Wang and Minami (1996) extended their proposed mechanism to include a potentiation of formaldehyde on chloramine inhibition of acetycholinesterase activity.

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 depleter 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, 1986b). These studies are discussed in Section 2.2. It is unlikely that these compounds would be found with chloromethane at hazardous waste sites.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chloromethane than will most persons exposed to the same level of chloromethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of chloromethane, or compromised function of target organs affected by chloromethane. Populations who are at greater risk due to their unusually high exposure to chloromethane are discussed in Section 5.7, Populations With Potentially High Exposure.

In general, people who have kidney or liver disease, anemia, or neurological deficits may be more susceptible to the toxic effects of chloromethane.

Two distinct populations of humans with differences in elimination of chloromethane have been identified. Some of the 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 Doom 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 hypothesis 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 2.8, 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.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chloromethane. However, because some of the treatments discussed may be experimental and

unproven, this section should not be used as a guide for treatment of exposures to chloromethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to chloromethane:

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1994. *Goldfrank's Toxicologic Emergencies.* Fifth edition. Norwalk. CT: Appleton & Lange, 1231-1244.

Ellenhorn MJ, Barceloux DG. 1988. *Medical Toxicology: Diagnosis and Treatment of Human Poisoning.* New York, NY. Elsevier, 982-983.

ATSDR. 1994. Agency for Toxic Substances and Disease Registry. *Medical Management Guidelines for Acute Chemical Exposures: Formaldehyde.* Atlanta, GA.

2.10.1 Reducing Peak Absorption Following Exposure

Acute inhalation exposure to high levels of chloromethane primarily causes neurological effects with signs and symptoms that 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. Because chloromethane is so rapidly absorbed, metabolized, and distributed; treatment to reduce absorption would have to be administered promptly. No treatments, however, were located in the literature except the general indication of supportive treatment. This usually consists of ensuring open airways, adequate supply of fresh air, and establishing and monitoring proper cardiovascular function.

2.10.2 Reducing Body Burden

No information was located on reducing body burdens of absorbed chloromethane.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism(s) of chloromethane toxicity remains unclear, and thus it is uncertain whether depletion or protection of glutathione pools would be appropriate for any given exposure or target organ.

Methanethiol and formaldehyde formation, and increased lipid peroxidation due to glutathione depletion have been suggested as the toxic intermediates and mechanism responsible for the toxicity of chloromethane (Dekant et al. 1995; Jager et al. 1988; Kombrust and Bus 1983, 1984; Ristau et al. 1989, 1990).

Dodd et al. (1982) also proposed possible mechanisms for the toxicity of chloromethane related to glutathione depletion including enhancement of the toxicity of chemicals that are detoxified via conjugation with GSH; prevention of GSH from acting as a cellular reducing agent, thereby interfering with a variety of physiological functions; or an increase in chloromethane-glutathione conjugates that are then further metabolized to putative toxic metabolite (e.g., formaldehyde or methanethiol).

Chellman et al. (1986b), however, concluded that the depletion of GSH protected mice from cerebellar damage due to exposure to chloromethane. The mechanism may involve conjugation of chloromethane with glutathione in the liver, followed by biliary excretion and enterohepatic circulation of the glutathione conjugate or possibly a cysteine conjugate and further metabolism by kidney and/or gut flora beta-lyase to methanethiol. Methanethiol produces similar central nervous system symptoms (tremors, convulsion, coma) as seen in animals or humans acutely intoxicated with chloromethane (Chellman et al. 1986b).

There is only a limited amount of information available from animal studies on interfering with putative mechanism of chloromethane-induced toxicity. Interference with specific toxic events has been demonstrated for BW755C, an anti-inflammatory agent, and for BSO, a depleter of glutathione, when administered to rats or mice that have been exposed to chloromethane by inhalation (Chellman et al. 1986a, 1986b). BW755C protected rats from chloromethane-induced epididymal or testicular lesions, but did not alter chloromethane metabolism, tissue distribution, or excretion of ^{14}C-chloromethane, or decrease hepatic glutathione content. An alternate mechanism for BW755C's protective effects against testicular damage could be an inhibition of leukotriene and prostaglandin synthesis.

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 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.

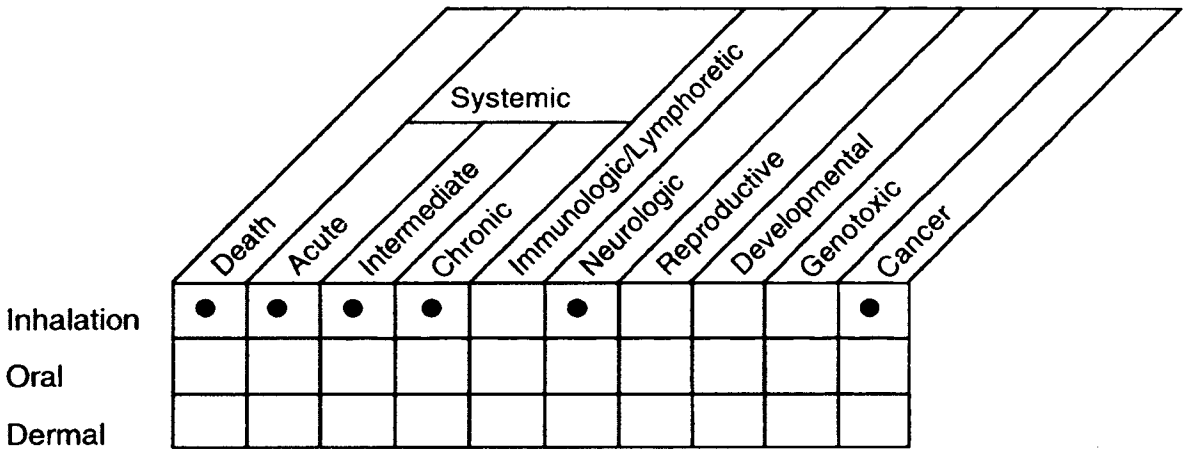
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.11.1 Existing Information on Health Effects of Chloromethane

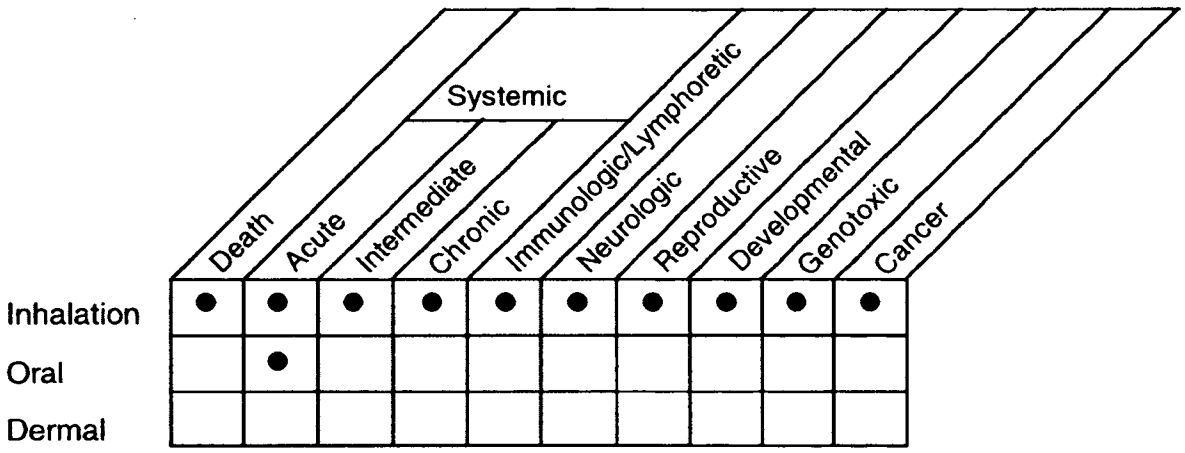
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chloromethane are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of chloromethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 2-5, information on the health effects in humans exposed to chloromethane is available only for inhalation or occupational exposures. Accidental leaks of chloromethane from refrigeration units or from occupational sources involves dermal as well as inhalation exposure; however, the primary exposure route during an accidental spill or leak is inhalation exposure. The organs or systems adversely affected in humans after exposure to chloromethane include the liver, kidney, neurological system (including behavioral alterations), and the cardiovascular and gastrointestinal systems (possibly secondary to the neurological effects). Death may occur at sufficiently high doses. Information on the adverse health effects of chloromethane has been presented for occupational exposures of acute, intermediate, and chronic duration. One epidemiological study found no association between exposure to chloromethane and cancer at any site. One epidemiological study found a slight excess of mortality from all cancers, and more specifically, from lung cancers, 32 years following an acute high level exposure to inhaled chloromethane. No information was available regarding immunological, developmental, reproductive, or genotoxic effects in humans exposed to chloromethane by any route.

Figure 2-5. Existing Information on Health Effects of Chloromethane



Human



Animal

● Existing Studies

There have been no studies to determine if children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane, or if chloromethane affects the developing fetus or the development of young children. There is no information on the potential movement of chloromethane or its metabolites across the placenta and into the developing young. We also do not know if chloromethane or its metabolites can migrate into breast milk.

A number of studies have evaluated the health effects of chloromethane exposure in animals 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 increased mortality, liver damage, kidney damage and tumors, neurological damage; and adverse reproductive, genotoxic and possibly developmental effects. In the only oral study in animals, an attempt was made to compare the hepatotoxicity of chloromethane with that of carbon tetrachloride and chloroform. The administered dose of chloromethane, however, was too low to produce hepatic effects, and the use of a higher dose was precluded due to neurotoxicity.

2.11.2 Identification of Data Needs

Chloromethane is highly volatile, and chloromethane in water or soil will likely evaporate to the air (Chapter 5). Given the volatility of chloromethane, inhalation exposures and toxicity are of primary concern and have been the most studied. The oral and dermal routes of exposure are also of concern because chloromethane is ubiquitous in the environment; yet, with the exception of a single-dose oral study (Reynolds and Yee 1967) and ocular effects from a presumptive dermal exposure in whole-body inhalation chambers (CIIT 1981; McKenna et al. 1981a, 1981b; Mitchell et al. 1979), 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, additional studies using oral and dermal routes of exposure are also needed.

Acute-Duration Exposure. Case reports of humans exposed acutely to high concentrations of chloromethane have described severe neurological effects, sometimes followed by death (Baird 1954; Battigelli and Perini 1955; Borovska et al. 1976; Gudmundsson 1977; Jones 1942; Kegel et al. 1929;

Lanham 1982; McNally 1946; Spevak et al. 1976; Thordarson et al. 1965). Effects on the cardiovascular system, liver, and kidney have also been described in case reports of humans exposed for brief periods, or occupationally for more prolonged periods (Gummert 1961; Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Rafnsson and Gudmundsson 1997; Schamweber et al. 1974; Spevak et al. 1976; Verriere and Vachez 1949). Only one epidemiology study addressed cancer following an acute exposure (Rafnsson and Gudmundsson 1997). The results indicate a slight elevation in death from all cancers, and a clear increase in deaths due to cardiovascular disease, but the usefulness of the study conclusions are limited due to assumptions about similar lifestyle factors between the exposed population and the reference group, including smoking and drinking habits.

Acute inhalation exposure levels of chloromethane causing death in animals are available for rats and mice (Burek et al. 1981; Chellman et al. 1986a, 1986b, 1987; Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982; Smith and von Oettingen 1947a, 1947b; von Oettingen et al. 1949, 1950; Wolkowski-Tyl et al. 1983a, 1983b). Numerous acute inhalation studies have identified the liver and kidney as target organs in rats and mice (Burek et al. 1981; Chapin et al. 1984; Chelhnan et al. 1986a; Jiang et al. 1985; Landry et al. 1985; Morgan et al. 1982); the spleen as a target organ in mice (Landry et al. 1985); the central nervous system as a target system in rats, mice, and dogs (Chellman et al. 1986a, 1986b; Jiang et al. 1985; McKenna et al. 1981a; Smith and von Oettingen 1947a, 1947b); and the testes and epididymides as target organs in rats (Chapin et al. 1984; Chellman et al. 1987; Morgan et al. 1982; Working et al. 1985b). The respiratory and cardiovascular systems may be targets in dogs (Dunn and Smith 1947; Smith 1947; Smith and von Oettingen 1947a, 1947b; von Oettingen et al. 1949, 1950). These studies have shown that species differ in susceptibility, and that lower levels are needed when administered continuously to produce toxicity compared with the higher levels needed in intermittent exposures. Some information on the mechanism of hepatic, renal, neurological, and reproductive effects in mice is available, but more is needed.

The data for acute effects 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 reported, and this was not sufficient to derive an MRL. 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.

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

Pharmacolcinetic data are insufficient to identify target organs of chloromethane after oral and dermal exposure and more studies are needed. As discussed above, the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, however, chloromethane is ubiquitous in the environment. Therefore, acute studies in animals exposed by oral or dermal routes are needed to identify target organs and dose-response relationships for these routes.

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 conducted in rats, mice, and dogs have identified the liver as a target organ in rats and mice (CIIT 1981; Mitchell et al. 1979; Smith and von Oettingen 1947a); the testes as a target organ in rats (CIIT 1981; Hamm et al. 198.5); and the kidney, spleen, and central nervous system as targets in mice (CIIT 1981). 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. Intermediate-duration studies in animals exposed by oral or dermal routes are needed to identify target organs and dose-response relationships for these routes.

Chronic Duration Exposure and Cancer. Only one study was located regarding effects of chloromethane in humans after chronic inhalation exposure. No studies were located for other routes.

A 2-year inhalation study in animals has been conducted in which both sexes of rats and mice were exposed to several concentrations of chloromethane (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 animals after chronic oral or dermal exposure to chloromethane. Pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. 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 are needed to identify target organs and dose-response relationships for these routes.

The carcinogenic effects of chloromethane were observed in male, but not female mice nor in rats of either sex. Male mice had 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, the further metabolism of the glutathione conjugate, and body weight effects make it probable that mice received a higher internal dose than rats. It is possible, therefore, that the exposure concentration was not sufficient in rats to produce kidney tumors. Additional chronic inhalation studies are needed to provide more information on differences in species susceptibility and to further evaluate the potential for and the mechanisms of chronic and carcinogenic effects of chloromethane in humans.

Genotoxicity. Chloromethane has been shown to be genotoxic (Chellman et al. 1986c; Ristau et al. 1990; Rushbrook 1984; Working et al. 1985a). DNA strand breaks have been evaluated in human lymphoblasts (Fostel et al. 1985). Genotoxic effects have also been evaluated for mutations in *S. typhimurium* (Andrews et al. 1976; DuPont 1977; Simmon et al. 1977), sister-chromatid exchange (Fostel et al. 1985) unscheduled DNA synthesis in rat hepatocytes (Working et al. 1986), effects on spermatocytes and tracheal epithelial cells (Working et al. 1986), and DNA viral transformation in primary hamster embryo cells (Hatch et al. 1982, 1983). 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 (Chellman et al. 1986c). There remains, however, some controversy about chloromethane's alkylating and genotoxic potential, and additional studies are needed to evaluate the genotoxic risks to humans.

Reproductive Toxicity. No information was available regarding reproductive effects of chloromethane in humans.

Several inhalation studies, however, have demonstrated that chloromethane is a reproductive toxicant in male rats (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, 1986b, 1987; CIIT 1981; Hamm et al. 1985; Morgan et al. 1982; Working and Bus 1986; Working et al. 1985a, 1985b). The mechanism of this reproductive toxicity has 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 (McKenna et al. 1981a), but the exposure concentrations may not have been high enough. Species differences in sensitivity exist for other end points as well. No studies were located regarding the

reproductive effects of chloromethane in animals after oral or dermal exposure, and pharmacokinetic data are insufficient to support the potential for reproductive effects across routes of exposure. Therefore, additional inhalation, oral, and dermal studies for reproductive effects in other species at higher exposure levels are needed to further evaluate the potential adverse reproductive effects in humans from exposure to chloromethane.

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 (Wolkowski-Tyl et al. 1983a). In rats, delayed fetal development was found at a concentration that also resulted in maternal toxicity. Positive results in mice have been reported (Wolkowski-Tyl 1985); however there is some controversy related to conflicting results reported from other laboratories (John-Greene et al. 1985). Additional studies are needed to further evaluate the pharmacokinetics and the potential teratogenic effects of exposure to chloromethane.

No studies were located regarding the developmental effects of chloromethane in animals after oral and dermal exposure, and the pharmacokinetic data are insufficient to extrapolate to these routes of exposure. Additional studies in mice and other species are needed to evaluate the potential developmental risks to humans from these routes of exposure.

Immunotoxicity. No information was located regarding immunotoxic effects in humans after exposure to chloromethane by any route.

The immunotoxic effects reported in the literature from exposure to chloromethane were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed by inhalation to chloromethane for 2 years (CIIT 1981). Cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than the control (McKenna et al. 1981a), but 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 could not be ruled out. Additional studies are needed to further evaluate the potential immunotoxicity of chloromethane to humans.

Neurotoxicity. The neurotoxic effects in humans from inhalation exposure to chloromethane are described in numerous case studies (Baird 1954; Battigelli and Perini 1955; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; Lanham 1982; MacDonald 1964; McNally 1946; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951), but the mechanism is unclear. S-methylcysteine appears to be a metabolite in humans (Kornbrust and Bus 1983), and mechanisms involving conjugation with glutathione are likely to be relevant to human toxicity. Methanethiol produces similar central nervous system effects as seen in humans and animals exposed to chloromethane (Jager et al. 1988; Kornbrust and Bus 1983, 1984).

The neurotoxic effects of inhalation exposure to chloromethane are also well defined in animals (Burek et al. 1981; Chelhnan et al. 1986a, 1986b; CIIT 1981; Kolkmann and Volk 1975; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). 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 (Chellman et al. 1986b). The relative importance of conjugation with glutathione in other species has not been determined.

Monkeys provide a better animal model compared with rodents when evaluating neurobehavioral effects in humans. Neurobehavioral studies in monkeys and additional mechanistic studies in rodents are needed to further evaluate the mechanism and dose-response relationships of chloroform-induced neurotoxicity in humans.

No studies were located regarding the neurotoxic effects of chloromethane in animals after oral and dermal exposure, and pharmacokinetic data are insufficient to extrapolate to other routes of exposure.

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 human 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 human volunteers exposed to 200 ppm for 3 hours (Putz-Anderson et al. 1981a). An epidemiology study on a cohort of 24 Icelandic fishermen reported a slight increase in excess mortality from all cancers (more specifically, lung cancer) and a clear increase in death from cardiovascular disease (Rafnsson and Gudmundsson 1997). The study was conducted 32 years after an acute (i.e., 2 days) high level exposure to chloromethane from a leaking refrigerator (although no estimates of exposure levels were reported). The usefulness of these results are limited because confounding factors for lifestyle and smoking were not explicitly controlled, but assumed to be similar based on controls for age, social class, and occupation. Exposure levels were also not quantified. Additional epidemiology and dosimetry studies are therefore needed to further evaluate the occupational and environmental health risk from exposure to chloromethane.

Biomarkers of Exposure and Effect.

Exposure. A number of studies have unsuccessfully tried to relate blood and alveolar air levels of chloromethane and urinary levels of S-methylcysteine with exposure (DeKok and Antheunius 1981; Nolan et al. 1985; Stewart et al. 1980; Van Doorn et al. 1980). 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.

Although Xu et al. (1990) reported low chloromethane reactivity with hemoglobin, protein adducts may still hold promise as potential biomarkers for chloromethane exposure. In view of chloromethane's genotoxicity in short-term assays, an assay for a DNA adduct or indicator of oxidative damage to DNA from chloromethane exposure might also be pursued. Further studies are, therefore, needed to identify a metabolite or biomarker that can be used to monitor chloromethane exposure.

Effect. 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 (Putz-Anderson et al. 1981a; Repko et al. 1977). Blood and alveolar levels are highly variable and are not sensitive indicators of neurological function or behavior. Further studies are needed to identify a metabolite or biomarker that can be correlated with the known toxic end point and that would lead to early detection and possibly 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, incorporated into macromolecules, and excreted as CO_2 or other metabolites in the urine (Dekant et al. 1995; Dodd et al. 1982; Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Kornbrust et al. 1982; Landry et al. 1983a, 1983b; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; Van Doorn et al. 1980; von Oettingen et al. 1949, 1950). Differences in the rate and extent of absorption, metabolic pathways, and disposition will have a profound effect on the toxicity of chloromethane. Oral and dermal routes of exposure may be of particular concern because chloromethane is ubiquitous in the environment. Additional pharmacokinetic studies are needed to evaluate the potential for delivery of toxic levels of chloromethane to human target tissues from different routes of exposure and durations of exposure.

Comparative Toxicokinetics. Studies on the pharmacokinetics of chloromethane following inhalation exposure have been conducted in rats, mice, dogs, and humans (Dekant et al. 1995; Dodd et al. 1982; Heck et al. 1982; Jager et al. 1988; Kombrust and Bus 1983, 1984; Kombrust et al. 1982; Landry et al. 1983a, 1983b; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; Van Doorn et al. 1980; von Oettingen et al. 1949, 1950). The kinetics of chloromethane in humans were similar to those in rats and dogs, with data for each species consistent with a 2-compartment model. Some species differences can be explained by differences in respiratory minute volumes and basal metabolic rates (rat > dog > human). Additional pharmacokinetic studies in different species and with different routes of exposure are needed to further evaluate the target tissues and the differences in potential toxic metabolites. Additional studies are especially needed to resolve the relative importance of glutathione conjugation and P-450 oxidation to the toxicity of chloromethane. These studies should be performed in different tissues, species, and sexes to resolve potential differences. Additional studies are needed to evaluate the importance of varying levels of human endogenous erythrocyte, glutathione transferase (as has been recently shown to exist) to the toxicity of chloromethane and to the identification of potentially susceptible populations.

Methods for Reducing Toxic Effects. Additional studies are needed to further define the mechanism of chloromethane's toxicity. Especially important are studies to determine whether depletion or protection of glutathione pools is needed to protect against toxicity for any given exposure route or target organ. The mechanisms and the beneficial or detrimental contribution of glutathione may be different for different end points or target tissues.

Children's Susceptibility. There have been no studies on whether children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane, or if chloromethane affects the developing fetus or the development of young children. There have also been no studies in which young animals were exposed to chloromethane.

Only limited information is available from rat and mouse studies on potential effects in the developing young (see above in Data Needs for Developmental Toxicity). In one rat study (Wolkowski-Tyl et al. 1983a), at levels that also produced maternal toxicity, fetal effects consisted of reduced fetal body weight and crownrump 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 hindlimbs. Wolkowski-Tyl et al. (1983a) also found increased incidences of heart malformations in the fetuses of mouse dams exposed to 500 ppm chloromethane during Gd 6-17; however, heart malformation were not found in fetuses of mouse dams exposed to higher concentrations of chloromethane during Gd 11.5-12.5 (John-Greene et al. 1985). The developmental toxicity of chloromethane in mice is, therefore, controversial, and further studies are needed to determine potential adverse effects on development from maternal and fetal exposure to chloromethane.

There is no information on the movement of chloromethane or its metabolites across the placenta or into the developing young. There is no information on the movement of chloromethane or its metabolites into a nursing women's milk. Chloromethane is broken down and eliminated from the body very quickly in adults (Nolan et al. 1985) and animals (Landry et al. 1983a; von Oettingen et al. 1949, 1950). Thus, it is unlikely that chloromethane would be stored in maternal tissues or be mobilized (i.e., released from stores) during pregnancy or lactation. However, further studies are needed to answer these questions.

In adults, there appear to be two distinct populations with regard to metabolism and elimination of chloromethane. One population has higher amounts of the metabolizing enzyme, glutathione-S-transferase, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with glutathione (Chellman et al. 1986b; Jager et al. 1988; Kombmst and Bus 1983, 1984; Nolan et al. 1985; Stewart et al. 1980; Warholm et al. 1995). It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis. If a polymorphism is present in children, then some children (i.e., those with higher levels of glutathione-S-transferase) would be more susceptible to the toxic effects of chloromethane. Moreover, cytochrome P-450 dependent metabolism of methanethiol may yield formaldehyde and formic acid whose carbon atoms can then enter the one-carbon

pool for incorporation into macromolecules or formation of CO_2 (Heck et al. 1982; Jager et al. 1988; Kombrust and Bus 1983). Guengerich and Shimada (1991) suggest that the human cytochrome P-450 enzyme 2El is a major catalyst in the oxidation of chloromethane. Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination. Studies are therefore needed to evaluate the differences among and between children and adults for P-450 and transferase levels and isoforms, and for differences in chloroform metabolism.

There are no PBPK models for children, adults, or test animal models. There are no good biomarkers of exposure for children (or adults), although clinical symptoms of drunkenness or food poisoning, and a sweet odor of the breath may alert a physician. Attempts to use urinary levels of S-methylcysteine as an indicator of chloromethane exposure have not been successful. Further studies are needed to evaluate the toxicokinetics of chloromethane and its metabolites in children and to develop better biomarkers of exposure and effects.

Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

No ongoing studies were found that address the health effects of chloromethane.

The National Science Foundation is sponsoring a study to analyze the degradation products of a methane oxidizing bacteria (methanotrophic degradation) for selected contaminants including chloromethane to demonstrate that no toxic products are formed. A laboratory scale treatment column will also be used to optimize conditions for the removal of chlorinated aliphatics from contaminated waters. The principal researcher is Samuel Fogel, Cambridge Analytical Associates, Inc., Boston, Massachusetts.

3. CHEMICAL AND PHYSICAL INFORMATION

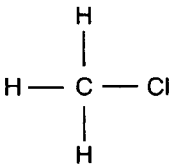
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chloromethane is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chloromethane is located in Table 3-2.

Table 3-1. Chemical Identity of Chloromethane

Characteristic	Information	Reference
Chemical name	Chloromethane	CAS 1988; Weast 1988
Synonym(s)	Methyl chloride, monochloromethane	CAS 1988; SANSS 1988
Registered trade name(s)	Artic R 40 Freon 40	HSDB 1998; SANSS 1988
Chemical formula	CH_3Cl	CAS 1988
Chemical structure		EPA 1991b
Identification numbers:		
CAS Registry	74-87-3	CAS 1988
NIOSH RTECS	PA6300000	RTECS 1988
EPA Hazardous Waste	UO45	HSDB 1998
OHM/TADS	7216794	OHM-TADS 1988
DOT/UN/NA/IMCO Shipping	UN 1063; IMO2.0	HSDB 1998; RTECS 1988
HSDB	883	HSDB 1998
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	Information	Reference
Molecular weight	50.49	Weast 1988
Color	Colorless	Holbrook 1992
Physical state	Gas	Holbrook 1992; Weast 1988
Melting point	-97.7 °C -97.1 °C	Holbrook 1992 Weast 1988
Boiling point	-23.73 °C -24.2 °C	Holbrook 1992 Weast 1988
Density:		
Liquid at 20/4 °C	0.920 g/mL	Holbrook 1992
Gas at 0 °C, 1 atm	2.3045 g/L	Holbrook 1992
Specific gravity	1.74 (air = 1)	Holbrook 1992
Odor	Ethereal, nonirritating	Merck 1989
Odor threshold:		
Water	No data	
Air	10.0 ppm (21 mg/m^3) 21 mg/m^3 (10 ppm)	Fazzalari 1978 EPA 1991b
Solubility:		
Fresh water at 25 °C	5,325 mg/L 4,800 mg/L	Horvath 1982 Holbrook 1992
Fresh water at 20 °C	3,030 mL/L	Merck 1989
Organic solvents[a]		
Benzene	4,723 (99,200 mg/L)	Holbrook 1992
Carbon tetrachloride	3,756 (78,900 mg/L)	Holbrook 1992
Glacial acetic acid	3,679 (77,259 mg/L)	Holbrook 1992
Absolute alcohol	3,740 (78,540 mg/L)	Holbrook 1992
Partition coefficients:		
Log K_{ow}	0.91 (experimental) 1.086 (calculated)	Hansch and Leo 1985 SRC 1995
Log K_{oc}	Does not tend to adsorb to soil	HSDB 1998; Lyman 1982
Vapor pressure:		
at 20 °C	3,670 mmHg (489 kPa)	Holbrook 1992
at 25 °C	4,310 mmHg (575 kPa)	Riddick et al. 1986
Henry's law constant:		
at 25 °C	8.82×10^{-3} atm-m^3/mol 8.88×10^{-3} atm-m^3/mol	Gossett 1987 SRC 1994

Table 3-2. Physical and Chemical Properties of Chloromethane (continued)

Property	Information	Reference
Hydrolysis half-life	0.93 years at 25 °C 88 years at 0 °C 14 years at 10 °C 0.7–1.1 years at 25 °C 4.6 years at 15 °C 2.5 years at 20 °C ≈ 2 years at 20°C	Mabey and Mill 1978 Zafiriou 1975 Zafiriou 1975 Elliot and Rowland 1995 Elliot and Rowland 1995 Zafiriou 1975 Heppolette and Robertson 1959
Half-life resulting from reaction with hydroxyl radicals in the atmosphere	0.5 years 0.75–2 years 1–2 years 2–3 years	Crossley 1997; Atkinson 1985 Atkinson 1985 Khalil and Rasmussen 1981 Crutzen and Gidel 1983; Singh et al. 1979
Half-life resulting from photodissociation in the upper atmosphere (30 km)	2.2 years	Robbins 1976
Autoignition temperature	632 °C	Holbrook 1992
Flashpoint, open cup	-46°C	Holbrook 1992
Flammability limits	10.7–17.4 vol % 8.1–17.2 vol:vol	Holbrook 1992 Merck 1989; NFPA 1994
Reactivities	Reacts with ammonia to form methyl amine hydrochlorides; slowly decomposes in presence of water to form HCl, which is corrosive to metals	Holbrook 1992
	Reacts explosively with lithium, sodium, potassium, magnesium. Spontaneously flammable aluminum trimethyl formed upon reaction of chloromethane with aluminum in presence of trace aluminum chloride	NFPA 1994
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C mg/m^3 to ppm (v/v) in air at 25 °C	ppm (v/v) x 2.064 = mg/m^3 mg/m^3 x 0.4845 = ppm (v/v)	Calculated

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

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Table 4-1 lists the facilities in each state that manufacture or process chloromethane, the intended use, and the range of maximum amounts of chloromethane that are stored on site. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI96 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Based on the most current TRI information, there are currently 96 facilities that produce or process chloromethane in the United States.

Chloromethane (also commonly known as methyl chloride) 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 reaction of methanol and hydrogen chloride (HCl) or by chlorination of methane (Edwards et al. 1982a; Holbrook 1992; Key et al. 1980). While the reaction of methanol with HCl is the most common method, the choice of process depends, in part, on the HCl balance at the site (the methane route produces HCl, the methanol route uses it) (Edwards et al. 1982a; Holbrook 1992). 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 (Holbrook 1992; Key et al. 1980). 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 inhouse or treated and discharged (Holbrook 1992; Key et al. 1980). The chloromethane is then dried by treatment with concentrated sulfuric acid, 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 (Holbrook 1992; 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

Table 4-1. Facilities That Manufacture or Process Chloromethane

FACILITY	LOCATION [a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
HULS AMERICA INC.	THEODORE , AL	1,000 - 9,999	PRODUCE , BYPRODUCT
INTERNATIONAL PAPER	MOBILE , AL	0 - 99	PRODUCE , IMPURITY
CPS CHEMICAL CO.	WEST MEMPHIS , AR	100,000 - 999,999	REACTANT
INTERNATIONAL PAPER	PINE BLUFF , AR	0 - 99	PRODUCE , IMPURITY
AMVAC CHEMICAL CORP.	LOS ANGELES , CA	0 - 99	PRODUCE , BYPRODUCT
BOULDER SCIENTIFIC CO.	MEAD , CO	1,000 - 9,999	REACTANT
SYNTEX CHEMICALS INC.	BOULDER , CO	10,000 - 99,999	PRODUCE , BYPRODUCT , REACTANT
PFIZER INC-GROTON SITE	GROTON , CT	10,000 - 99,999	PRODUCE , BYPRODUCT , REACTANT
SPONGES INTL.	SHELTON , CT	10,000 - 99,999	MANUFACTURING AID
ZENECA INC.	NEW CASTLE , DE	10,000 - 99,999	REACTANT
BUCKEYE FLORIDA L.P.	PERRY , FL	0 - 99	PRODUCE , IMPURITY
BLACKMAN UHLER CHEMICAL DIV.	AUGUSTA , GA	10,000 - 99,999	REACTANT
GILMAN PAPER CO.	SAINT MARYS , GA	10,000 - 99,999	PRODUCE , IMPURITY
NUTRASWEET KELCO CO.	AUGUSTA , GA	1,000 - 9,999	PRODUCE , BYPRODUCT
TENNECO PACKAGING	CLYATTVILLE , GA	0 - 99	PRODUCE , BYPRODUCT , IMPURITY
MONSANTO CO.	MUSCATINE , IA	100 - 999	PRODUCE , BYPRODUCT
AKZO NOBEL CHEMICALS INC.	MORRIS , IL	100,000 - 999,999	REACTANT
AKZO NOBEL CHEMICALS INC.	MC COOK , IL	100,000 - 999,999	REACTANT
CABOT CORP.	TUSCOLA , IL	0 - 99	PRODUCE , BYPRODUCT
HENKEL CORP.	KANKAKEE , IL	10,000 - 99,999	REACTANT
LONZA INC.	MAPLETON , IL	10,000 - 99,999	REACTANT
MORTON INTL. INC.	RINGWOOD , IL	10,000 - 99,999	REACTANT
SHEREX CHEMICAL CO. INC.	MAPLETON , IL	100,000 - 999,999	REACTANT
ECOLAB INC.	HUNTINGTON , IN	10,000 - 99,999	REACTANT
ALLCO CHEMICAL CORP.	GALENA , KS	100,000 - 999,999	REACTANT
PALMER MFG. & TANK INC.	GARDEN CITY , KS	100 - 999	ANCILLARY/OTHER USE
VULCAN CHEMICALS	WICHITA , KS	1,000,000 - 9,999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT
DOW CORNING CORP.	CARROLLTON , KY	1,000,000 - 9,999,999	PRODUCE , ON-SITE USE/PROCESSING , REACTANT
WESTVACO CORP.	WICKLIFFE , KY	10,000 - 99,999	PRODUCE , BYPRODUCT
DOW CHEMICAL CO.	PLAQUEMINE , LA	1,000,000 - 9,999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , IMPURITY , REACTANT , ANCILLARY/OTHER USE
EXXON CHEMICAL	BATON ROUGE , LA	100,000 - 999,999	CHEMICAL PROCESSING AID
FERRO CORP.	ZACHARY , LA	100,000 - 999,999	REACTANT
GEORGIA-PACIFIC CORP.	ZACHARY , LA	100 - 999	PRODUCE , BYPRODUCT
INTERNATIONAL PAPER CO.	BASTROP , LA	0 - 99	PRODUCE , IMPURITY
MONSANTO CO.	LULING , LA	1,000 - 9,999	PRODUCE , IMPURITY
RHONE-POULENC INC.	BATON ROUGE , LA	100,000 - 999,999	REACTANT
VULCAN MATERIALS CO.	GEISMAR , LA	1,000,000 - 9,999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT
WITCO CORP.	KILLONA , LA	100,000 - 999,999	REACTANT
FMC CORP.	BALTIMORE , MD	100 - 999	PRODUCE , BYPRODUCT
WESTVACO CORP.	LUKE , MD	100 - 999	PRODUCE , IMPURITY

Table 4-1. Facilities That Manufacture or Process Chloromethane (continued)

FACILITY	LOCATION [a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
BASF CORP.	WYANDOTTE, MI	1,000 - 9,999	PRODUCE, BYPRODUCT, REACTANT
CYTEC IND. INC.	KALAMAZOO, MI	10,000 - 99,999	REACTANT
DOW CHEMICAL USA	MIDLAND, MI	100,000 - 999,999	PRODUCE, BYPRODUCT, IMPURITY, REACTANT
DOW CORNING CORP.	MIDLAND, MI	100,000 - 999,999	BYPRODUCT, PRODUCE, ON-SITE USE/PROCESSING, SALE/DISTRIBUTION, IMPURITY, CHEMICAL PROCESSING AID, MANUFACTURING AID
ESCO CO.	MUSKEGON, MI	10,000 - 99,999	REACTANT
DIVERSIFOAM PRODS.	ROCKFORD, MN	10,000 - 99,999	IMPORT, ON-SITE USE/PROCESSING, FORMULATION COMPONENT, CHEMICAL PROCESSING AID
BAYER CORP.	KANSAS CITY, MO	100 - 999	PRODUCE, BYPRODUCT
DUCOA L.P.	VERONA, MO	100,000 - 999,999	REACTANT
SYNTEX AGRIBUSINESS INC.	SPRINGFIELD, MO	100,000 - 999,999	REACTANT
INTERNATIONAL PAPER	NATCHEZ, MS	0 - 99	PRODUCE, IMPURITY
INTERNATIONAL PAPER	REDWOOD, MS	0 - 99	PRODUCE, BYPRODUCT
CHAMPION INTL. CORP.	CANTON, NC	0 - 99	PRODUCE, IMPURITY
FEDERAL PAPER BOARD CO. INC.	RIEGELWOOD, NC	0 - 99	PRODUCE, IMPURITY
CPS CHEMICAL CO. INC.	OLD BRIDGE, NJ	100,000 - 999,999	REACTANT
DUPONT CHAMBERS WORKS	DEEPWATER, NJ	1,000 - 9,999	PRODUCE, BYPRODUCT, ANCILLARY/OTHER USE
GE CO.	WATERFORD, NY	1,000,000 - 9,999,999	PRODUCE, ON-SITE USE/PROCESSING, REACTANT
AMOCO PERFORMANCE PRODS. INC.	MARIETTA, OH	10,000 - 99,999	REACTANT
ARISTECH CHEMICAL CORP.	HAVERHILL, OH	10,000 - 99,999	PRODUCE, BYPRODUCT
LINDERME TUBE CO.	EUCLID, OH	10,000 - 99,999	ANCILLARY/OTHER USE
MARSULEX INC.	OREGON, OH	10,000 - 99,999	ANCILLARY/OTHER USE
MORTON INTL. INC.	CINCINNATI, OH	100,000 - 999,999	REACTANT
AIR PRODS. & CHEMICALS INC.	TAMAQUA, PA	100,000 - 999,999	REPACKAGING
PPG IND. INC.	FOLCROFT, PA	1,000 - 9,999	REACTANT
PRESSURE CHEMICAL CO.	PITTSBURGH, PA	1,000 - 9,999	REACTANT
ROHM & HAAS CO.	PHILADELPHIA, PA	10,000 - 99,999	REACTANT
MERCK SHARP & DOHME QUIMICA	BARCELONETA, PR	10,000 - 99,999	PRODUCE, BYPRODUCT
ALBRIGHT & WILSON AMERICAS	CHARLESTON, SC	1,000 - 9,999	PRODUCE, BYPRODUCT
BALCHEM CORP.	GREEN POND, SC	10,000 - 99,999	REPACKAGING
BAYER CORP. BUSHY PARK	GOOSE CREEK, SC	10,000 - 99,999	REACTANT
NIPA HARDWICKE INC.	ELGIN, SC	10,000 - 99,999	REACTANT
ENENCO INC.	MEMPHIS, TN	100,000 - 999,999	REACTANT
GREAT LAKES CHEMICAL CORP.	NEWPORT, TN	100 - 999	PRODUCE, BYPRODUCT
TENNECO PACKAGING	COUNCE, TN	0 - 99	PRODUCE, BYPRODUCT
ZENECA SPECIALTIES	MOUNT PLEASANT, TN	0 - 99	PRODUCE, BYPRODUCT, REACTANT
AKZO NOBEL CHEMICALS INC.	DEER PARK, TX	1,000 - 9,999	REACTANT
BASF CORP.	BEAUMONT, TX	100,000 - 999,999	REACTANT
CORSICANA TECHS. INC.	CORSICANA, TX	10,000 - 99,999	REACTANT
DOW CHEMICAL CO.	FREEPORT, TX	1,000,000 - 9,999,999	PRODUCE, ON-SITE USE/PROCESSING, SALE/DISTRIBUTION, IMPURITY, REACTANT, ANCILLARY/OTHER USE

Table 4-1. Facilities That Manufacture or Process Chloromethane (continued)

FACILITY	LOCATION [a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
EASTMAN CHEMICAL CO.	LONGVIEW , TX	0 - 99	PRODUCE , IMPURITY
EXXON CHEMICAL AMERICAS	BAYTOWN , TX	100,000 - 999,999	MANUFACTURING AID
INLAND PAPERBOARD & PACKAGING	ORANGE , TX	0 - 99	PRODUCE , BYPRODUCT
ISK BIOSCIENCES CORP.	HOUSTON , TX	100,000 - 999,999	IMPORT , ON-SITE USE/PROCESSING , REACTANT
OCCIDENTAL CHEMICAL CORP.	GREGORY , TX	1,000 - 9,999	PRODUCE , BYPRODUCT
PETROLITE CORP.	PASADENA , TX	10,000 - 99,999	REACTANT
RHONE-POULENC INC.	FREEPORT , TX	10,000 - 99,999	PRODUCE , BYPRODUCT
SACHEM INC.	CLEBURNE , TX	100,000 - 999,999	REACTANT
STERLING CHEMICALS INC.	TEXAS CITY , TX	100 - 999	PRODUCE , BYPRODUCT
WITCO CORP.	HOUSTON , TX	10,000 - 99,999	REACTANT
ZENECA INC.	PASADENA , TX	100,000 - 999,999	REACTANT
HICKSON DANCHEM CORP.	DANVILLE , VA	10,000 - 99,999	REACTANT
MERCK & CO. INC.	ELKTON , VA	100 - 999	PRODUCE , BYPRODUCT
UNION CAMP CORP.	FRANKLIN , VA	0 - 99	PRODUCE , BYPRODUCT
BELL AROMATICS	MILWAUKEE , WI	10,000 - 99,999	REACTANT
SHEREX CHEMICAL WHOLLY OWNED	JANESVILLE , WI	100,000 - 999,999	REACTANT
TOMAH PRODS. INC.	MILTON , WI	100,000 - 999,999	REACTANT
DU PONT	BELLE , WV	100 - 999	PRODUCE , BYPRODUCT
OSI SPECIALTIES INC.	FRIENDLY , WV	10,000 - 99,999	PRODUCE , BYPRODUCT , REACTANT , MANUFACTURING AID

Source: TRI96 1998

[a] Post Office state abbreviations used

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 scrubbed with dilute NaOH to remove any HCl, dried, compressed, cooled, and then fractionally distilled to separate the four chloromethanes. While there are some variations to this process, including the use of catalysts, this is a general overview of the basic steps in the process.

It is difficult to estimate the total production levels for chloromethane at specific plants because many of the producers consume their output internally as a feedstock for other chemicals, including silicones and higher chlorinated methanes. Current production capacity in the United States is estimated to be in the neighborhood of 920 million pounds (417.3 million kg) per year (CMR 1995). The seven facilities with the largest production capacities are: (1) Dow Chemical Company plant at Freeport, Texas; (2) Dow Chemical Company plant at Plaquemine, Louisiana; (3) Dow Corning Corporation plant at Carrolton, Kentucky; (4) Dow Corning Corporation plant at Midland, Michigan; (5) GE Plastics Company plant at Waterford, New York; (6) Vulcan Chemical Company plant at Geismar, Louisiana; and (7) Vulcan Chemical Company plant at Wichita, Kansas (CMR 1995). All these facilities have production capacities in excess of 50 million pounds per year. At the GE Plastics facility and the two Dow Corning facilities, all the chloromethane generated is used on-site in silicone production; a large percentage of the output from the Dow plant in Freeport, Texas, and the two Vulcan facilities are also used on-site as feedstocks in the manufacture of other chemicals and products (CMR 1995).

Available estimates for annual production show a growth in output from the early 1980s through the mid-1990s. These production trends are documented in Table 4-2 (C&EN 1992, 1995). In addition to direct manufacture, chloromethane is also produced naturally and from a number of human industrial activities (e.g., the manufacture of vinyl chloride) that can lead to the inadvertent production and release of chloromethane to environmental media. These releases are discussed in Chapter 5.

4.2 IMPORT/EXPORT

In the period from 1990 through 1994, U.S. imports of chloromethane showed considerable fluctuations, with annual import levels ranging from 2,241,040 kg (4,930,288 lbs) in 1990 to a low value of 119,171 kg (262,176 lbs) in 1991. During 1992, imports rebounded to 657,612 kg (1,446,746 lbs); more recently, imports have increased to 1,682,383 kg (3,701,242 lbs) in 1993 and 1,916,523 kg (4,216,350 lbs) in 1994 (USDOC 1996). During the same period, exports also showed considerable volatility, with export levels

Table 4-2. Trends in U.S. Chloromethane Production

Year	Annual production in millions of pounds	Annual production in millions of kilograms
1981	405	183.7
1982	366	166.0
1983	409	185.5
1984	482	218.6
1985	410	185.9
1986	605	274.4
1987	373	169.2
1988	597	270.8
1989	461	209.1
1990	772	350.2
1991	916	415.5
1992	966	438.2
1993	1,053	477.6
1994	995	451.3

Source: based on data from C&EN 1992,1995

outpacing imports by a factor of about 2. In the period from 1991 through 1995, export levels ranged from 5,092,969 kg (11,204,532 lbs) in 1992 to 7,107,860 kg (15,637,292 lbs) in 1991 (USDOC 1996).

4.3 USE

Chloromethane is used mainly (72%) in the production of silicones (CMR 1986; Holbrook 1992). Chloromethane has also been 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). It has been used in the past as a component or propellant in some cleansers and industrial solvents (Howard 1990). It has also apparently been used in the past as a foam blowing agent and as an agricultural pesticide or fumigant (HSDB 1998). At the present time, virtually all of the commercial uses for chloromethane are consumptive in that the chloromethane is reacted to form another product during use. Thus, almost all chloromethane will be consumed when used and will no longer be available for release, disposal, or reuse.

4.4 DISPOSAL

Limited information was located in the literature concerning the disposal of chloromethane. Since most chloromethane is used consumptively, little remains to be disposed. Nonetheless, some chloromethane is present in waste, and chloromethane has been detected in hazardous waste landfills. Its presence in hazardous waste sites may result from the landfilling of still bottoms or other residues from the manufacture and use of chloromethane. Its presence in municipal waste landfills suggests that consumer products containing chloromethane were landfilled (e.g., propellants for aerosol cans, old refrigerators). Since chloromethane is an impurity in vinyl chloride, the disposal of vinyl chloride may also lead to chloromethane contamination. Like other chlorinated hydrocarbons, chloromethane can inhibit the combustion of such fuels as methane. Chloromethane has a considerable inhibitory effect on combustion when mixed with methane, the principal component of natural gas (Philbrick et al. 1993). Changes in the amounts of chloromethane added to the methane fuel stock did not produce well-defined relations with the combustion characteristics. Such phenomena would complicate the disposal of chloromethane using incineration technologies. When incineration was attempted under oxygen-starved conditions (Taylor and Dellinger 1988), chloromethane was shown to combine with other components of the combustion mixture to form, among other compounds, chlorinated ethanes, hexachlorobenzene, and octachlorostyrene.

Chloromethane is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA). Disposal of wastes containing chloromethane is controlled by a number of federal regulations (see Chapter 7).

5. POTENTIAL FOR HUMAN EXPOSURE

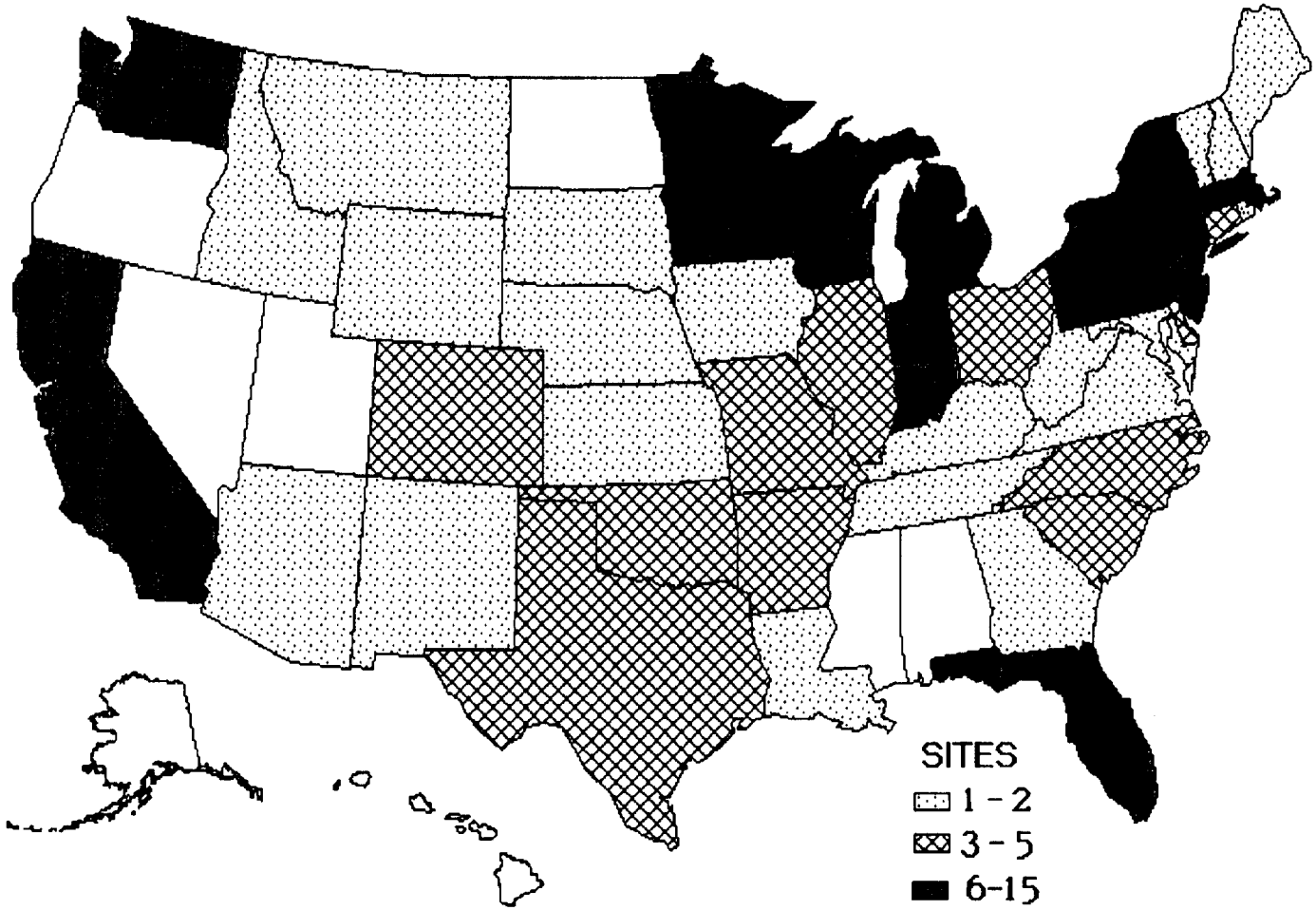
5.1 OVERVIEW

Chloromethane has been identified in at least 172 of the 1,467 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1998). However, the number of sites evaluated for chloromethane is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 171 are located in the United States and 1 is located in the Commonwealth of Puerto Rico (not shown).

Chloromethane (also commonly known as methyl chloride) is a natural and ubiquitous constituent of the oceans and atmosphere (both the troposphere and the stratosphere). It is a product of biomass combustion and is also created from biogenic emissions by wood-rotting fungi. Chloromethane has been detected in surface waters, drinking water, groundwater, and soil. Chloromethane is a constituent of municipal and industrial solid waste leachate; it is a component of industrial waste discharges, and is also present in the effluents of publicly owned treatment works (POTWs). It is an impurity in vinyl chloride (Zaidman et al. 199 l), so chloromethane could be released to the environment during the manufacture of vinyl chloride or introduced into NPL sites from vinyl chloride wastes. Chloromethane in air has a half-life of about 1 year (see Table 3-2) with various estimates in the range of 0.6-3 years (see Section 5.3.2.1 below). Chloromethane is the dominant organochlorine species in the atmosphere. In the upper atmosphere, chloromethane, through its sheer abundance, plays a role in chemical reactions that remove ozone from the upper troposphere and stratosphere (Crutzen and Gidel 1983; Gidel et al. 1983; Singh et al. 1983). Since these processes are believed to be largely part of natural background cycles, chloromethane has not been the focus of ozone depletion control efforts under the Clean Air Act (CAA) and the Montreal Protocol, which are targeted at such anthropogenic halogenated compounds as chlorofluorocarbons (EPA 1996b; Finlayson-Pitts and Pitts 1986; IPCC 1995).

In water, chloromethane is expected to volatilize rapidly (Mabey and Mill 1978). It is not expected to sorb to sediments or to 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, it will probably leach into groundwater. In groundwater, hydrolysis may be the only removal mechanism available to chloromethane, with an estimated half-life of ~4 years based on available data

Figure 5-1. Frequency of NPL Sites with Chloromethane Contamination



Derived from HazDat 1998

(Elliott and Rowland 1995; Mabey and Mill 1978). Air concentrations of chloromethane are generally in the low per billion range, but urban locations appear to have elevated concentrations compared to background concentrations. Although detailed information is lacking, water concentrations are likely to vary considerably depending on the season and the 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 is expected to be ≈0.7-0.9 ppb. Occupational exposure to chloromethane may result in exposures of ≈ 10 parts per million (ppm); however, the database for occupational exposure is outdated (late 1980s or earlier) and not sufficiently comprehensive 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

According to the Toxics Release Inventory (TRI), in 1996, a total of 4,827,803 pounds (2,189,855 kg) of chloromethane was released to the environment from 96 processing facilities (TRI96 1998). This total consists of chloromethane released to air (4,457,775 pounds), water (803 pounds), soil (80 pounds), and via underground injection (99,705 pounds). Table 5-1 lists the amounts released to the environment by each site. In addition, an estimated 9,758 pounds (4,426 kg) were released by manufacturing and processing facilities to POTWs and an estimated 259,682 pounds (117,790 kg) were transferred off-site (TRI96 1998). The TRI data should be used with caution because only certain types of facilities are required to report this information. This is not an exhaustive list.

Chloromethane has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 172 of the 1,467 current and former NPL hazardous waste sites (HazDat 1998).

5.2.1 Air

According to the TRI, in 1996, the estimated release of chloromethane of 4,457,775 pounds (2,022,013 kg) into the air from at least 95 processing facilities accounted for about 92.3% of total anthropogenic environmental releases (TRI96 1998). Table 5-1 lists the amounts released from these facilities. The TRI

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Chloromethane

STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
AL	MOBILE	INTERNATIONAL PAPER	38,005	0	0	0	0	0	38,005
AL	THEODORE	HULS AMERICA INC.	8,924	0	0	0	0	250	9,174
AR	PINE BLUFF	INTERNATIONAL PAPER	43,005	5	0	0	0	0	43,010
AR	WEST MEMPHIS	CPS CHEMICAL CO.	4,250	0	0	0	0	0	4,250
CA	LOS ANGELES	AMVAC CHEMICAL CORP.	0	0	0	0	0	26	26
CO	BOULDER	SYNTEX CHEMICALS INC.	5,070	0	0	0	0	3,000	8,070
CO	MEAD	BOULDER SCIENTIFIC CO.	740	0	0	0	0	0	740
CT	GROTON	PFIZER INC-GROTON SITE	71,300	250	0	0	0	0	71,550
CT	SHELTON	SPONGES INTL.	253,791	0	0	0	0	0	253,791
DE	NEW CASTLE	ZENECA INC.	18	0	0	0	61	0	79
FL	PERRY	BUCKEYE FLORIDA L.P.	36,013	1	0	0	0	0	36,014
GA	AUGUSTA	BLACKMAN UHLER CHEMICAL DIV.	730	0	0	0	0	0	730
GA	AUGUSTA	NUTRASWEET KELCO CO.	45,002	0	0	0	0	0	45,002
GA	CLYATTVILLE	TENNECO PACKAGING	27,000	0	0	0	0	0	27,000
GA	SAINT MARYS	GILMAN PAPER CO.	35,005	5	0	0	0	5	35,015
IA	MUSCATINE	MONSANTO CO.	9,300	0	0	0	0	0	9,300
IL	KANKAKEE	HENKEL CORP.	5,560	0	0	0	0	0	5,560
IL	MAPLETON	LONZA INC.	1,393	0	0	0	0	0	1,393
IL	MAPLETON	SHEREX CHEMICAL CO. INC.	75,000	0	0	0	5	0	75,005
IL	MC COOK	AKZO NOBEL CHEMICALS INC.	214,600	0	0	0	0	0	214,600
IL	MORRIS	AKZO NOBEL CHEMICALS INC.	157,000	0	0	0	0	5	157,005
IL	RINGWOOD	MORTON INTL. INC.	331	0	0	0	0	0	331
IL	TUSCOLA	CABOT CORP.	7,079	0	0	0	0	0	7,079
IN	HUNTINGTON	ECOLAB INC.	10,320	0	0	0	0	0	10,320
KS	GALENA	ALLCO CHEMICAL CORP.	34,600	0	0	0	0	0	34,600
KS	GARDEN CITY	PALMER MFG. & TANK INC.	1	0	0	0	0	1,850	1,851
KS	WICHITA	VULCAN CHEMICALS	138,033	0	0	73,441	0	0	211,474
KY	CARROLLTON	DOW CORNING CORP.	33,948	150	0	0	0	144,108	178,206
KY	WICKLIFFE	WESTVACO CORP.	27,405	0	0	0	0	0	27,405
LA	BASTROP	INTERNATIONAL PAPER CO.	31,027	0	0	0	0	0	31,027
LA	BATON ROUGE	EXXON CHEMICAL	92,000	14	0	0	0	1,632	93,646
LA	BATON ROUGE	RHONE-POULENC INC.	4,261	0	0	0	0	0	4,261
LA	GEISMAR	VULCAN MATERIALS CO.	259,500	0	0	0	0	5	259,505
LA	KILLONA	WITCO CORP.	4,175	0	0	0	0	0	4,175
LA	LULING	MONSANTO CO.	12,900	0	0	20,000	0	0	32,900
LA	PLAQUEMINE	DOW CHEMICAL CO.	26,400	0	60	0	0	0	26,460
LA	ZACHARY	FERRO CORP.	288	2	0	0	0	0	290
LA	ZACHARY	GEORGIA-PACIFIC CORP.	54,007	0	0	0	0	0	54,007
MD	BALTIMORE	FMC CORP.	162	0	0	0	71	4,090	4,323
MD	LUKE	WESTVACO CORP.	32,000	0	0	0	5,800	0	37,800
MI	KALAMAZOO	CYTEC IND. INC.	4,696	0	0	0	250	748	5,694
MI	MIDLAND	DOW CHEMICAL USA	9,963	0	0	0	0	0	9,963
MI	MIDLAND	DOW CORNING CORP.	13,041	0	0	0	0	71,788	84,829
MI	MUSKEGON	ESCO CO.	1,500	0	0	0	1	0	1,501

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Chloromethane (continued)

STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
MI	WYANDOTTE	BASF CORP.	14,060	0	0	0	499	852	15,411
MN	ROCKFORD	DIVERSIFOAM PRODS.	81,018	0	0	0	0	0	81,018
MO	KANSAS CITY	BAYER CORP.	6,595	0	9	0	0	0	6,604
MO	SPRINGFIELD	SYNTEX AGRIBUSINESS INC.	26,640	0	0	0	0	0	26,640
MO	VERONA	DUCOA L.P.	342	0	0	0	0	0	342
MS	NATCHEZ	INTERNATIONAL PAPER	38,009	1	0	0	0	0	38,010
MS	REDWOOD	INTERNATIONAL PAPER	31,000	0	0	0	0	0	31,000
NC	CANTON	CHAMPION INTL. CORP.	33,000	0	0	0	0	0	33,000
NC	RIEGELWOOD	FEDERAL PAPER BOARD CO. INC.	32,010	1	0	0	0	0	32,011
NJ	DEEPWATER	DUPONT CHAMBERS WORKS	44,070	119	0	0	0	0	44,189
NJ	OLD BRIDGE	CPS CHEMICAL CO. INC.	1,902	0	0	0	0	0	1,902
NY	WATERFORD	GE CO.	74,000	45	0	0	0	0	74,045
OH	CINCINNATI	MORTON INTL. INC.	126,200	0	0	0	51	0	126,251
OH	EUCLID	LINDERME TUBE CO.	165,000	0	0	0	0	30,900	195,900
OH	HAVERHILL	ARISTECH CHEMICAL CORP.	31,000	0	0	0	0	0	31,000
OH	MARIETTA	AMOCO PERFORMANCE PRODS. INC.	220,750	0	0	0	0	0	220,750
PA	FOLCROFT	PPG IND. INC.	5	0	0	0	0	0	5
PA	PHILADELPHIA	ROHM & HAAS CO.	5,747	0	0	0	0	0	5,747
PA	PITTSBURGH	PRESSURE CHEMICAL CO.	10,006	0	0	0	0	0	10,006
PA	TAMAQUA	AIR PRODS. & CHEMICALS INC.	2,700	0	0	0	0	0	2,700
PR	BARCELONETA	MERCK SHARP & DOHME QUIMICA	38	0	0	0	0	0	38
SC	CHARLESTON	ALBRIGHT & WILSON AMERICAS	219,074	0	0	0	0	0	219,074
SC	ELGIN	NIPA HARDWICKE INC.	66	0	0	0	0	30	96
SC	GOOSE CREEK	BAYER CORP. BUSHY PARK	2,445	3	5	0	0	0	2,453
SC	GREEN POND	BALCHEM CORP.	204	0	0	0	0	0	204
TN	COUNCE	TENNECO PACKAGING	26,005	0	0	0	0	0	26,005
TN	MEMPHIS	ENENCO INC.	106,000	0	6	0	820	6	106,832
TN	MOUNT PLEASANT	ZENECA SPECIALTIES	200	0	0	0	0	0	200
TN	NEWPORT	GREAT LAKES CHEMICAL CORP.	337	0	0	0	27	0	364
TX	BAYTOWN	CHEMICALS INC.	250	0	0	0	0	0	250
TX	BAYTOWN	EXXON CHEMICAL AMERICAS	430,000	150	0	0	0	0	430,150
TX	BEAUMONT	BASF CORP.	5,080	0	0	0	0	0	5,080
TX	CLEBURNE	SACHEM INC.	421	0	0	0	0	13	434
TX	CORSICANA	CORSICANA TECHS. INC.	1,665	0	0	0	0	0	1,665
TX	DEER PARK	AKZO NOBEL CHEMICALS INC.	12	0	0	0	0	0	12
TX	FREEPORT	DOW CHEMICAL CO.	10,100	0	0	0	0	0	10,100
TX	FREEPORT	RHONE-POULENC INC.	14,930	0	0	0	0	0	14,930
TX	HOUSTON	ISK BIOSCIENCES CORP.	6,847	0	0	0	0	334	7,181
TX	HOUSTON	WITCO CORP.	21	0	0	0	0	0	21
TX	LONGVIEW	EASTMAN CHEMICAL CO.	200,150	0	0	0	0	0	200,150
TX	ORANGE	INLAND PAPERBOARD & PACKAGING	30,000	0	0	0	0	0	30,000
TX	PASADENA	PETROLITE CORP.	2,011	0	0	0	1,900	40	3,951
TX	PASADENA	ZENECA INC.	77,924	0	0	0	0	0	77,924
TX	TEXAS CITY	STERLING CHEMICALS INC.	174,007	0	0	6,264	0	0	180,271

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Chloromethane (continued)

STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
VA	DANVILLE	HICKSON DANCHEM CORP.	6,494	0	0	0	4	0	6,498
VA	ELKTON	MERCK & CO. INC.	8,970	0	0	0	0	0	8,970
VA	FRANKLIN	UNION CAMP CORP.	26,000	0	0	0	0	0	26,000
WI	JANESVILLE	SHEREX CHEMICAL WHOLLY OWNED	23,164	0	0	0	250	0	23,414
WI	MILTON	TOMAH PRODS. INC.	6,514	1	0	0	1	0	6,516
WI	MILWAUKEE	BELL AROMATICS	8,184	0	0	0	18	0	8,202
WV	BELLE	DU PONT	108,000	0	0	0	0	0	108,000
WV	FRIENDLY	OSI SPECIALTIES INC.	189,265	56	0	0	0	0	189,321
		TOTALS	4,457,775	803	80	99,705	9,758	259,682	4,827,803

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility

[b] Post office state abbreviations used

[c] The sum of fugitive and stack releases are included in releases to air by a given facility

[d] The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly owned treatment works

data should be used with caution, however, since only certain types of facilities are required to report this information. This is not an exhaustive list.

Chloromethane has been identified in air samples collected at 16 of the 172 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

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 manufacturing and use (fugitive emissions) as well as from production resulting from human and natural activities. Chloromethane present in waste waters also may be released to air during aeration (Pincince 1988). Release from all sources amounts to 7-18 billion pounds ($3.2\text{-}8.2\times10^9$ kg) annually on a worldwide basis. Sources include the oceans, forest fires, burning wood, burning coal, volcanoes, 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 1985; Harper and Hamilton 1988; Harper et al. 1988), and release from some trees (Isidorov et al. 1985). It is estimated that biomass burning in grasslands and forested areas accounts for about 20% (range, 10-40%) of the total global budget of chloromethane, with emissions from the oceans making another significant contribution (Rudolph et al. 1995). Various estimates of average global annual production rates, and significantly different estimates of the contributions from different natural production, sources have been made. Estimates from terrestrial ecologists tend to emphasize the role of such sources as biomass burning, while oceanographers may emphasize the role of biogenic emissions from marine phytoplankton. The global budget figures presented below are based on a study by Edwards et al. (1982b) and are used primarily to emphasize the overwhelming contributions from nonindustrial production.

In comparison with an estimated total global budget of 7-18 billion pounds ($3.2\text{-}8.2\times10^9$ kg) annually, 1980 worldwide production of chloromethane was ≈ 794 million pounds (3.6×10^8 kg) (Edwards et al. 1982b), of which ≈6% was released into the environment from production, storage, transport, and use emissions (Edwards et al. 1982a; Singh et al. 1981a, 1981b). This amounts to worldwide releases of 47.6 million pounds (2.1×10^7 kg) from manufacturing and use activities in 1980. U.S. production capacity

of chloromethane in 1995 was around 920 million pounds (417.3 million kg), with total releases to environmental media estimated from the 1996 TRI at around 4.8 million pounds (2.2 million kg) (CMR 1995; TRI96 1998). Thus, well over 90% (perhaps up to 99%) of ambient air concentrations of chloromethane on a global scale appear to come from releases from natural sources rather than from manufacturing or other emissions from anthropogenic processes or uses. Releases associated with manufacturing and production processes in the United States would constitute less than 1% of the global budget.

Typical estimates for the natural background concentrations of chloromethane in ambient air are ≈1 ppb (Harper et al. 1990). Chloromethane concentrations are often in excess of rural background concentrations in the ambient air of cities in the United States (Singh et al. 1982, 1983) (see Section 5.1). The authors suggested that this elevation may be the result of manufacturing or other anthropogenic emission sources in the urban areas, over and beyond releases from combustion or other background sources that would determine the levels in more rural areas. Other than data from the TRI or rough estimates based on global budgets, no studies were identified that attempt to make quantitative estimates for natural or anthropogenic releases of chloromethane to the air in the United States.

5.2.2 Water

According to the TRI, in 1996, there were estimated releases of chloromethane of 803 pounds (364 kg) to water from 15 documented processing facilities. These releases accounted for less than 0.1% of total anthropogenic environmental releases (TRI96 1998). Table 5-1 lists the amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report this information. This is not an exhaustive list.

Chloromethane is released into the 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) (Edwards et al. 1982a; Key et al. 1980). This water is stripped during manufacture and treatment to remove most of the dissolved chloromethane and then discharged (some chloromethane manufacturing plants use the process water on-site as a source of dilute hydrochloric acid [HCl] 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 waste water effluents, possibly as a result of its formation (Coleman et al. 1976; Gould et al. 1983) or incomplete removal during industrial waste water 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). Chloromethane has been identified in 21 surface water and 100 groundwater samples collected at the 172 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

5.2.3 Soil

According to the TRI, in 1996, the estimated release of chloromethane of 80 pounds (36.3 kg) to soil from four processing facilities accounted for less than 0.1% of total anthropogenic environmental releases (TRI96 1998). Table 5-1 lists the amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report this information. This is not an exhaustive list.

Chloromethane is probably released into the 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. Chloromethane has been identified in 34 soil and 13 sediment samples collected at the 172 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Most chloromethane discharged into the environment will be released into the 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 is high enough that small amounts may be removed from the atmosphere by precipitation; however, no information confirming this environmental pathway 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 for a pond developed by the Athens Environmental Research Laboratory of the EPA, the half-life for volatilization was calculated to be 2.5 hours. For a lake, the half-life was calculated to be 18 days. Input data included the molecular weight, the vapor pressure, Henry's law constant, the octanol/water partition coefficient, the sediment sorption coefficient, and the 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 waste water and in the air above the waste water at the Memphis North Wastewater Treatment Plant in Memphis, Tennessee. Based on the log octanol/water partition coefficient (Hansch and Leo 1985) 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 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 to diffuse to the surface and volatilize. The presence of chloromethane in groundwater confirms the importance of leaching as a transport route (Greenberg et al. 1982c; 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 thought 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. 1976a; 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. (1976a) (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).

Using the measured rate constants for the chloromethane reaction with hydroxyl radicals, several researchers have made estimates of tropospheric total lifetimes or half-lives (Crutzen and Gidel 1983; Dilling 1982; Fabian 1986; Khalil and Rasmussen 1981; Singh et al. 1979). The various half-life estimates are in the neighborhood of 1 year (see Table 3-2), with values ranging from 0.6 to 3 years. The differences in the estimated half-lives are associated mainly with differences in assumptions on the levels of hydroxyl free radical concentrations in the upper troposphere.

5.3.2.2 Water

In water, chloromethane can degrade by hydrolysis or by 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 (bi-molecular) 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}, with a half-life of 10.6 days. When extrapolated to 20 °C and neutral conditions using the thermodynamic constants calculated by Heppolette and Robertson (1959), a rate

constant was calculated of 1.04×10^{-8} sec^{-1} with a half-life of ≈ 2.1 years. More recent hydrolysis data from Elliot and Rowland (1995) are in good agreement with the estimates of Mabey and Mill (1978) and the measurements of Zafiriou (1975). Actual measurements conducted at 22 and 9 °C in pure water, sea water, and salt solution yield the same values of k (not listed), from which the Arrhenius relation was derived: $k(\text{in } s^{-1}) = 9.5 \times 10^{10} e^{-12,800/T}$. This relation was used to estimate the values at 25 and 15 °C given in Table 3-2. These rates are expected to be unaffected by pH ranges normally encountered in the environment (Mabey and Mill 1978). The hydrolysis half-lives are too long to be of environmental significance in surface waters, 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 more significant factor. Biodegradation may also occur in groundwater, but rates are thought to be highly variable.

Very little information is available concerning the biodegradation of chloromethane in water. In studies involving such bacteria as *Methylococcus capsulatus,* formaldehyde was a product of chloromethane biodegradation (Stirling and Dalton 1979). In pure culture conditions, some microbial strains can degrade chloromethane. Hartmans et al. (1986) reported that pure cultures of a *Hyphomicrobium sp.* were obtained with a chloromethane-minimal medium. Abiotic hydrolytic dehalogenation was not significant, so that the observed cell growth and chloride formation confirmed biodegradation as the predominant transformation process (Hartmans et al. 1986). Since these laboratory conditions do not commonly occur in the environment, these same species may not degrade chloromethane in the environment to any significant degree. Biodegradation of chloromethane, however, cannot be ruled out based on the available information. As with reactions of other chloroalkanes, chloromethane may degrade anaerobically via reductive dechlorination to form methane (Vogel et al. 1987).

5.3.2.3 Sediment and Soil

Very limited information concerning soil transformation and degradation of chloromethane was located in the literature. In lower soil horizons, hydrolysis may be the only relevant abiotic process since no other non-biological removal mechanisms have been identified. Biological processes, especially from some fungi, can release chloromethane (Fabian 1986; Harper 1985; Harper and Hamilton 1988; Harper et al. 1988). Research also suggests that members of the so-called white rot fungus family may degrade (mineralize) chloromethane (Harper et al. 1990). These same fungi (especially *Phanerochaete chrysosporium)* can also dehalogenate aliphatic halocarbons such as chloroform, dichloromethane, and carbon tetrachloride

(Khindaria et al. 1995) possibly forming chloromethane as an intermediate product that, in turn, could be further dehalogenated.

Doronina et al. (1996) isolated eight strains of non-methane-utilizing bacteria that are able to grow on chloromethane as the carbon and energy source. The new isolates were classified as *Hyphomicrobium* spp. (strains CMl, CM2, CM9, CM29,CM35) and *Methylbacterium* spp. (strains CM4, CM30, CM34). All strains possessed an inducible but unknown enzyme that catalyzed the conversion of chloromethane to HCI and formaldehyde. The formaldehyde was oxidized via formate to CO_2 or assimilated through icl^+ or icl^- variants of the serine pathway. Vanelli et al. (1998) found that *Methylobacterium* sp. (strain CM4) metabolized chloromethane quantitatively with a molar yield of 2.8 g of whole-cell protein/mol of C. Based on the protein yield data and the properties of the transposon mutants, they proposed a pathway for chloromethane metabolism that depends on methyltransferase and dehydrogenase activities.

Under anaerobic conditions as encountered in deeper soil profiles or in many sediments, a bacterial strain called MC isolated from municipal anaerobic digester sludge flora seems capable of metabolizing chloromethane into acetate (Messmer et al. 1993; Zitomer and Speece 1995). It is not clear, however, that such anaerobic biodegradation processes are common around waste sites with chloromethane site contamination. The biochemistry of chloroaliphatics degradation in the newer aerobic isolates is largely unexplored, but progress has been made in understanding some of the anaerobic dehalogenation reactions (Leisinger 1996).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chloromethane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on chloromethane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

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, more than 242 sites in the United States were monitored for chloromethane during a 5-year period (Eichler and Mackey 1986).

Table 5-2 presents monitoring data for chloromethane for urban/suburban and rural/remote air masses. The ranges and averages presented in Table 5-2 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.

A volatile organic carbon (VOC) database reported by Shah and Singh (1988) contained 706 data points (300 cities from 42 states), with the following results for chloromethane concentration:

	Concentration of chloromethane
Average	740 ppt
Upper quartile	721 ppt
Median	652 ppt
Lower quartile	607 ppt

The average value is higher than the upper quartile (75% value) and may be skewed because of a few high values. Thus, the median may be a better representation of chloromethane concentration. The data were also grouped by types of air mass 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, it appears that source contributions from industrial processes do not have a significant impact on the ambient concentration of chloromethane, although some elevation may occur. There are fewer data points, however, for rural/remote data than for urban/suburban data, so a direct comparison is difficult.

Average urban levels reported by Singh et al. (1982, 1983) were 660–960 ppt, while background levels were 600–700 ppt. For these results, the ambient air levels of chloromethane in cities in the United States may be slightly elevated from background levels, due to the higher numbers of combustion sources.

Table 5-2. Detection of Chloromethane in Air[a]

Media type/location	Sampling dates	No. of samples	Sample type	Analytical method	Concentration (ppt) Range	Concentration (ppt) Mean	Percent occurrence	Reference
Urban/suburban air								
Los Angeles, CA	4/9–21/79	NS	Continuous	GC/ECD	1,037–7,761	3,001	100	Singh et al. 1981b
Phoenix, AZ	4/23/79–5/6/79	NS	Continuous	GC/ECD	1,231–5,685	2,391	100	Singh et al. 1981b
Oakland, CA	6/28/79–7/10/79	NS	Continuous	GC/ECD	483–5,000	1,066	100	Singh et al. 1981b
Houston, TX	5/15–24/80	NS	Continuous	GC/ECD	531–2,284	955	100	Singh et al. 1982
St. Louis, MO	5/30/80–6/8/80	NS	Continuous	GC/ECD	531–1,015	732	100	Singh et al. 1982
Denver, CO	6/16–26/80	NS	Continuous	GC/ECD	519–1,157	763	100	Singh et al. 1982
Riverside, CA	7/2–12/80	NS	Continuous	GC/ECD	437–1,593	703	100	Singh et al. 1982
Staten Island, NY	3/27/80–4/5/80	NS	Continuous	GC/ECD	466–1,280	701	100	Singh et al. 1982
Pittsburgh, PA	4/8–16/80	NS	Continuous	GC/ECD	450–852	665	100	Singh et al. 1982
Chicago, IL	4/21–30/80	NS	Continuous	GC/ECD	575–1,311	856	100	Singh et al. 1982
Los Angeles, CA	4/29/76–5/4/76	NS	Grab	GC/ECD	708–944	834	100	Singh et al. 1977a
Stanford Hills, CA	11/24–30/75	NS	Grab	GC/ECD	700–1,700[a]	1,022	100	Singh et al. 1977a
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 NW	3/11/76	34[c]	Grab	GC/ECD	428–611[d]	569	100	Cronn et al. 1977

Table 5-2. Detection of Chloromethane in Air[a] (continued)

Media type/location	Sampling dates	No. of samples	Sample type	Analytical method	Concentration (ppt)		Percent occurrence	Reference
					Range	Mean		
Point Arena, 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	680–1,700[a]	1,260	100	Singh et al. 1977a
Yosemite Park, CA	5/12–17/75	NS	Grab	GC/ECD	654–999	713	100	Singh et al. 1977a
Palm Springs, CA	5/24–27/76	NS	Grab	GC/ECD	645–2,128	1,058	100	Singh et al. 1977a

[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 detection; GC/MS = gas chromatography/mass spectroscopy; ND = not detected; NS = not specified

In accordance with provisions of the Clean Air Act Amendments (CAAAs) of 1990, chloromethane (or methyl chloride) was among 189 compounds designated as hazardous air pollutants (HAPS). Aside from the public health impacts from direct exposures to these chemicals, most of the HAPS are VOCs that, in combination with other air pollutants, can lead to the formation of ozone and photochemical smog. The EPA has collected available ambient measurements to compile an HAP database (Kelly et al. 1994). This database adds monitoring information to earlier databases that focused on VOCs. The national median ambient air concentration from the HAP database for chloromethane is 1.3 $\mu g/m^3$ (629 ppt [v/v]).

5.4.2 Water

Chloromethane has been detected in surface water, groundwater, drinking water, municipal and hazardous waste landfill leachate, and industrial effluents (Table 5-3). 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, Pennsylvania; Miami, Florida; Seattle, Washington; Ottumwa, Iowa; and Cincinnati, Ohio) 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 as well as 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 more than 4,000 samples from 46 industrial categories and subcategories were reported in the EPA database (Bursey and Pellizzari 1982). Concentrations ranged from 6 to 4,194 mg/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 currently be estimated.

In a study of groundwater samples from 479 active waste disposal sites, chloromethane was detected at 20 of these sites (Plumb 1991). Information from HazDat (1998) documents at least 100 current or past NPL sites with detections in groundwater. There is virtually no reporting of actual concentration values or ranges for groundwater detections in the available literature. The presence of chloromethane in groundwater may

Table 5-3. Detection of Chloromethane in Water and Sediments[a]

Media type/location	Sampling dates	No. of samples	Sample type	Analytical method	Concentration (ppt) Range	Concentration (ppt) Mean	Percent occurrence	Reference
Surface water								
Delaware River and Raritan Canal	NS	NS	Grab	NS	ND	NS	0	Grantsrom 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	1,058[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

Table 5-3. Detection of Chloromethane in Water and Sediments[a] (continued)

Media type/location	Sampling dates	No. of samples	Sample type	Analytical method	Concentration (ppt) Range	Concentration (ppt) Mean	Percent occurrence	Reference
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 U.S. cities	NS	86	Grab	GC/MS	ND	ND	0	Cole et al. 1984
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.

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 and leaching to groundwater could become an important transport pathway. Chloromethane may also be a product from the anaerobic metabolism of higher chlorinated methanes present in the soil (Vogel et al. 1987).

5.4.3 Sediment and Soil

Information from HazDat (1998) documents the presence of chloromethane in soils at 34 waste sites and in sediments at 13 waste sites. Information on background levels in soils and sediments is very limited in the available literature. 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.

5.4.4 Other Environmental Media

As presented in Section 5.2.1, chloromethane is released from wood smoke, burning coal, 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; Palmer 1976; Rasmussen et al. 1980; Singh et al. 1982; Tassios and Packham 1985). Palmer (1976) suggested that 1 cm^3 of chloromethane gas (2.2 mg) was produced for each gram of cellulose burned (glowing combustion). 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 the temperature of the bum. Thus, quantification of chloromethane in these media will be representative of the specific source and the exact conditions of the burn rather than of general emission levels. Chloromethane has not been detected in auto exhaust (detection limit of 1 ppm) (Hasanen et al. 1979).

Chloromethane was present in the expired air of all 3 tested groups of 62 nonsmoking adults, including a control, a prediabetic, and a 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 solutions used to chlorinate drinking water did not contain chloromethane, but other higher chloromethanes were present (Otson et al. 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Chloromethane is a ubiquitous low-level constituent of air and is probably found at very low concentrations in many drinking water supplies that have used chlorine treatment for disinfection. As such, the general population will be exposed to low background levels at all times, while those living in urban centers may be exposed to slightly higher levels.

According to one report, persons living in Los Angeles, California; Phoenix, Arizona; and Oakland, California; would have daily intakes of ≈ 140.4, 108.6, and 59.7 μg/day, respectively (Singh et al. 1981a), based on a total respirable air volume of 23 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 could have been associated with leaking refrigerators that used chloromethane as a refrigerant. While refrigeration-grade chloromethane may still be available, it is not known whether it is currently used to any significant degree in refrigeration equipment. Without this information, potential exposures cannot be estimated.

Chloromethane is an impurity in vinyl chloride when the vinyl chloride is produced from the thermal dehydrochlorination of 1,2-dichloroethane (Zaidman et al. 1991). Exposures to chloromethane could take place during the manufacture of vinyl chloride or when vinyl chloride wastes have been released to the environment or to waste sites. Information is lacking to make any firm estimates of such exposure potentials. Of the 172 current or past NPL sites in HazDat (1998) showing site contamination with chloromethane, 128 of these sites (about 75%) also showed site contamination related to vinyl chloride.

Current and empirically based estimates of exposures to chloromethane in various occupations are lacking. Some insights can be gleaned from the National Institute for Occupational Safety and Health's (NIOSH's)

National Occupational Hazard Survey (NOHS) database (the NOHS database is also called the National Occupational Exposure Survey or NOES database) that estimates the number of potentially exposed workers in a variety of manufacturing jobs (Sieber et al. 1991). Based on conditions typical of the mid-1970s it was estimated that 39,343 workers had potential exposures to chloromethane (NOES 1991). The majority of these potential exposures involved occupations where chloromethane could have been used as a cleaner or pest control fumigant. There is virtually no mention in NOHS of current applications such as use as a process chemical in the manufacture of silicone rubbers. While the NOHS data are of some historical value, it is therefore doubtful whether they accurately reflect the potential number of workers subject to current occupational exposures. A number of regulations, however, are in place to protect workers from exposure to levels of chloromethane that are considered harmful.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Children are members of the general population and encounter the same exposures that are described in Section 5.5. No data were found on the measurement of chloromethane or its metabolites in amniotic fluid, meconium, cord blood, or neonatal blood that would indicate prenatal exposure. It is not known whether chloromethane in the body can cross the placenta and enter into the developing young. Since chloromethane is broken down and eliminated from the body quickly in adults, it is unlikely that chloromethane would be stored in maternal tissues or mobilized during pregnancy or lactation. Chloromethane was present in 2 of 8 samples of mothers' milk from Bayonne and Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton

Rouge, Louisiana (Pellizzari et al. 1982). No concentrations were reported and no information was given concerning the source of the chloromethane in the milk.

The levels that children could be exposed to through accidents involving chloromethane may be higher than levels affecting adults because chloromethane is heavier than air (i.e., greater concentrations near the ground).

Parents can inadvertently carry certain hazardous materials home from work on their clothes, skin, hair, tools and in their vehicles. However, since chloromethane is so volatile, it is unlikely that children would be exposed by this route. No incidents of home contamination by chloromethane were reported in the Workers' Home Contamination Study conducted under the Workers' Family Protection Act (29 U.S.C. 671a) (DHHS 1995).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

All humans are probably exposed to low concentrations of chloromethane. Those with potentially higher than average exposures include workers employed in the manufacturing and use (by analogy) industries. In addition to individuals occupationally exposed to chloromethane (see Section 5.5), there are several groups within the general population that could have exposures higher than background levels. These populations include individuals living in proximity to sites where chloromethane was produced or disposed, and individuals living near one of the 172 NPL hazardous waste sites where chloromethane has been detected in some environmental media (HazDat 1998). Chloromethane may also be a constituent in other materials such as vinyl chloride. Chloromethane exposure risks may be of concern to individuals working or living in the vicinity of sites where vinyl chloride was produced or where there is evidence vinyl chloride has been disposed.

People with very old refrigeration equipment in which chloromethane is used as a refrigerant are a population with potentially very high exposures. These refrigerators can leak and result in very high local air concentrations of chloromethane. This population is, however, likely to be small since the number of refrigerators using chloromethane has been decreasing.

5.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 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. The data on known physical and chemical properties 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, Import/Export, 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 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 (CBI) 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 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The fate of chloromethane in air is well-described because extensive air photolysis and photo-oxidation studies are available that characterize these processes. Biodegradation studies in surface water and groundwater are not as complete. 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 or municipal landfills. 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. Limited research suggests that common soil fungi may be able to generate chloromethane as well as to dehalogenate, and thus degrade, it. Since these wood rot fungi can also break down other halogenated aliphatic compounds, there is the possibility that some of the chloromethane found at waste sites could have been produced through the action of such fungi on other waste compounds. More research is needed to document the importance of these biodegradation mechanisms and to determine whether the net effects tend toward a progressive reduction in the levels of chloromethane found in contaminated soils and sediments at waste sites.

Bioavailability from Environmental Media. Experimental inhalation studies in animals and humans indicate that chloromethane is bioavailable from the atmosphere. Studies for the oral and dermal routes of exposure may be of lesser research importance than studies on inhalation pathways and the bioavailability of chloromethane from water, soil, and other environmental media.

Food Chain Bioaccumulation. The log K_{ow} for chloromethane is in the range of 0.91 to 1.086 (see Chapter 3, Table 3-2). Such low values generally mean that the BCF will be low, suggesting that chloromethane will not tend to concentrate in aquatic organisms. However, no information was identified on experimental determinations of BCF levels for chloromethane. Determinations of BCF values for organisms at various trophic levels are needed to estimate human dietary intake of chloromethane.

Exposure Levels in Environmental Media. Extensive environmental monitoring data are available for chloromethane in air, while the available data are very limited 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, or groundwater. Almost no data are available for soils. These data are needed to determine the ambient concentrations of chloromethane so that exposure of the general population as well as of terrestrial and aquatic organisms can be estimated.

Reliable monitoring data for the levels of chloromethane in contaminated media at hazardous waste sites are needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The database for chloromethane exposure levels in humans is limited to determinations of chloromethane in breast milk. A more complete database is needed to determine the current exposure levels and to estimate 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. The available NOES database of potential occupational exposures was assembled in the late 1980s and is becoming outdated. An update to this statistically based database of potential occupational exposures is needed.

Exposures of Children. Chloromethane was present in 2 of 8 samples of mothers' milk from Bayonne and Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana (Pellizzari et al. 1982). No concentrations were reported and no information was given concerning the source of the chloromethane in the milk. Studies to determine current chloromethane residues and sources in breast milk of women in the general population and in the work force are needed. Well water surveys should be conducted in areas near landfills where chloromethane has been detected at significant levels. Ingestion of chloromethanecontaminated drinking water could be an important route of exposure in children.

Current information on whether children are different in their weight-adjusted intake of chloromethane via oral and dermal exposures was not available. A study to determine this information is needed.

Exposure Registries. An exposure registry for chloromethane is not available. The development of a registry of exposures is needed to assess 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 presence of manufacturing and use facilities.

Although chloromethane is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry, it will be considered in the future. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

A project carried out at Cambridge Analytical Associates, Inc., under the direction of Dr. Samuel Fogel with NSF support will study the biodegradation of chlorinated aliphatic compounds by methane-utilizing bacteria (FEDRIP 1998).

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Methods used to analyze biological samples for chloromethane are summarized in Table 6-1. S-methyl-cysteine may be a urinary 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 (DeKok and Antheunius 1981) Analysis is performed on a reversed-phase high-performance liquid chromatography (HPLC) column using methanol and sodium hydrogen phosphate buffer gradient elution with a fluorescence detector. The reported detection limit is 1 mg/L. S-methylcysteine, along with other methylthio- compounds, can also be analyzed as methanethiol following alkaline hydrolysis and acidification (van Doom et al. 1980).

Breast milk was analyzed for chloromethane by expressing a 60 mL sample into a wide-mouth bottle and then freezing until analysis (Pellizzari et al. 1982). Analysis was performed by warming the sample and then purging it with helium and directing the chloromethane and other volatilized compounds through a Tenax adsorbant. The analytes were thermally desorbed from the Tenax onto a gas chromatography (GC) column and analyzed by mass spectrometry (MS). No recovery or accuracy information was reported. A headspace analysis for chloromethane in blood has been described (Landry et al. 1983a) as has a method for chloromethane in exhaled air (Nolan et al. 1985). No limits of detection (LODs) or recovery information were available for these methods.

Table 6-1. Analytical Methods for Determining Chloromethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (S-methyl-cysteine)	Dilution with water followed by derivatization with phthaldialdehyde.	HPLC/fluorescence	1 mg/L (ppm)	No data	DeKok and Antheunius 1981
Urine (S-methyl-cysteine and other methyl thio compounds)	Hydrolysis of 4 mL urine sample with 2 mL of 4 N sodium hydroxide at 100 °C followed by acidification to form methanethiol; introduction of aliquot of headspace into GC.	GC/FID	No data	No data	van Doorn et al. 1980
Exhaled air	Collection of breath into gas sampling bag followed by introduction of internal standard and introduction of aliquot into GC.	GC/ECD	No data	No data	Nolan et al. 1985
Rat blood (applied to human blood by Nolan et al. 1985)	Equilibration of sample at 37 °C for 3 minutes followed by injection of an aliquot of headspace into GC. (Nolan et al. 1985 added the step of heating to 100 °C to reduce rate of chloromethane loss.)	GC/ECD	No data	No data	Landry et al. 1983b
Breast milk	Warming of sample followed by purging with inert gas and adsorption of chloromethane onto Tenax; thermal desoprtion onto GC.	GC/MS	No data	No data	Pellizzari et al. 1982

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; MS = mass spectrometry

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of chloromethane in environmental samples are presented in Table 6-2. In air, chloromethane can be analyzed by NIOSH Method 1001 (NIOSH 1994). This method involves drawing a 0.4-3 L sample through a coconut charcoal tube followed by methylene chloride desorption and analysis by GC with flame ionization detection (FID). The method has a working range of 66-670 mg/m^3 for a 1.5 L sample and an LOD of 0.01 mg/tube. The method of Oliver et al. (1996) also uses a preconcentration approach, but analyte recovery is accomplished via thermal desorption. The large sample concentration factor combined with the sensitivity of the ion trap detector (ITD) provides for an LOD of less than 1 ppb. Chloromethane can also be trapped cryogenically from an aliquot of air collected into an evacuated canister followed by determination using GC with either electron capture or mass spectrometric detection (EPA 19888). LODs were reported to be in the low ppb range. Loss of chloromethane from air samples stored in canisters can impact the accuracy of the determination. Kelly and Holdren (1995) reported a 17% loss for chloromethane at 2.1 ppb stored for 33 days. On the other hand, Brymer et al. (1996) showed a loss of approximately 5% over a 30-day period for chloromethane in a canister at 2.3 ppb (v/v). They also reported a method detection limits of 0.82 ppbv and a recovery of 124%. Potential changes in analyte concentration as function of time after sample collection indicates that field control samples should be used. Field controls are always appropriate regardless of the collection approach used. Fukui and Doskey (1996) reported using a canister-based approach to collect chloromethane and other volatile compounds emitted from grasslands. Extreme care must be taken, especially at very low air concentrations, to ensure that no contamination is introduced into the sampling and analysis method; method blanks must always be used to verify the cleanliness of the sample collection and analysis system.

Chloromethane can be analyzed in municipal and industrial waste water by EPA Test Method 601-Purgeable Halocarbons or EPA Test Method 624Purgeables (EPA 1982a). Both methods are adequate for measuring chloromethane in waste waters. However, care must be exercised during sample collection because chloromethane is volatile and some of the chemical might 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 (called the "purge and trap" method). After the purging is complete, the trap is heated to desorb the chloromethane. The desorbed chloromethane is analyzed by GC using an electrolytic conductivity (EC) 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

Table 6-2. Analytical Methods for Determining Chloromethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Pumping of air through solid sorbent tubes (coconut shell charcoal) followed by elution using dichloromethane.	GC/FID (Method 1001)	0.003 mg/m^3 (1.5 ppb)	104	NIOSH 1994
Air	Collection of air into evacuated canister; introduction of aliquot of air and internal standard onto cryotrap; thermal desorption.	GC/FID/ECD, GC/SIM (Method TO-14)	low ppb	No data	EPA 1988g
Air	Pumping of air through multisorbent trap followed by a dry helium purge; thermal desorption onto a cryotrap followed by thermal desorption onto GC column.	GC/ITD	0.53 ppb (0.0011 mg/m^3)	approx. 95% (4.9% RSD at 5 ppb)	Oliver et al. 1996
Water	Addition of internal standards and purging of water sample with inert gas; adsorption of chloromethane onto adsorbent trap followed by thermal desorption.	GC/MS (Method 6210D)	No data	101% (4.7% RSD) at 0.5 µg/L (ppb) using narrow-bore GC column	Greenberg et al. 1992a
Waste water (municipal and industrial discharges)	Addition of internal standards and purging of water sample with inert gas; adsorption of chloromethane onto adsorbent trap followed by thermal desorption.	GC/EC (Method 6230B)	0.08 µg/L (0.08 ppb)	95% at 1 µg/L	Greenberg et al. 1992b
Water	Purging of sample with inert gas and trapping vapors onto adsorbent with subsequent thermal desorption of trap.	GC/EC (Method 502.1)	0.01 µg/L (0.01 ppb)	93% (8.5% RSD) at 0.40 µg/L	EPA 1989a
Water	Addition of surrogate standards followed by purging of sample with inert gas and trapping vapors onto adsorbent with subsequent thermal desorption of trap.	GC/MS (Method 524.2)	0.13 µg/L (0.13 ppb) using wide bore column	93–110% (9% RSD) at 0.1 to 10 µg/L	EPA 1989b

Table 6-2. Analytical Methods for Determining Chloromethane in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (standards)	Addition of standard compounds and internal standard to saturated salt water; immersion of SPME fiber in water for 5 minutes with stirring; removal of fiber from water and insertion of fiber into injection port for thermal desorption.	GC/MS	<25 ppb	No data	Shirey 1995
Aqueous culture medium (phytoplankton culture)	Purging of chloromethane with helium from 10 mL with adsorption onto Poropak-Q followed by thermal desorption onto GC.	GC/ECD	7 pM (0.35 ppt)	No data	Tait and Moore 1995
Water, soil, solid waste	Purging of sample with inert gas with adsorption of chloromethane onto adsorbent with subsequent thermal desportion onto GC column.	GC/EC (EPA Method 8010B)	12.5 μg/kg[a] (ppb) for high concentration soil, sludge	95% at 1 μg/L[a]	EPA 1986b
Water, soil, solid waste	Purging of sample with inert gas with adsorption of chloromethane onto adsorbent with subsequent thermal desorption onto GC column.	GC/FID/EC (EPA Method 8021A)	0.03 μg/L[a] (water)	96% (9.3% RSD)[a]	EPA 1986c
Water/waste water	Purging of sample with inert gas with adsorption of chloromethane onto adsorbent with subsequent thermal desorption onto GC column.	GC/EC (EPA Method 601) GC/MS (EPA Method 624)	0.08 μg/L (0.08 ppb) No data	91.4% 99±24%	EPA 1982a
Water (river, sea)	Injection of 1 mL of sample into flow injection analysis system.	MIMS/ITD	10 ppb	No data	Bauer and Solyom 1994

[a] Detection limits and recoveries will vary depending on the particular matrix.

EC = electrolytic conductivity; ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; ITD = ion trap detector (mass spectrometer); MIMS = membrane introduction mass spectrometry; MS = mass spectrometry; RSD = relative standard deviation; SIM = selected ion monitoring; SPME = solid-phase microextraction

(Tenax GC), and silica gel; analysis is made by GC/MS. Overpurging 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 waste water 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; extracting the volatiles, including chloromethane, for 1 minute; and then qualitatively analyzing the sample by GC/FID (EPA 1988a). The quantitative analysis method for the sample is by GC/MS and is essentially identical to EPA Method 624 (EPA 1982a).

Three additional purge-and-trap approaches with LODs as low as 0.01 μg/L (0.01 ppb) have also been described for drinking water: Standard Method 6210D (Greenberg et al. 1992a), Method 502.1 (EPA 1989a), and Method 524.2 (EPA 1989b). A purge-and-trap approach to the determination of chloromethane in an aqueous culture medium provided an LOD of 0.35 ppt (Tait and Moore 1995). A technique known as solid-phase microextraction (SPME) has been demonstrated to be applicable to low ppb chloromethane concentrations in a water matrix (Shirey 1995). In this method, a polymer-coated fiber is equilibrated in a water sample until the chloromethane partitions into the polymer coating. The fiber is withdrawn and inserted into the hot injection port of a GC, where the analyte is thermally desorbed onto the GC column.

EPA Method 5030 for analysis of chloromethane in soil and solid waste (EPA 1986b) involves the direct purge-and-trap method for low-level samples or the methanolic extraction for high-level samples, based on a hexadecane extraction as described above. For low-level samples, the soil and solid waste are placed in a purge impinger, mixed with water, purged with an inert gas, and trapped on a Tenax GC and silica gel (EPA 1988a) or on a 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 and solid waste are mixed with methanol and shaken. An aliquot of the methanol is removed, diluted with water, and purged as described above for water samples. Overpurging the sample may result in loss of some chloromethane. Analysis is performed by EPA Method 8000 (Gas Chromatography/Mass Spectrometry for Volatile Organics) and Method 8010B (Halogenated Volatile Organics) or by Method 8240 (GC/MS for Volatile Organics) (EPA 1986b). Method 8010 uses GC with an electrolytic conductivity detector. EPA Method 8021A uses analysis by GC with photoionization detection and electron capture detection in series (EPA 1986c). LODs range from 0.03 μg/L with chloromethane in water (Method 8021A) (EPA 1986c) to 12.5 μg/kg for high-concentration soils and sludges (Method 8010B) (EPA 1986b). Other method characteristics are shown in Table 6-2.

No methods for chloromethane in foods were found. However, a purge-and-trap method applicable to the determination of trihalomethanes in liquid and viscous foods has been published by researchers at the U.S. Food and Drug Administration (FDA) (McNeal et al. 1995). This method is a modification of EPA Method 524.2 (EPA 1989b) and should be applicable to the determination of chloromethane in foods. However, this method has not been validated for chloromethane.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 2.6). Methods are available for the analysis of chloromethane in blood, expired air, and breast milk. In addition, a method exists for the analysis of the metabolite S-methylcysteine in urine. Quantitative relationships have not been established between exposure and measurement of chloromethane or S-methylcysteine in these biological media. The observed variability of metabolism (see the discussion of the 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 sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans. Thus, methods for biomarkers of exposure and effect are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods appear to be available for the analysis of chloromethane in all environmental media. Methods for drinking water, groundwater, surface water, and waste water (Bauer and Solyom 1994; EPA 1982, 1989a, 1989b; Greenberg et al. 1992a, 1992b; Shirey 1995) have LODs as low as 0.01 ppb; methods for soil and solid waste (EPA 1989b, 1989c), and for workplace and ambient air (EPA 19888; NIOSH 1994; Oliver et al. 1996) have LODs in the 0.5 to 1.5 ppb range. The MRL for chronic inhalation exposure to chloromethane is 0.05 ppm and all of the methods reported for air are adequate. No MRLs have been established for ingestion exposures. No methods were identified for chloromethane in foods; the need for analytical methods would be driven by oral MRLs. 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 Ongoing Studies

No ongoing studies were located in which new methods for chloromethane might be developed.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chloromethane in air, water and other media are summarized in Table 7-1.

An acute inhalation MRL of 0.5 ppm was derived from a NOAEL of 50 ppm for motor coordination and damage to the cerebellar granule cells in a study by Landry et al. (1985).

An intermediate inhalation MRL of 0.2 ppm was derived from a LOAEL of 51 ppm for increased liver enzymes in male mice at the 6-month time point in a 2-year study by CIIT (1981).

A chronic inhalation MRL of 0.05 ppm was derived from a LOAEL of 51 ppm for axonal swelling in male mice in a 2-year study by CIIT (1981).

The risk assessments for establishing a reference concentration (RfC) for chronic inhalation exposures and a reference dose (RfD) for chronic oral exposures to chloromethane are undergoing review by an EPA work group (IRIS 1997). However, the EPA Office of Water reports an RfD of 0.004 mg/kg/day (EPA 1996a).

The EPA has not assigned a carcinogenicity classification for chloromethane (IRIS 1997). Health advisories published by the EPA Office of Water assign chloromethane to cancer group C, which indicates that the substance is a possible human carcinogen (EPA 1996a). The International Agency for Research on Cancer (IARC) has classified chloromethane as Group 3; not classifiable as to its carcinogenicity to humans (IARC 1987). The National Toxicology Program (NTP) has not classified the chemical for carcinogenicity. The National Institute for Occupational Safety and Health (NIOSH) recommends that chloromethane be treated as a potential occupational carcinogen (NIOSH 1992).

Chloromethane is on the list of chemicals subject to the requirements of "The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) (EPA 1988c). Section 313 of Title III of EPCRA, requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media (U.S. Congress 1986).

OSHA requires employers of workers who are occupationally exposed to chloromethane to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use controls and practices, if feasible, to reduce exposure to or below an g-hour time-weighted average (TWA) of 100 ppm (OSHA 1974). The acceptable ceiling concentration for chloromethane is 200 ppm. The acceptable maximum peak above this ceiling concentration is 300 ppm. Therefore, during an g-hour work shift a person may be exposed to a concentration of chloromethane measuring 200 ppm or greater, but never more than 300 ppm and only for a maximum period of 5 minutes within any 3-hour period. An exposure such as this must be compensated by exposures to concentrations less than 100 ppm so that the cumulative exposure for the g-hour shift does not exceed the 100 ppm exposure limit (OSHA 1974).

The EPA regulates chloromethane under the Clean Air Act (CAA) and has designated chloromethane as a hazardous air pollutant (HAP). The major source category for which chloromethane emissions are controlled is the synthetic organic chemicals manufacturing industry (SOCMI) and includes equipment leaks (EPA 1983b) distillation operations (EPA 1990), and reactor processes (EPA 1993a).

Chloromethane is regulated by the Clean Water Effluent Guidelines in Subchapter N of Title 40 of the Code of Federal Regulations. Electroplating is the points source category for which chloromethane is controlled as a total toxic organic (EPA 1981a). The point source categories for which chloromethane has specific regulatory performance standards include organic chemicals, plastics, and synthetic fibers (EPA 1987b, 1987c, 1987d, 1987e, 1987f, 19878, 1987h, 19871, 1987j, 1987k), steam electric power generators (EPA 1982c), metal finishing (EPA 1983c).

The Resource Conservation and Recovery Act (RCRA) identifies chloromethane as a hazardous waste from non-specific sources and has assigned it the hazardous waste numbers F024 and F025 (EPA 1981c).

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), owners of vessels or facilities are required to immediately report release of chloromethane equal to or greater than the reportable quantity of 100 pounds (45.4 kg) (EPA 1985).

Table 7-1. Regulations and Guidelines Applicable to Chloromethane

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	Drinking-water guideline values for health-related organics	None	WHO1984
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
NATIONAL			
Regulations: a. Air:			
OSHA	Air contaminants		
	Permissible Exposure Limit (PEL) 8-hr. Time weighted average (TWA)	100 ppm	29 CFR 1910.1000 OSHA 1974[b]
	Acceptable ceiling concentration	200 ppm	
	Acceptable maximum peak above ceiling for an 8-hour shift (max. duration of 5 min. in any 3 hours)	300 ppm	
EPA OAR	Hazardous Air Pollutants	Yes	Clean Air Act Amendment Title III, Section 112 (b) U.S. Congress 1990
	Standards of Performance for New Stationary Sources-		
	Subpart VV: Equipment leaks of VOCs in the Synthetic Organic Chemicals Manufacturing Industry (SOCMI)--chemicals produced by affected facilities	Yes	40 CFR 60.489 EPA 1983b
	Subpart NNN: VOC emissions from SOCMI distillation operations--chemical affected	Yes	40 CFR 60.667 EPA 1990a
	Subpart RRR: VOC emissions from SOCMI reactor processes--chemicals affected	Yes	40 CFR 60.707 EPA 1993a
	National Emission Standards for Hazardous Air Pollutants for Source Categories		
	National Emission Standards for Organic Hazardous Air Pollution from the Synthetic Organic Chemical Manufacturing Industry-Delegation of Authority	Yes	40 CFR 63.106 EPA 1994a

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
b. Water			
EPA ODW	National Primary Drinking Water Regulations		
	Special regulations, including monitoring regulations and prohibitions on lead use	Yes	40 CFR 141.40 EPA 1987a
EPA OW			
	EPA Administered Permit Programs: The NPDES-		
	Organic toxic pollutants in each of four fractions in analysis by GC/MS	Yes	40 CFR 122, Appendix D EPA 1983d
	Criteria and Standards for the NPDES-		
	Methods for organic chemical analysis of municipal and industrial wastewater (Methods 601, 624, and 1624)	Yes	40 CFR 136, Appendix A EPA 1973
	General pretreatment regulations for existing and new sources of pollution-		
	Pollutants elegible for a removal credit	Yes	40 CFR 403, Appendix G EPA 1981a
	Electroplating Point Source Category-		
	General definition	Yes	40 CFR 413.02 EPA 1981a
	Organic Chemicals, Plastics, and Synthetic fibers		
	Subpart B-Rayon Fibers-PSES		40 CFR 414.25 EPA 1987c
	Maximum for any one day	295 µg/L	
	Maximum for monthly average	110 µg/L	
	Subpart C-Other Fibers-PSES		40 CFR 414.35 EPA 1987e
	Maximum for any one day	295 µg/L	
	Maximum for monthly average	110 µg/L	
	Subpart D-Thermoplastic Resins-PSES		40 CFR 414.45 EPA 1987g
	Maximum for any one day	295 µg/L	
	Maximum for monthly average	110 µg/L	
	Subpart E-Thermosetting Resins		40 CFR 414.55 EPA 1987f
	Maximum for any one day	295 µg/L	
	Maximum for monthly average	110 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Subpart F-Commodity Organic Chemicals		40 CFR 414.65 EPA 1987h
	Maximum for any one day	295 µg/L	
	Maximum for monthly average	110 µg/L	
	Subpart G-Bulk Organic Chemicals-		
	Applicability; description of the bulk organic chemicals subcategory	Yes	40 CFR 414.70 EPA 1987i
	PSES		
	Maximum for any one day	295 µg/L	40 CFR 414.75
	Maximum for monthly average	110 µg/L	EPA 1987j
	Subpart H-Speciality Organic Chemicals--		
	PSES		
	Maximum for any one day	295 µg/L	40 CFR 414.85
	Maximum for monthly average	110 µg/L	EPA 1987o
	Subpart I-Direct Discharge Point Sources that Use End-of-Pipe Biological Treatment-effluent limitations: BAT and NSPS		40 CFR 414.91 EPA 1987k
	Maximum for any one day	190 µg/L	
	Maximum for monthly average	86 µg/L	
	Subpart J-Direct Discharge Point Sources That Do Not use End-of Pipe Biological Treatment-effluent limitations: BAT and NSPS		
	Maximum for any one day	295 µg/L	40 CFR 414.101
	Maximum for monthly average	110 µg/L	EPA 1987m
	Steam Electric Power Generating Point Source Category		
	Pretreatment standards for new sources (PSNS)		40 CFR 423.17 EPA 1982d
	Maximum for any time	0.2 mg/L	
	List of 126 priority pollutants	Yes	40 CFR 423, Appendix A EPA 1982e
	Metal Finishing Point Source Category		
	Metal finishing subcategory-Definition of total toxic organics (TTO)	>0.01 mg/L	40 CFR 433.10 EPA 1983e

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Pesticide Chemicals		
	Subpart D-Test Methods for Pesticide Pollutants		40 CFR 455.50, Table 4 EPA 1993b
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that use end-of-pipe biological treatment		
	Daily maximum	190 µg/L	
	Monthly average	86 µg/L	
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that do not use end-of-pipe biological treatment		40 CFR 455.50, Table 5 EPA 1993b
	Daily maximum	295 µg/L	
	Monthly average	110 µg/L	
	PSES and PSNS for priority pollutants		40 CFR 455.50, Table 6 EPA 1993b
	Daily maximum	295 µ/L	
	Monthly average	110 µg/L	
EPA OW	Ambient Water Quality Criteria For the Protection of Human Health:		EPA 1980
	Ingestion of water and aquatic organisms	1.4 mg/L	
	Ingestion of aquatic organisms only	3.28 mg/L	
c. Other:			
DOT	Hazardous Materials Table	UN 1975	49 CFR 172.101 DOT 1990a
	Hazardous substances other than radio nuclides: RQ	1000 pounds (454 kg)	49 CFR 172.101, Appendix A DOT 1990b
EPA-OERR	List of Hazardous Substances and Reportable Quantities		
	Statutory	1 pound	40 CFR 302.4 EPA 1985
	Final RQ	100 pounds (45.4 Kg)	
	Toxic Chemical Release Reporting: Community Right-to-know		
	Specific toxic Chemical Listings	Yes	40 CFR 372.65 EPA 1988c

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA-OSW	Criteria for Municipal Solid Waste Landfills		
	Constituents for detection monitoring	Yes	40 CFR 258, Appendix I EPA 1991a
	List of hazardous inorganic and organic constituents	Yes	40 CFR 258, Appendix II EPA 1991b
	Lists of Hazardous Wastes		
	Hazardous wastes from non-specific sources- F024, F025 wastes	Yes	40 CFR 261.31 EPA 1981c
	Chemical analysis methods	Yes	40 CFR 261, Appendix III EPA 1983c
	Basis for listing hazardous waste	Yes	40 CFR 261, Appendix VII EPA 1981d
	Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities		
	Ground-water monitoring list	Yes	40 CFR 264, Appendix IX EPA 1987n
	Land Disposal Restrictions-		
	Waste prohibitions-solvent wastes	Yes	40 CFR 268.30 EPA 1988b
	Treatment standards for hazardous waste--Technical amendment of final rule (40 CFR 268.40; waste code F039)	Wastewater 0.19 mg/L Nonwastewater 30 mg/kg	62 FR 7502 EPA 1997
	Universal treatment standards--Technical amendment of final rule (40 CFR 268.48)	Wastewater 0.19 mg/L Nonwastewater 30 mg/kg	
	Land Disposal Restrictions for Newly Identified and Listed Hazardous Wastes and Hazardous Soil (proposed rule)	Yes	58 FR 48092 EPA 1993c
EPA OPPTS	Chemical Information Rules		
	Chemical lists and reporting periods	Yes	40 CFR 712.30 EPA 1982c
	Health and Safety Data Reporting		
	Affected substances and mixtures	Yes	40 CFR 716.120 EPA 1988d

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
Guidelines:			
a: Air:			
ACGIH	Ceiling Limit for Occupation Exposure		
	TLV-TWA (skin)	50 ppm 103 mg/m^3	ACGIH 1996
	TLV-STEL (skin)	100 ppm (207 mg/m^3)	
NIOSH	Recommended Exposure Limit for Occupation Exposure--Time-weighted average (TWA)-up to 10 hours per 40-hour workweek	lowest feasible concentration (1.6 LOQ)	NIOSH 1992
b. Water:			
EPA ODW	1-d Health Advisory (child	9 mg/L	EPA 1996a
	10-d Health Advisory (child)	0.4 mg/L	
	Lifetime Health Advisory (adult)	0.003 mg/L	
	Longer-term Health Advisory.	0.4 mg/L (child) 1 mg/L (adult)	
	RfD	0.004 mg/kg/d	
d. Other:			
ACGIH			
	Carcinogenicity Designation (Proposed)	A4[c]	ACGIH 1996
EPA	Cancer Classification	C	EPA 1996a
	RfD	0.004 mg/kg/day	
	DWEL	0.1 mg/L	
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations		NATICH 1992
AZ	1 hour	3.6x10^{+1} µg/m^3 (0.017 ppm)	
	24 hour	9.5 µg/m^3 (0.005 ppm)	
	Annual	2.6x10^{-2} µg/m^3 (0.013 ppb)	
CT	8 hour	2.10x10^{+3} µg/m^3 (1.02 ppm)	
FL-FtLdle	8 hour	1.10 mg/m^3 (0.053 ppm)	
FL-Pinella	8 hour	1.05 x10^{+3} µg/m^3 (1.02 ppm)	
	24 hour	2.52 x10^{+2} µg/m^3 (0.122 ppm)	

Table 7-1. Regulations and Guidelines Applicable to Chloromethane (continued)

Agency	Description	Information	References
STATE (cont.)			
KS	Annual	7.14 μg/m^3 (0.003 ppm)	
KS-KC	Annual	7.14 μg/m^3 (0.003 ppm)	
KY	8 hour	5.25 mg/m^3 (2.54 ppm)	State of Kentucky 1986
LA	Annual	5.56x10^{+1} μg/m^3 (0.027 ppm)	
ME	15 minutes	2.10x10^{+4} μg/m^3 (10.17 ppm)	
	24 hour	1.70x10^{+3} μg/m^3 (0.823 ppm)	
MI	Annual	1.6 μg/m^3 (0.001 ppm)	NATICH 1992
ND	1 hour	2.07 mg/m^3 (4.27 ppm)	
	8 hour	1.03 mg/m^3 (0.499 ppm)	
NV	8 hour	2.50 mg/m^3 (1.21 ppm)	
NY	1 year	2.10x10^{+3} μg/m^3 (1.017 ppm)	
OK	24 hour	1.05x10^{+3} μg/m^3 (0.508 ppm)	
PA-Phil.	1 year	2.52x10^{+3} μg/m^3 (1.22 ppm)	
	Annual	1.20x10^{+3} ppb (2.48x10^3 μg/m^3)	
TX	30 minutes	1.03x10^{+3} μg/m^3 (0.499 ppm)	
	Annual	1.03x10^{+2} μg/m^3 (0.050 ppm)	
VA	24 hour	1.70x10^{+3} μg/m^3 (0.823 ppm)	
VT	Annual	1.00x10^{-2} μg/m^3 (0.005 ppb)	
WA-SWEST	24 hour	3.50x10^{+2} μg/m^3 (0.169 ppm)	
b. Water			
	Water Quality Criteria: Human Health		
AZ	Drinking water	0.50 μg/L	NATICH 1988
AZ	Drinking water (guideline)	0.19/L	FSTRAC 1990
KS	Drinking water (guideline)	0.19 μg/L	

[a] Group 3 = The IARC working group has concluded that chloromethane is not classifiable as to its carcinogenicity to humans.
[b] A U.S. Court of Appeals rescinded the 1989 PELs promulgated by OSHA. Only PELs in place prior to the 1989 rule are currently allowed.
[c] A4 = Not classifiable as a human carcinogen: there are inadequate data on which to classify the agent in terms of its carcinogenicity in humans and/or animals.

BAT = Best Available Technology Economically Achievable; BEI = Biological Exposure Indicies; DWEL = Drinking Water Equivalent Level; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; GC/MS = Gas Chromatography/Mass Spectroscopy; IARC = International Agency for Research on Cancer; LOQ = Limits of Quanitation; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; NSPS = New Source Performance Standards; OAR - Office of Air and Radiation; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; PEL = Permissible Exposure Limit; PSES = Pretreatment Standards for Existing Sources; RfD = Reference Dose; RQ = Reportable Quantities; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; STEL = Short-term exposure Limit; TLV= Threshold Limit Value; TWA = Time-weighted Average; VOC = Volatile Organic Compound; WHO = World Health Organization

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9. GLOSSARY

Absorption-The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption-The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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.

Benchmark Dose (BMD)-is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD,, would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model-is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

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.

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.

Case-Control Study-A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report-describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series-describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

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.

Cohort Study-A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study-A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs-substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship--the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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. Epidemiology-refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity-A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life-A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

Incidence-The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

Immunological Effects-are functional changes in the immune response.

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 has been reported 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 exposure level 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.

Lymphoreticular Effects-represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL) -An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)-A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors The default value for a MF is 1.

Morbidity-State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality-Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen-A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy-The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)-The dose of a 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 Coeffkient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio-a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound-A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)-An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an &hour shift of a 40 hour workweek. Pesticide--general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics-is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model-is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model-is a type of physiologically-based doseresponse model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model-is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 4such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence-The number of cases of a disease or condition in a population at one point in time.

Prospective Study-A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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 μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)-A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a lo-hour workday during a 40-hour workweek.

Reference Concentration (RfC)-An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 No-Observed-Adverse-Effect Level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 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.

Retrospective Study-A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk-the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor-An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)-The American Conference of Governmental Industrial Hygienists (ACGIH) 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 Threshold Limit Value - Time Weighted Average (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)-An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic $Dose_{(50)}$ (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.

Toxicokinetic-The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)-A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced LF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic-any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	Chloromethane
CAS number(s):	74-87-3
Date:	November 1998
Profile status:	Draft 2 Post-Public Comment
Route:	[X] Inhalation [ ] Oral
Duration:	[X] Acute [ ] Intermediate [ ] Chronic
Key to figure:	43
Species:	Mouse

Minimal Risk Level: 0.5 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Landry DL, Quast JF, Gushow TS, Mattsson. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundamental and Applied Toxicology 5:87-98.

Experimental design: An acute MRL of 0.5 ppm was derived from a NOAEL of 50 ppm for no effect on motor coordination or damage to the cerebellar granule cells. Landry et al. (1985) evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice. Groups of 12 mice each were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. The mice were subjected to neurofunctional testing (ability to stay on a rotating 4 cm diameter rod) on days 4, 8, and 11. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. Animals were sacrificed at various times during the experiment, and the following tissues were collected, weighed, and prepared for histological evaluation: brain (cerebellum, cerebrum, brain stem), sciatic nerve, vertebral bone with spinal cord, liver, kidneys, and thymus.

Effects noted in study and corresponding doses: The MRL was derived from effects observed in the continuously exposed mice. The 400 ppm exposed mice died or were sacrificed by day 4, and the 200 ppm group by day 5, due to severe toxicity. Mice exposed to 150 ppm were sacrificed in moribund condition by day 10.5. At 200 ppm, the mice were ataxic and fell on their sides after 3 days. At 150 to 400 ppm, the mice developed motor incoordination. Performance on a rotating rod was significantly decreased at 150 ppm and greater. No effects were seen at 50 ppm or below. Histologically, degenerative changes in the cerebellum granule cells were seen at ≥100 ppm, and consisted of nuclear pyknosis and karyorrhexis. At 150 ppm on day 4, there was a moderate intracellular and extracellular cerebellar vacuolation in the Purkinje and/or molecular cell layer and in the white matter. This vacuolation was transient and not seen after day 6 or later. These effects were more pronounced in the 400 ppm mice. Similar effects were seen in mice exposed to higher concentrations intermittently (see separate entries). The apparent greater susceptibility to continuous exposure may be related to the conversion of chloromethane to a toxic metabolite, to decreased respiration at concentrations that are intolerable when exposure is continuous, and/or to diurnal susceptibility.

15 and 50 ppm	= No neurologic effects or histopathologic damage observed.
100 ppm	= Slight degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis.
150 ppm	= Moderate cerebellar lesions and severe performance decrement on neuromotor tests.

200 ppm = Incapacitated after 4 days, severe cerebellar lesions.
400 ppm , = Incapacitated after 2 days, severe cerebellar lesions.

Dose end ooint used for MRL derivation: 50 ppm; no neurological effects or histopathologic damage observed

[X] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

[ ]1 [ ]3 [ ] 10 (for use of a LOAEL)
[ ]1 [ ]3 [X] 10 (for extrapolation from animals to humans)
[ ]1 [ ]3 [X] 10 (for human variability)

Was a conversion factor used from prim in food or water to a mg/body weight dose?
If so explain: No conversion factor used.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the acute exposure NOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$NOAEL_{[HEC]}\ (ppm) = NOAEL_{[ADJ]}\ (ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$

$$= 50\ ppm \times [1] = 50\ ppm$$

where,

$NOAEL_{[HEC]}$ = the NOAEL human equivalent concentration
$NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration
Hb/g = the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A, H = the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL: 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 refrigerators (Baird 1954; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; 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.

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, 1986b; Landry et al. 1985; McKenna et al. 198 la; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have also been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice are more susceptible than rats (Morgan et al. 1982; CIIT 1981), and 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 makes the mouse a good model for the neurotoxicological effects seen in humans.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	Chloromethane
CAS number(s):	74-87-3
Date:	November 1998
Profile status:	Draft 2 Post-Public Comment
Route:	[X] Inhalation [ ] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	73
Species:	Mouse

Minimal Risk Level: 0.2 [ ] mg/kg/day [Xl ppm [ ] mg/m^3

Reference: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 408120717. Microfiche 511310.

Experimental design: An intermediate MRL of 0.2 ppm (rounded to one significant figure from 0.17) was derived from a LOAEL of 51 ppm for significantly increased serum levels of alanine amino transferase (indicative of hepatotoxicity) in male mice at the 6 month time point in a 2-year study. The objective of the study was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and B6C3F$_1$ mice. Animals (120 per sex per exposure level) were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to two years. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure (n=10, 10, 20, 80 for rats; and n=10, 10, 10, 90 for mice; respectively). Actual measured concentrations averaged for the 24-month exposure overall were 0.3±4, 51±9, 224±6, and 997±65 ppm. All animals were observed twice daily for signs of toxicity, abnormal behavior, anorexia, or abnormal physical condition. Body weights were collected weekly for 6 months and biweekly thereafter. Ophthalmic exams were performed at baseline and at sacrifice. Prior to the 18- and 24-month sacrifices, neurofunction exams were performed. Blood samples were collected from selected animals at each scheduled necropsy period for hematological and clinical chemistry evaluations; 16-hour urine samples were collected from the same animals for urinalysis. At necropsy, a gross pathology examination was performed, organs (heart, brain, gonads, liver, kidneys, and lungs) were weighed and tissue samples were collected. Histological evaluation of tissues was performed only on tissues collected from the high dose and control animals. Target organ tissues in rats (reproductive tissues, kidney liver, lung) and mice (liver, kidney, spleen) were histologically evaluated in animals of all dose groups.

Effects noted in study and corresponding doses: A dose-response effect for liver toxicity was observed in male mice. Females also had increased ALT, but the increase was not associated with treatment-related histopathological changes in the liver. Liver necrosis and other pathological changes in the liver of high dose male mice was also observed at 12, 18, and 24 months.

51 ppm	= Increased ALT levels in male mice; no histopathological changes in the liver.
224 ppm	= Increased ALT levels in male mice; no histopathological changes in the liver.
997 ppm	= Increased ALT levels; histopathological changes including necrosis, karyomegaly, polykarocytes.

Dose end point used for MRL derivation:51 ppm; increased ALT levels.

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/bodv weight dose?
If so explain: No conversion factor used.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the intermediate exposure LOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b). The $LOAEL_{[ADJ]}$ = LOAEL = 51 ppm.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$LOAEL_{[HEC]}\ (ppm) = LOAEL_{[ADJ]}(ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$

$$= 51\ ppm \times [1] = 51\ ppm$$

$LOAEL_{[HEC]}$	= the LOAEL human equivalent concentration
$LOAEL_{[ADJ]}$	= the LOAEL adjusted for duration (see above)
Hb/g	= the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A H	= the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL:
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 195 l), but exposure concentrations were not known.

Hepatic effects have been observed in animals exposed by inhalation to chloromethane at concentrations >l,000 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 ALT and AST with no necrosis). Furthermore, no hepatic lesions were observed in rats over the course of 2 years of inhalation exposure to 1,000 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 toxifying rather than detoxifying (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 finding that mice exposed to 2,500 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.

Agency Contact (Chemical Manager): Alfred Dorsey

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	hloromethane
CAS number(s):	74-87-3
Date:	November 1998
Profile status:	Draft 2 Post-Public Comment
Route:	[X] Inhalation [ ] Oral
Duration:	[ ] Acute [ ] Intermediate [X] Chronic
Key to figure:	115
Species:	Mouse

Minimal Risk Level: 0.05 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 40-8120717. Microfiche 511310.

Experimental design: A chronic MRL of 0.05 ppm (rounded to one significant figure from 0.051) was derived from a LOAEL of 51 ppm for neurological effects (swelling and degeneration of the axons of the spinal cord) in male and female mice at 18 months in a 2-year study. The objective of the study was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and B6C3F$_1$ mice. Animals (120 per sex per exposure level) were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to 2 years. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure (n=10, 10, 20, 80 for rats; and n=10, 10, 10, 90 for mice; respectively). Actual measured concentrations averaged for the 24-month exposure overall were 0.3±4, 51±9, 224±16, and 997±65 ppm. All animals were observed twice daily for signs of toxicity, abnormal behavior, anorexia, or abnormal physical condition. Body weights were measured weekly for 6 months and biweekly thereafter. Ophthalmic exams were performed at baseline and at sacrifice. Prior to the 18- and 24-month sacrifices, neurofunction exams were performed. Blood samples were collected from selected animals at each scheduled necropsy period for hematological and clinical chemistry evaluations; 16-hour urine samples were collected from the same animals for urinalysis. At necropsy, a gross pathology examination was performed, organs (heart, brain, gonads, liver, kidneys, and lungs) were weighed and tissue samples were collected. Histological evaluation of tissues was performed only on tissues collected from the high dose and control animals. Target organ tissues in rats (reproductive tissues, kidney liver, lung) and mice (liver, kidney, spleen) were histologically evaluated in animals of all dose groups.

Effects noted in study and corresponding doses: There was a consistent dose-response for neurological effects in male and female mice. At the high dose, there was a mild reduction in the number of neurons in the granular cell layer of the cerebellum with decreased width of the granular cell layer. In the high, mid, and low dose groups, axonal swelling and degeneration of minimal severity was observed in the spinal nerves and the cauda equina associated with the lumbar spinal cord.

51 ppm = Swelling and degeneration of axons in the spinal cord.

224 ppm = Swelling and degeneration of axons in the spinal cord.

997 ppm = Tremor, paralysis, mild reduction in the number of cerebellar neurons in the granular cell layer.

Dose end point used for MRL derivation:51 ppm; axonal swelling and slight degeneration of axons in the spinal cord

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/bodv weight dose?
If so explain: No conversion factor used.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the chronic exposure LOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$LOAEL_{[HEC]}\,(ppm) = LOAEL_{[ADJ]}\,(ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$
$$= 51\ ppm\ x\,[1] = 51\ ppm$$

where,

$LOAEL_{[HEC]}$	=	the LOAEL human equivalent concentration
$LOAEL_{[ADJ]}$	=	the LOAEL adjusted for duration (see above)
Hb/g	=	the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A,H	=	the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL: 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; 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.

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, 1986b; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have also been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice are more susceptible than rats (Morgan et al. 1982; CIIT 1981), and 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 makes the mouse a good model for the neurotoxicological effects seen in humans.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

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

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 1 S), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

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

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

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

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

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

LEGEND

See Figure 2-1

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

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

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

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

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

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

1 →

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

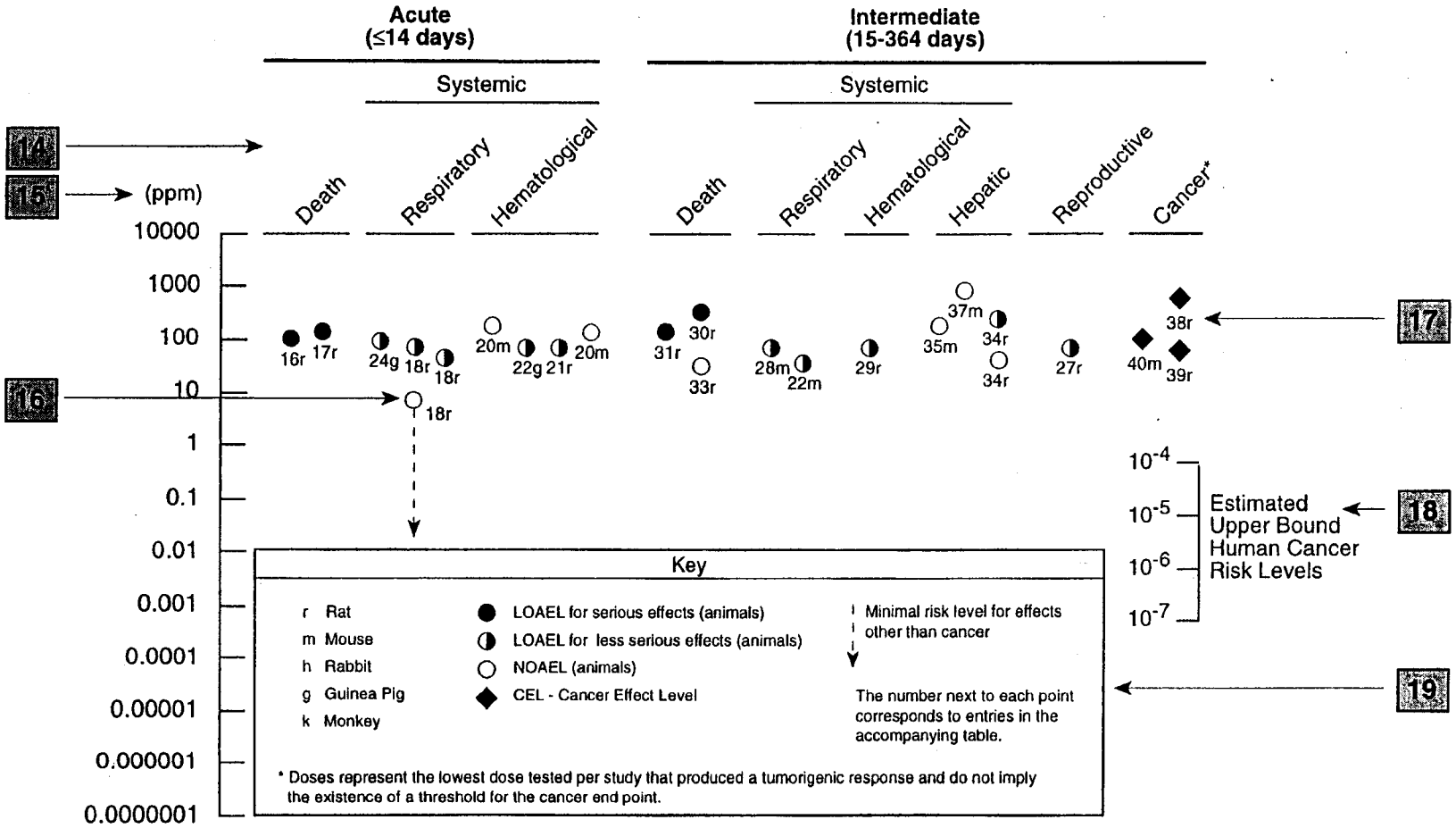
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

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

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

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level

APPENDIX C

MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA

PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to

APPENDIX C

$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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