TOXICOLOGICAL PROFILE FOR CHLOROETHANE

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for chloroethane was released in December 1989. 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:

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

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:

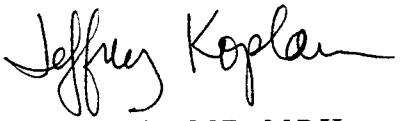
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



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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 17,199O (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: l-800-447-1544 (to be replaced by l-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://atsdrl.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 Centerfor 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.dgsys.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.

PEER REVIEW

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

1. Dr. Martin Alexander, Cornell University, Ithaca, NY.

2. Dr. Syed GhiasUddin, Toxicologist, Indiana Department of Environmental Management, Indianapolis, IN.

3. Dr. Shane Que Hee, UCLA School of Public Health, Los Angeles, CA.

These experts collectively have knowledge of chloroethane'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 chloroethane 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 activities. Chloroethane has been found in at least 282 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which chloroethane is found may increase. This information 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 chloroethane, 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 CHLOROETHANE?

Chloroethane, also called ethyl chloride, is a colorless gas at room temperature and pressure, with a characteristically sharp odor. People can smell chloroethane in the air at levels above 4 parts

chloroethane in a million parts of air by volume (ppm). It can be smelled in water at levels above 0.02 parts chloroethane in a million parts of water (ppm). In pressurized containers, chloroethane exists as a liquid. However, the liquid evaporates quickly when exposed to air. It catches fire easily and is very dangerous when exposed to heat or flame. Chloroethane does not occur naturally in the environment. It is present in the environment as a result of human activity.

In the past, the largest single use for chloroethane was for the production of tetraethyl lead, which is a gasoline additive. However, production of chloroethane has decreased dramatically as a result of stricter government regulations controlling lead in gasoline. Other applications include use in the production of ethyl cellulose, dyes, medicinal drugs, and other commercial chemicals, and use as a solvent and refrigerant. It is used to numb skin prior to medical procedures such as ear piercing and skin biopsies, and it is used in the treatment of sports injuries.

1.2 WHAT HAPPENS TO CHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Most of the chloroethane released to the environment ends up as a gas in the atmosphere, while much smaller amounts enter groundwater as a result of passage through soil. Once in the atmosphere, chloroethane breaks down fairly rapidly by reaction with substances in the air. It takes about 40 days for half of any given amount of chloroethane that is released to the atmosphere to disappear. In groundwater, chloroethane changes slowly to ethanol and a chloride salt as a result of reaction with water. In addition, some types of bacteria present in the water may break down chloroethane to smaller compounds. However, not enough is known about chloroethane to be sure if this occurs or how long it may remain in groundwater. For more information, see Chapters 3,4, and 5.

1.3 HOW MIGHT I BE EXPOSED TO CHLOROETHANE?

Humans can be exposed to chloroethane from environmental, occupational, and consumer sources. During the mid-to-late 1970s and the early 1980s chloroethane was detected in samples of outdoor air. Air samples collected in urban and suburban areas contained

chloroethane at an average level of 41-140 parts of chloroethane in a trillion parts of air (ppt; 1 ppt is l,000,000 times less than 1 ppm). Rural air samples contained less than 5 ppt. Current levels of chloroethane in the air are expected to be even lower than levels found in the past because of the sharp decrease in chloroethane production in the United States and the decrease in chloroethane release. Occurrences of chloroethane in air can be attributed to releases from factories that manufacture or use chloroethane; evaporation from some landfills, solvents, refrigerants, and anesthetics; and releases in fumes from the burning of plastics and other materials found in trash. Based on the limited amount of information available on the occurrence of chloroethane in drinking water, it can be concluded that extremely low levels of chloroethane may occur in some drinking water supplies as a result of formation during chlorination, contamination of rivers and lakes used as drinking water supplies, or seepage into groundwater resulting from storage of chemical wastes or disposal at waste sites. However, there is not enough information available to indicate what levels of chloroethane occur in drinking water under these circumstances. No data were located that indicate that chloroethane is found in food.

Exposure may also result from contact with various consumer products including some solvents, paints, and refrigerants. People may be exposed to chloroethane through skin contact as the result of its use as an agent to numb skin before ear piercing, before skin biopsy, as a treatment for sports injury, and for other medical reasons. Occupational exposure may result from inhalation or skin contact. Workers who may be exposed to chloroethane include physicians, nurses, and other medical workers, automobile mechanics, office machine mechanics, household appliance and accessory installers, assemblers, professional painters, heavy-equipment mechanics, diesel mechanics, plumbers, and pipe fitters. According to a National Institute for Occupational Safety and Health (NIOSH) survey conducted between 1981 and 1983, au estimated 49,212 workers in the United States were exposed to chloroethane in the workplace. More recent data are not available to determine how many workers might be exposed to chloroethane per year in the United States. For further information, see Chapter 5.

1.4 HOW CAN CHLOROETHANE ENTER AND LEAVE MY BODY?

Chloroethane can enter the body when a person breathes air containing chloroethane vapor. Chloroethane may also enter the body through the skin, although most of it quickly evaporates from the skin's surface. When a person drinks water containing chloroethane, it enters the body through the digestive tract. After chloroethane enters the body, it may leave the body through the lungs. Some chloroethane may also be changed to acetate, which is normally found in the body. Other chemicals formed from chloroethane leave the body in the urine.

People who happen to be near hazardous waste sites containing chloroethane are most likely to be exposed to the compound by breathing potentially contaminated air. People may also be exposed to chloroethane by drinking potentially contaminated water. See Chapter 2 for more information.

1.5 HOW CAN CHLOROETHANE AFFECT MY HEALTH?

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.

Brief exposure to high levels of chloroethane vapor can produce temporary feelings of drunkenness, and at still higher levels, lack of muscle coordination and unconsciousness. Adults have felt dizzy and have suffered decreased reaction times as a result of inhaling chloroethane. They have

also experienced stomach cramps, nausea, vomiting, and eye irritation after breathing high concentrations of chloroethane for a short time.

Workers who breathed chloroethane vapors for 1.5 to 3 years (levels of chloroethane unknown) had significantly decreased defensive responses against illness. Inhalant abusers who intentionally breathe chloroethane vapors at much higher concentrations than those found in any work environment or near any hazardous waste site have experienced these neurological effects. Long term abuse of high chloroethane concentrations causes the most adverse effects of chloroethane exposure, namely, those to the nervous system. In the worst recorded cases of chloroethane abuse by sniffing, the abusers have had severe symptoms including jerking eye movements, an inability to control muscles in voluntary movements, difficulty in speaking clearly, an inability to perform finger tapping exercises, sluggish lower limb reflexes, seizures, difficulties in walking, disorientation, short-term memory loss, and hallucinations affecting their sight and hearing. In one case, damage to motor and sensory nerves occurred.

Human patients have died after breathing chloroethane concentrations high enough to induce anesthesia. Dogs have suffered irregular heart rhythms, followed by death, when given anesthetic doses of chloroethane. Due to the risk of accidental death, chloroethane is no longer medically used as a general anesthetic during major surgery. Chloroethane can, however, be applied to the skin in the form of chloroethane spray as a numbing agent prior to minor surgery. If this spray is applied for too long, frostbite can result. Some adults have had allergic reactions to the chloroethane spray while others experienced mild pain after being sprayed for 10 seconds.

Studies have shown that chloroethane can enhance the effects of alcohol in rats. It is unknown if similar interactions between chloroethane and alcohol occur in humans.

It is not known whether chloroethane produces cancer in humans. However, long-term exposure to high levels of chloroethane vapor has been shown to produce cancer in mice. There have been no animal or human studies involving the ability of chloroethane to cause cancer when either eaten or applied to the skin. The International Agency for Research on Cancer (IARC) has reviewed

the information available concerning the abiIity of chloroethane to cause cancer. They concluded that chloroethane is not classifiable as to its carcinogenicity in humans. See Chapter 2 for more information.

1.6 HOW CAN CHLOROETHANE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

There are no known unique exposure pathways by which children may be exposed to chloroethane.

In children, there have been few recorded reports of exposures to chloroethane or adverse health effects resulting from this exposure. Brief inhalation exposure of children to very high concentrations of chloroethane has resulted in stimulation of certain nerves followed by a decrease in heart rate. One teenager died from lung paralysis during general anesthesia with chloroethane. In addition to these health effects seen specifically in children, the observed adverse effects of chloroethane exposure in adults are also expected in children. It is unknown whether children differ from adults in their susceptibility to health effects from chloroethane exposure.

We do not know whether chloroethane exposure can affect development in humans. There is not enough information to know whether chloroethane affects development in animals. Only one developmental study has been done in animals. This study with mice showed that exposure to high levels of chloroethane during pregnancy delayed bone development in the offspring.

We do not know whether chloroethane or its breakdown products within the body can reach and cross the mother's placenta into her developing baby. One study has shown that chloroethane can be found in mother's milk, but we do not know if the mothers were exposed to the compound by breathing it, eating it, or having it sprayed on their skin.

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

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

Little information exists concerning the concentrations of chloroethane that might be present in drinking water. However, past data indicate that chloroethane is not a frequent contaminant in drinking water, and therefore the risk to families from drinking water containing chloroethane is low.

Chloroethane is found in common household products such as paints, solvents, air fresheners, and deodorant sprays. Inhaling or ingesting toxic amounts of chloroethane from these products is possible. Therefore, household products such as these should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

Sometimes older children sniff household chemicals in an attempt to get high. Chloroethane is sold in drug paraphernalia shops as Ethyl Gaz, Ethyl Four Star, Black Jac, and Maximum Impact. Your children may be exposed to chloroethane by inhaling products containing it and are putting their health at serious risk if they do so. Talk with your children about the dangers of sniffing chemicals.

When household products that contain chloroethane are used properly and are not abused, the concentrations of chloroethane within them are not high enough to pose a risk of significant exposure to children.

The tendency of chloroethane to evaporate upon contact with air makes it highly unlikely that the compound could be taken home on the parents' work clothes.

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

Although there are complex analytical tests that chemists use to measure chloroethane in the blood, milk, or urine, there are no commonly used medical tests available to determine whether or not a person has been exposed to chloroethane. A breath test to determine exposure may be possible but is not commonly used.

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

The federal government develops regulations and recommendations 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 chloroethane include the following:

Chloroethane levels in the workplace are regulated by QSHA. The occupational exposure limit for an g-hour work day of a 40-hour work week is 1,000 ppm. The EPA requires industry to report discharges or spills of 100 pounds or more. See Chapter 7 for more information.

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: l-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 nrofnes. contact

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

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 chloroethane. 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.

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 (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverseeffect 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 anattempt 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 chloroethane are indicated in Table 2- 1 and Figure 2-l.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chloroethane. 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

Some of the data on the health effects of chloroethane following inhalation exposure were taken from a study by Troshina (1966). This report does not provide an adequate description of experimental methods or results. Consequently, the results of the study are not included in Table 2-l or plotted in Figure 2-l as levels of significant exposure.

2.2.1.2 Death

Use of chloroethane as a general anesthetic has occasionally resulted in the death of human patients (Konietzko 1984; Kuschinsky 1970; Lawson 1965; Lehman and Flury 1943). In the years between 1945 and 1964, there were 71 deaths attributed to chloroethane inhalation in the United Kingdom (Dawkins 1964). Only chloroform has been blamed for more anesthetic deaths than chloroethane (Lawson 1965). Death from respiratory paralysis (Kuschinsky 1970) and toxic injury to the heart (Lehman and Flury 1943) have been reported following anesthesia with chloroethane. Death of a man following abuse of chloroethane has also been reported (Yacoub et al. 1993). Although the blood concentration of chloroethane was 65 mg/dL in this man shortly after death, the study authors believed that because of resuscitation attempts for about 65 minutes, concentrations of chloroethane resulting in death were actually greater than the measured concentration. Levels of significant exposure are not reported in Table 2- 1 or plotted in Figure 2- 1 because concentrations of chloroethane lethal to humans are not known.

Mortality produced by inhalation of high concentrations of chloroethane vapor has been studied quantitatively in animals. The minimum lethal concentration of chloroethane in a 2-hour exposure study in mice was 56,860 ppm (Lazarew 1929). In another 2-hour exposure test, the minimum lethal concentration was 54,948 ppm in rats and mice (Troshina 1966). In this case, death was probably caused by asphyxiation. Exposure to 19,000 ppm chloroethane for 4 hours did not produce mortality in rats or mice (NTP 1989). The lethal concentration of chloroethane increased as the duration of exposure decreased in guinea pigs exposed to chloroethane concentrations ranging from 0 to 241,000 ppm for 5 minutes to 13.5 hours (Sayers et al.1929). Exposure to 20,000 ppm chloroethane for 9 hours was not lethal to guinea pigs in this study. Death was reported during or after exposure of guinea pigs to 40,000 ppm for 9 hours (2/6), 87,000 ppm for 4.5 hours (6/6), 76,000 ppm for 90 minutes (4/4), and 51,000 ppm for 40 minutes (l/3).

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
ACUTE EXPOSURE									
Death									
1	Mouse (NS)	2 hr					56860	(minimum lethal concentration)	Lazarew 1929
2	Gn Pig (NS)	540 min					40000	(2/6 died)	Sayers et al. 1929
Systemic									
3	Human	8.5 min	Gastro	25000	33600	(nausea, vomiting during recovery from anesthesia)			Davidson 1925
4	Human	2-4 breaths	Gastro		20000	(mild abdominal cramps)			Sayers et al. 1929
			Ocular	20000	40000	(slight eye irritation)			
5	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d	Resp	9980					Landry et al. 1982
			Cardio	9980					
			Gastro	9980					
			Hemato	9980					
			Musc/skel	9980					
			Hepatic	9980					
			Renal	9980					
			Endocr	9980					
			Dermal	9980					
			Ocular	9980					
			Bd Wt	9980					

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
6	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d	Bd Wt	19000			NTP 1989
7	Mouse (B6C3F1)	11 d 23 hr/d	Resp	4843			Landry et al. 1987, 1989
			Cardio	4843			
			Gastro	4843			
			Hemato	4843			
			Musc/skel	4843			
			Hepatic	4843			
			Renal	4843			
			Endocr	4843			
			Dermal	4843			
			Ocular	4843			
			Bd Wt	4843			
8	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d	Bd Wt	19000			NTP 1989
9	Mouse (CF-1)	Gd 6-15 6 hr/d	Hepatic	4946 F			Scortichini et al. 1986
			Bd Wt	4946 F			

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
10	Gn Pig (NS)	90-540 min	Resp	20000	40000	(slight parabronchial pneumonia)			Sayers et al. 1929
			Cardio	20000			40000	(degeneration of heart muscle of guinea pigs that died)	
			Hepatic		20000	(liver pathology not further described)			
			Renal	20000			40000	(fatty or granular degeneration of the cortex)	
11	Dog (Beagle)	2 wk 5 d/wk 6 hr/d	Resp	9980 M					Landry et al. 1982
			Cardio	9980 M					
			Gastro	9980 M					
			Hemato	9980 M					
			Musc/skel	9980 M					
			Hepatic	9980 M					
			Renal	9980 M					
			Endocr	9980 M					
			Dermal	9980 M					
			Ocular	9980 M					
			Bd Wt	9980 M					
Immunological/Lymphoreticular									
12	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		9980					Landry et al. 1982
13	Mouse (B6C3F1)	11 d 23 hr/d		4843					Landry et al. 1987, 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
14	Dog (Beagle)	2 wk 5 d/wk 6 hr/d		9980 M					Landry et al. 1982
	Neurological								
15	Human	up to 22 min			13000	(subjective feeling of intoxication, increased reaction times)	19000	(distinct intoxication, slight analgesia, decreased reaction times)	Davidson 1925
16	Human	8.5 min		25000	33600	(nausea, vomiting during recovery from anesthesia)			Davidson 1925
17	Human	2-4 breaths			20000	(marked dizziness)			Sayers et al. 1929
18	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d			9980	(slight lethargy)			Landry et al. 1982
19	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		19000					NTP 1989
20	Mouse (B6C3F1)	11 d 23 hr/d		4843					Landry et al. 1987, 1989
21	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d		19000					NTP 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
22	Gn Pig (NS)	540 min		10000	20000 (unsteady, sluggish, dizzy)		Sayers et al. 1929
23	Dog (Beagle)	2 wk 5 d/wk 6 hr/d			9980M (hyperactivity during exposure in 1/2 dogs)		Landry et al. 1982
	Reproductive						
24	Rat (Fischer- 344)	5d 6 h/day		15000			Fedtke et al. 1994a
25	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		9980			Landry et al. 1982
26	Mouse (B6C3F1)	5 d 6 hr/day			15000F (approximately 35% decrease in uterine weight)		Fedtke et al. 1994a
27	Mouse (B6C3F1)	11 d 23 hr/d		4843			Landry et al. 1987, 1989
28	Mouse (CF-1)	Gd 6-15 6 hr/d		4946 F			Scortichini et al. 1986
29	Dog (Beagle)	2 wk 5 d/wk 6 hr/d		9980 M			Landry et al. 1982

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
30	Mouse (CF-1)	Gd 6-15 6 hr/d		1504[b]	4946 (increased incidence of small centers of unossified bone in the skull)		Scortichini et al. 1986
INTERMEDIATE EXPOSURE							
Systemic							
31	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	19000			NTP 1989
			Cardio	19000			
			Gastro	19000			
			Hepatic	19000			
			Renal	19000			
			Endocr	19000			
			Dermal	19000			
			Bd Wt	19000			
32	Mouse (B6C3F1)	21 d 6 hr/d	Hepatic	15000			Bucher et al. 1995
			Endocr	15000			
			Bd Wt	15000			

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
33	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	19000			NTP 1989
			Cardio	19000			
			Gastro	19000			
			Hepatic	19000			
			Renal	19000			
			Endocr	19000			
			Dermal	19000			
			Bd Wt	19000			
Immunological/Lymphoreticular							
34	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
35	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
Neurological							
36	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
37	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Reproductive						
38	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
39	Mouse (B6C3F1)	21 d 6 hr/d			15000F (small increase in the average duration of the estrous cycle, no consistent changes in hormone levels)		Bucher et al. 1995
40	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
	CHRONIC EXPOSURE						
	Death						
41	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d				15000 (decreased survival)	NTP 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Systemic							
42	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d	Resp	15000			NTP 1989
			Cardio	15000			
			Gastro	15000			
			Musc/skel	15000			
			Hepatic	15000			
			Renal	15000			
			Endocr	15000			
			Dermal	15000			
			Bd Wt	15000			
43	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d	Resp	15000			NTP 1989
			Cardio	15000			
			Gastro	15000			
			Musc/skel	15000			
			Hepatic	15000			
			Renal	15000 M	15000F	(scattered foci of tubular regeneration, minimal glomerulosclerosis)	
			Endocr	15000			
			Dermal	15000			
			Bd Wt	15000			
Immunological/Lymphoreticular							
44	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
45	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000			NTP 1989
	Neurological						
46	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989
47	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000 M	15000F (hyperactivity during exposure)		NTP 1989
	Reproductive						
48	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989
49	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000			NTP 1989

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

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL			Reference
					Less serious (ppm)	Serious (ppm)		
Cancer								
50	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d				15000 M	(CEL: 5/50 skin trichoepithelioma, sebaceous gland adenoma, or basal cell carcinoma)	NTP 1989
						15000 F	(CEL: 3/50 malignant astrocytomas in the brain significantly different from historical but not concurrent controls)	
51	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d				15000 F	(CEL: 43/50 uterine carcinomas; 8/48 hepatocellular carcinomas or adenomas)	NTP 1989
						15000 M	(CEL: 10/48 lung adenomas or carcinomas)	

[a] The numbers correspond to entries in Figure 2-1. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[b] The acute-duration inhalation minimal risk level (MRL) of 15 ppm was derived by dividing the 1,504-ppm NOAEL by an uncertainty factor of 100 (10 for interspecies extrapolation, 10 for human variability).

Bd Wt = body weight; Cardio = cadiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)

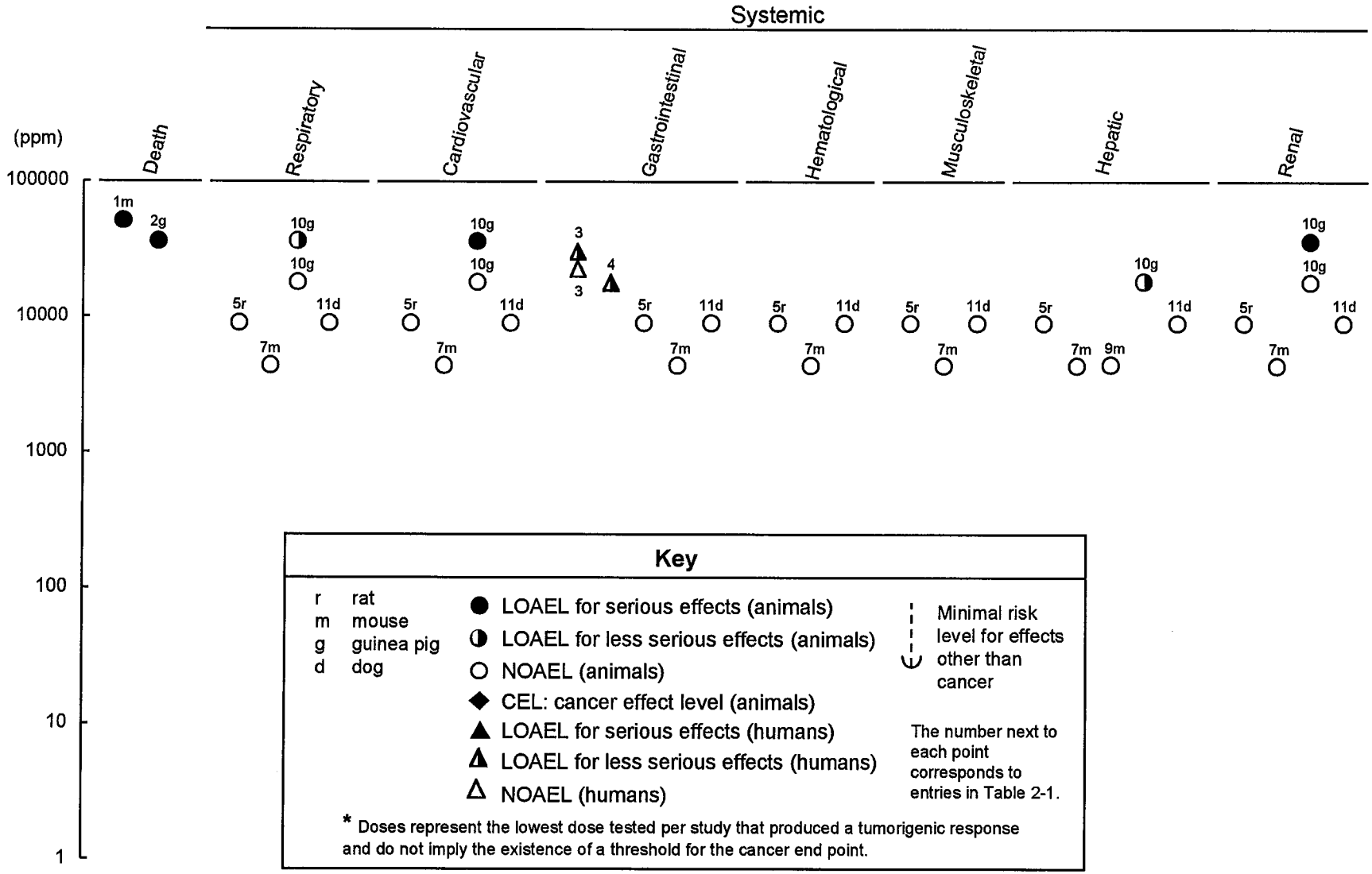


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Acute (≤14 days)

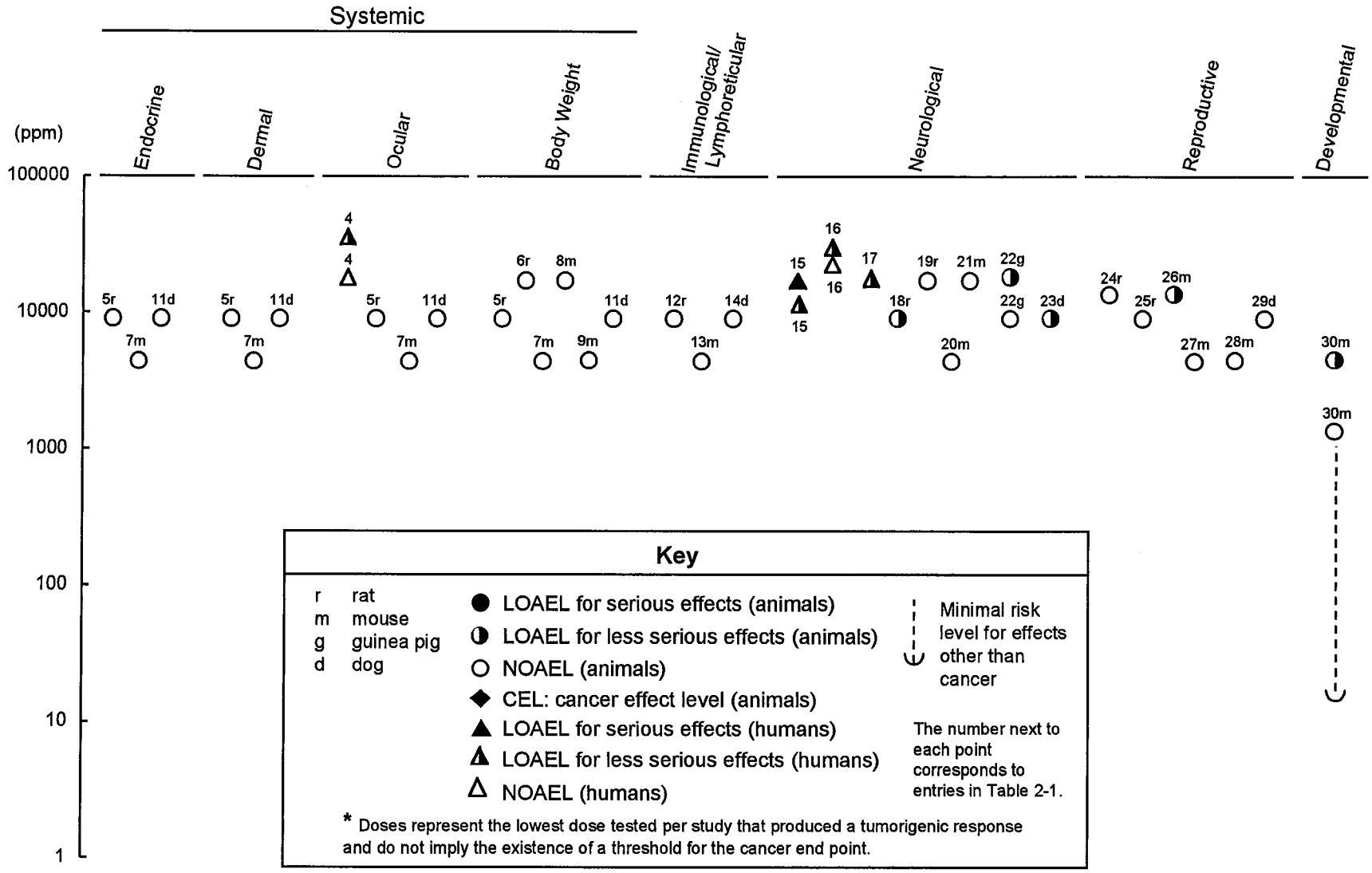


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Intermediate (15-364 days)

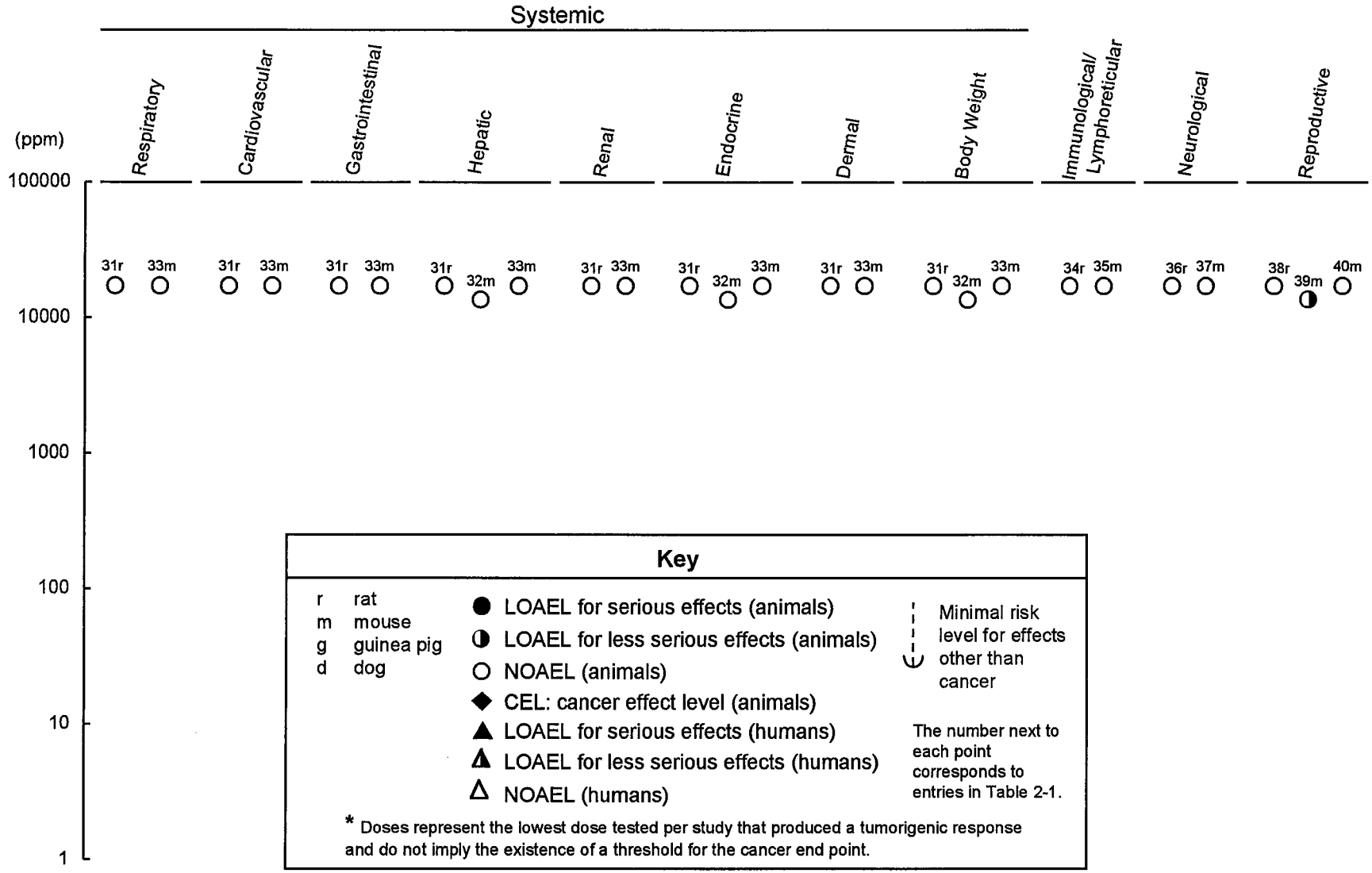
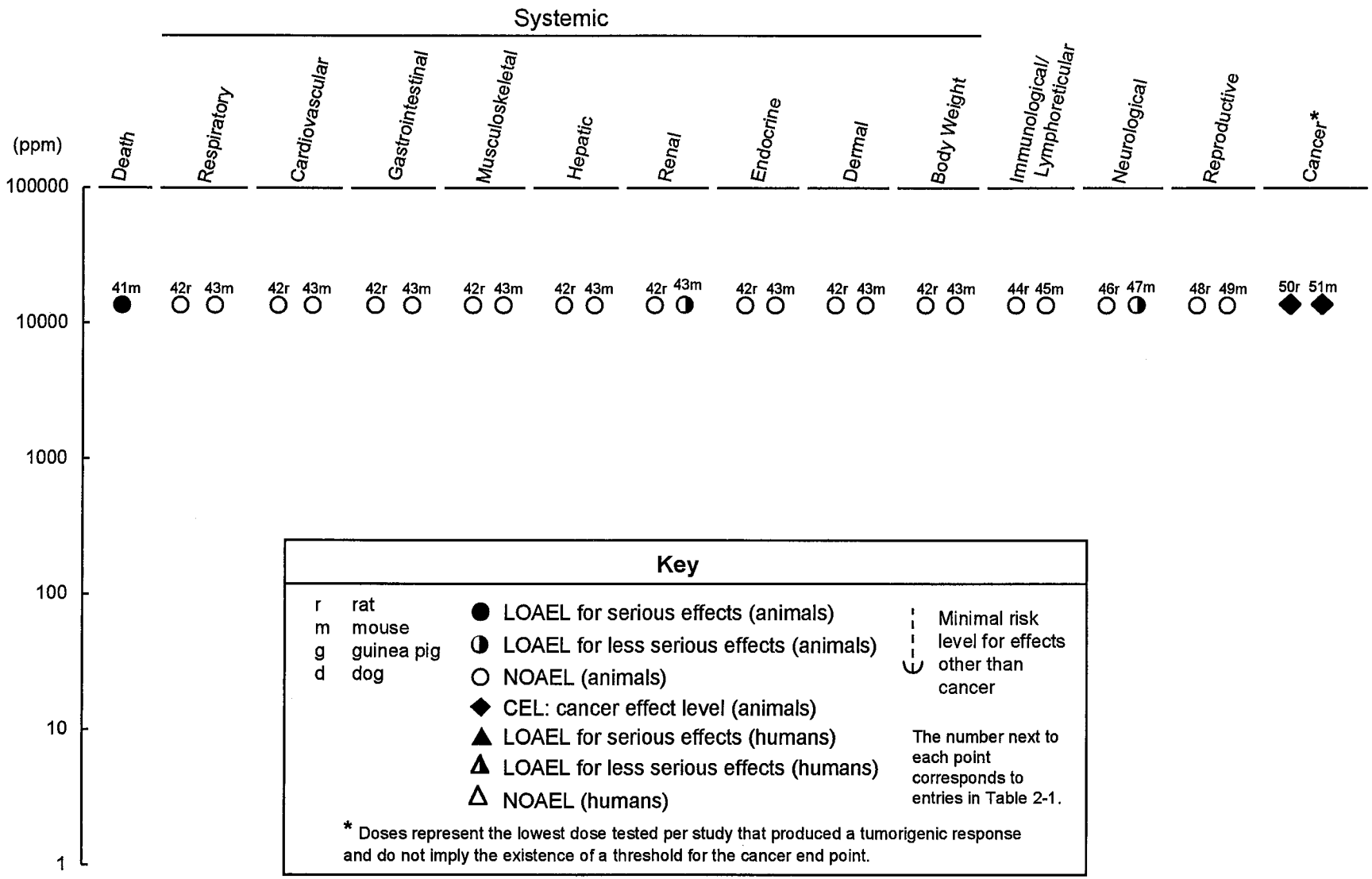


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Chronic (≥365 days)



Studies in which animals were repeatedly exposed to chloroethane for 14 days or less did not report deaths resulting from inhalation of this compound. No mortality was reported in rats exposed to 436 ppm 4 hours/day for 8 exposures in 10 days (Gohlke and Schmidt 1972; Schmidt et al. 1972), in mice exposed to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), in rats and dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982) or in rats and mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989).

Mortality was not increased significantly by chloroethane exposure in studies of intermediate duration (15-364 days). Mortality was not observed in rats or mice exposed to chloroethane at 19,000 ppm 6 hours/day, 5 days/week for 13 weeks (NTP 1989). At 10,000 ppm, 1 male mouse died. No discussion was provided on whether or not this death was exposure related. Therefore, this death is not included in Table 2-l or Figure 2- 1.

In a chronic inhalation study, rat survival was not reduced compared to controls following exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 1102 weeks (NTP 1989). The concurrent controls, however, had abnormally low survival rates after week 90 of the study. Survival was significantly reduced in mice following exposure to 15,000 ppm chloroethane for 100 weeks; the effect was found in males after 330 days and in females after 574 days (NTP 1989). An ascending urinary tract infection may have contributed to the reduced survival in male mice. The decreased survival in female mice was attributed to uterine cancer.

All LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. The results of the study by Troshina (1966) were not used as levels of significant exposure because experimental methods and results were not described in sufficient detail.

Respiratory Effects. Chloroethane in combination with nitrous oxide and oxygen was used to maintain anesthesia in human patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Respiration usually remained smooth and even, but some cases of tachypnea were seen. Respiratory rate was stimulated in 16 of 23 patients tested in a second similar study using 36,000 ppm chloroethane (Cole 1967). This study was not reported in Table 2-l or plotted in Figure 2- 1 as a NOAEL or LOAEL for the acute respiratory effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970). A level of significant exposure was not based on this report because the concentration of chloroethane administered was not known.

Studies in animals also indicate that inhalation of chloroethane may affect respiration. Exposure to 10 ppm chloroethane for 10 minutes had no consistent effect on the respiratory rate of rabbits (Watanabe 1983). This study was not used as the basis for a NOAEL because changes in respiratory rate occurred, even though no trend was found. Inhalation of 20,000 ppm chloroethane for 9 hours resulted in only very mild tissue changes, but congestion, hemorrhage, and edema were found in the lungs of guinea pigs that died following exposure to 40,000 ppm or more (Sayers et al. 1929).

Hypertrophic bronchial tubes and interstitial pneumonia were found in rats given eight 4-hour exposures to 436 ppm chloroethane; however, these effects were also present to a lesser extent in controls (Gohlke and Schmidt 1972). Consequently, these results were not considered to be indicative of adverse respiratory effects produced by chloroethane. The only other respiratory effect reported by this study was a mild transitory increase in relative lung weight, which was also not considered adverse (Schmidt et al. 1972). Absolute and relative lung weights were not affected in rats or mice exposed to chloroethane at 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). Histopathological changes were not observed in the respiratory tracts of mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987,1989). Histopathological examinations of respiratory organs and tissues were performed following inhalation of chloroethane for 6 hours/day, 5 days/week for 2 weeks at a concentration of 9,980 ppm in rats and dogs (Landry et al. 1982) and 19,000 ppm in rats and mice (NTP 1989). No effects were reported in either study

The NTP (1989) study is limited in that organs of only 3 of 10 exposed rats and 3 of 10 exposed mice were examined microscopically. Therefore, this study is not presented in Table 2-l or Figure 2-l for respiratory effects.

In an intermediate-duration study, inhalation of 19,000 ppm cbloroethane for 13 weeks (6 hours/day, 5 days/week) failed to produce lesions in the respiratory tissue of rats or mice as documented by complete histopathological examinations (NTP 1989). Inhalation of 216 ppm chloroethane for 6 months (4 hours/day, 6 days/week) caused thickening of the alveolar septa in the lungs of rats; the effect was produced by an increase in the number of macrophages (Troshina 1966). No respiratory effects were reported at 22.7 ppm.

Chronic exposure to 15,000 ppm chloroethane for approximately 2 years (6 hours/day, 5 days/week) had no non-neoplastic histopathological effects on the respiratory system in rats or mice (NTP 1989).

Cardiovascular Effects. There is some evidence that inhalation of chloroethane has cardiovascular effects in humans. Vagal stimulation followed by direct depression of cardiac tissues was reported in children exposed briefly to high concentrations of chloroethane (Bush et al. 1952). This study was not reported in Table 2-l or plotted in Figure 2-l because the effective concentration of chloroethane was not reported. A mixture of chloroethane, nitrous oxide, and oxygen was used to maintain anesthesia in patients previously made unconscious by administration of thiopentone (thiopental), or nitrous oxide, or the mixture described above (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to concentrations as low as 5,000 ppm in some cases. Pulse rate remained strong and no clinically detectable arrhythmias or changes in heart rate were observed. A similar study using 36,000 ppm chloroethane found increased systolic blood pressure and pulse rate in 16 of 25 patients tested, but again no cardiac arrhythmias were detected (Cole 1967). This study was not reported in Table 2-l or plotted in Figure 2- 1 as a NOAEL or LOAEL for the acute cardiovascular effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents.

The cardiovascular effects of chloroethane have also been studied in animals. In dogs, acute exposure to anesthetic concentrations of chloroethane resulted in cardiac irregularities, including ventricular tachycardia and asystole (Haid et al. 1954; Morris et al. 1953). Chloroethane also sensitized the heart to the effects of epinephrine (Haid et al. 1954; Morris et al. 1953). Bush et al. (1952) found that cardiac depression occurred in dogs given anesthetic doses of chloroethane. This depression was initially due to stimulation of the vagus

nerve and occurred within 2 minutes of the onset of anesthesia. Direct depression of the cardiac tissue followed and was succeeded by ventricular fibrillation and asystole, which resulted in death. None of the above studies are presented in Table 2-1 or plotted in Figure 2-l because effective chloroethane concentrations were not reported.

Rabbits exposed to 10 ppm chloroethane for 10 minutes did not experience consistent changes in blood pressure or heart rate (Watanabe 1983). Although changes in these variables did occur, this study was not used as the basis for a NOAEL because no trend was found. The occurrence of undescribed “vascular disarrangements” was reported in rats and mice killed by exposure to over 54,948 ppm chloroethane for 2 hours (Troshina 1966). Degeneration of heart muscle was found in guinea pigs that died following exposure to 40,000 ppm chloroethane for 9 hours (Sayers et al. 1929). No effects were reported at lower concentrations.

Multiple-exposure studies of acute duration reported no significant cardiovascular effects. Rat heart weight was not affected by eight 4-hour exposures to 436 ppm chloroethane over a 10-day period (Schmidt et al.1972). When histopathological examination of rats and dogs exposed to 9,980 ppm chloroethane for 2 weeks (6 hours/day, 5 days/week) was done, no cardiovascular effects were found (Landry et al. 1982). Changes in heart weights and microscopic changes in the heart were not observed in mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987,1989). Microscopic examination of the heart in 3 of 10 rats and 3 of 10 mice exposed to chloroethane at 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l and Figure 2-l for cardiovascular effects.

Inhalation of 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, had no histopathological effect on the cardiovascular system of rats or mice (NTP 1989). Arterial blood pressure 24 mmHg below controls was reported in rats exposed 4 hours/day, 6 days/week for 6 months, to 2 16 ppm chloroethane (Troshina 1966). No effects on blood pressure were noted at 22.7 ppm.

In the only chronic inhalation study of chloroethane, histopathological examinations of the heart did not reveal any effects in rats or mice exposed to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

Gastrointestinal Effects. Gastrointestinal effects have been reported in humans exposed to chloroethane by inhalation. Sayers et al. (1929) reported that mild abdominal cramps occurred in healthy human subjects who inhaled 2 breaths of 40,000 ppm chloroethane or 2-4 breaths of 20,000 ppm chloroethane. Exposure to 33,600 ppm chloroethane caused nausea and vomiting in human subjects after approximately 8 minutes; subjects exposed to 25,000 ppm did not become nauseated even after 21 minutes (Davidson 1925). Vomiting occurred in 10 of 23 patients who were anesthetized with 36,000 ppm chloroethane combined with nitrous oxide and oxygen (Cole 1967). A LOAEL was not reported in Table 2-l or plotted in Figure 2-l because chloroethane was administered in conjunction with other anesthetic agents.

Gastrointestinal effects in animals were studied by necropsy and histopathological examination. Congestion of the intestines was found in guinea pigs that died following exposure to 80,000 ppm for up to 4.5 hours (Sayers et al. 1929). Chloroethane concentrations below 40,000 ppm did not produce gastrointestinal effects in this study.

Exposure to 9,980 ppm chloroethane for 2 weeks had no histopathological effects on the gastrointestinal organs of rats or dogs (Landry et al. 1982). Histopathological changes were not observed in the gastrointestinal tracts of mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al.1987, 1989), or in rats or mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The NTP (1989) study is not presented in Table 2-l or Figure 2-l for gastrointestinal effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

No gastrointestinal effects were found by histopathological examination in longer term studies. Chloroethane concentrations of 19,000 ppm for 13 weeks (6 hours/day, 5 days/week) in rats and mice and 15,000 ppm for approximately 2 years (6 hours/day, 5 days/week) in rats and mice (NTP 1989) were all without effect on this organ system.

Hematological Effects. There was a single report of a hematological effect following chloroethane inhalation in humans. A human subject exposed to 33,600 ppm chloroethane developed cyanosis within 8.5 minutes but only when the chloroethane was not mixed with oxygen (Davidson 1925). Therefore, this effect was probably due to lack of oxygen, and this result was not used as the basis for a LOAEL.

No effects on hematologic parameters (packed cell volume, hemoglobin, red blood cell counts, platelet counts, differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin) were noted in

mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), or in rats or dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Hematologic effects were not examined in other inhalation studies of chloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to chloroethane.

Histopathological examination of muscle and bone following exposure of mice to chloroethane at 4,843 ppm 23 hours/day for 11 days did not reveal any effects (Landry et al. 1987, 1989). Histopathologic changes in muscle and bone were also not observed in rats or dogs exposed to chloroethane at 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Rats and mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years, were also examined; no increase in the occurrence of bone lesions was found (NTP 1989). The National Toxicology Program (NTP) studies of shorter duration did not include examination of bone or muscle tissue.

Hepatic Effects. In a case report of a woman who sniffed chloroethane (about 200-300 ml/day) for 4 months, an enlarged liver and mild transient disturbance of liver function which was not further described were noted (Hes et al. 1979). The woman had previously used other drugs but was reported to be free of addiction for 2 years before starting to use chloroethane. Moderately elevated serum alanine aminotransferase was observed in a man who abused chloroethane for 30 years (Nordin et al. 1988). During the 4 months before the man was examined he inhaled at least 100 ml/day chloroethane (Nordin et al. 1988). This subject also had a history of alcohol and sedative abuse, so it is not known for certain if the liver effects were a result of the chloroethane abuse.

Hepatic effects in animals have been studied by a number of researchers. A single 5minute exposure to an unspecified concentration of chloroethane produced an increase in the ratio of adenosine triphosphate/adenosine diphosphate (ATP/ADP) in the livers of mice (Oura et al. 1966). The effective concentration of chloroethane in this study was not reported, so no level of significant exposure was determined. Pale appearance, edema, congestion, and degeneration were seen in the livers of guinea pigs exposed to at least 20,000 ppm chloroethane for up to 9 hours (Sayers et al. 1929). Liver non-protein sulfhydryl (NPSH) concentration was reduced in both rats and mice following a single 6-hour exposure to chloroethane concentrations of 9,980 ppm for rats and 4,000 ppm for mice, but the study authors considered this effect to

be more adaptive than toxicologic since the change was small and no associated liver lesions were found (Landry et al. 1982).

Following 5 daily 6-hour exposures to chloroethane at 15,000 ppm, glutathione levels in the liver were reduced in male rats but not in female rats or in mice of either sex (Fedtke et al. 1994b). Liver weights were not affected in rats or mice following 5 daily 6-hour exposures to chloroethane at 15,000 ppm (Fedtke et al.1994a).

Serum amino transaminase activity (alanine and aspartate), liver enzyme activity, lipid content, histopathology, and liver weight were not significantly altered in rats given eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). Histopathological effects were reported but apparently only in groups pre-treated with ethanol. It did not appear that significant tissue changes occurred in rats exposed to chloroethane alone. Mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days had increased relative liver weight and slightly increased hepatocellular vacuolation (Landry et al. 1987, 1989). The study authors considered these effects to be mild and not indicative of significant toxicity. No changes in liver weight were noted in mice exposed to chloroethane at 4,946 ppm 6 hours/day on gestation days 6-15 and sacrificed on gestation day 18 (Scortichini et al. 1986). There was a slight increase in relative liver weight in male rats exposed to 3,980 ppm or more for 6 hours/day, 5 days/week for 2 weeks, but since no other hepatic effects were reported, this effect was not thought to indicate significant liver toxicity (Landry et al. 1982). There were no hepatic effects in dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). No significant hepatotoxicity was observed in rats or mice examined histopathologically following exposure to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The NTP (1989) study is not presented in Table 2-l or Figure 2-l for hepatic effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

Liver weight and histopathologic changes in the liver were not observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Relative liver weights were significantly ($p<0.05$) increased in male rats but not female rats or mice of either sex exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks (NTP 1989). Because histopathological changes were not observed, the increased relative liver weight is not considered adverse. Interference with hepatic function in rats, as indicated by reduced hippuric acid elimination following sodium benzoate loading, occurred following both a 60-day exposure to 5,305 ppm chloroethane and a 6-month exposure to 216 ppm (Troshina 1966). Fatty

degeneration of hepatocytes also occurred following a 6-month exposure to 216 ppm chloroethane (Troshina 1966).

Chronic exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years, produced no increase in the incidence of non-neoplastic hepatic lesions in rats or mice (NTP 1989).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to chloroethane.

Inhalation of chloroethane has been shown to produce renal effects in animals. Pale appearance, congestion, and degeneration were seen in the kidneys of guinea pigs exposed to 40,000 ppm or more for up to 9 hours (Sayers et al. 1929). No effects were found following exposure to 20,000 ppm for 9 hours.

Exposure to 436 ppm chloroethane for 4 hours/day for 8 days had no effect on rat kidney histopathology, fat content, or weight (Gohlke and Schmidt 1972; Schmidt et al 1972). Inhalation of 4,843 ppm 23 hours/day for 11 days did not produce renal effects detectable by serum chemistry analysis or histopathological examination in mice (Landry et al. 1987, 1989). Absolute and relative kidney weights were not affected in rats or mice exposed to 15,000 ppm chloroethane for 5 daily 6-hour exposures (Fedtke et al. 1994a). Blood urea nitrogen (BUN) was decreased slightly in female rats following inhalation of at least 3,980 ppm for 2 weeks (Landry et al. 1982). However, the study authors did not consider this effect to be toxicologically significant since BUN is not a direct indicator of toxicity and no associated pathological lesions were found. No other renal effects were found in rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Histopathological examination of 3 of 10 exposed rats and 3 of 10 exposed mice showed no evidence of nephrotoxicity after exposure to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). Because of the small number of animals examined microscopically, this study is not presented in Table 2-l or Figure 2-l for renal effects.

Exposure to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, had no effect on the occurrence of kidney lesions in rats or mice (NTP 1989). Inhalation of chloroethane for 6 months increased urinary amino acid levels in the rat (Troshina 1966). The concentration at which this effect occurred is not stated. Therefore, a concentration is not presented in Table 2-l or Figure 2-l.

Chloroethane vapor at a concentration of 15,000 ppm produced signs of mild nephrotoxicity in mice exposed 6 hours/day, 5 days/week for 100 weeks (NTP 1989). There was an increase in the incidence of scattered foci of tubular regeneration and minimal glomerulosclerosis in treated female mice, while treated male mice exhibited only slight enlargement of renal tubular cell nuclei. No renal effects were found in rats exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks (NTP 1989).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to chloroethane.

No effects on thyroid weight, thyroid histopathology, or adrenocorticotropic hormone activity were noted in rats exposed to 436 ppm chloroethane 4 hours/day for 8 exposures over 10 days (Gohlke and Schmidt 1972;Schmidt et al. 1972). Histopathologic changes were not observed in the adrenals, pancreas, parathyroid, pituitary, or thyroid glands of mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989), or rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Microscopic examination of the adrenals, pancreas, parathyroid, pituitary, and thyroid glands from 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l and Figure 2-l for endocrine effects.

Histopathologic changes were not observed in the adrenals, pancreas, parathyroid glands, pituitary, or thyroid glands of rats or mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or those exposed to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure to chloroethane.

Dermal effects following inhalation exposure to chloroethane were not reported in animal studies. No histopathological effects on the skin were found in mice exposed to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989); in rats or dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982); or rats or mice exposed 6 hours/day, 5 days/week to 19,000 ppm for 2 weeks (NTP 1989), 19,000 ppm for 13 weeks (NTP 1989), or 15,000 ppm for approximately 2 years. The 2-week NTP (1989) study is not presented in Table 2-1 or Figure 2-B for dermal effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

Ocular Effects. Mild eye irritation occurred in volunteers exposed briefly to 40,000 ppm chloroethane (Sayers et al. 1929). No eye irritation was reported followmg exposure to 20,000 ppm. Additional reports of eye irritation in humans during exposure to cbloroethane vapor were not identified.

Histopathological examinations of the eyes did not reveal any effects in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987,1989), or in rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Ophthalmoscopic examination of the eyes of the chloroethane-exposed dogs also did not reveal any effects.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to chloroethane. Body weight gain was not significantly affected by exposures to 15,000 ppm chloroethane for 5 daily 6-hour exposures in rats or mice (Fedtke et al. 1994a); to 436 ppm 4 hours/day for 8 of 10 days in rats (Schmidt et al. 1972); to 4,843 ppm 23 hours/day for 11 days in mice (Landry et al. 1987, 1989); to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or dogs (Landry et al.1982); or 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or mice (NTP 1989). Exposure to 4,946 ppm chloroethane 6 hours/day on gestation days 6-l 5 did not affect body weight gain of pregnant mice (Scortichini et al. 1986).

Following longer duration exposures to chloroethane, body weight gain was not significantly affected in rats or mice by exposures to 19,000 ppm 6 hours/day, 5 days/week for 13 weeks, or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). Body weight gain of 62 g less than controls was reported in rats exposed to 216 ppm chloroethane for 6 months (Troshina 1966). Because experimental methods were not described in detail, the Troshina (1966) study is not presented in Table 2-l or Figure 2-l.

2.2.1.3 Immunological and Lymphoreticular Effects

One study of immunological effects in humans exposed to chloroethane was found. Troshina (1966) compared the leukocyte phagocytic activity of 25 workers who may have been exposed to chloroethane vapors for 1.5-3 years with that of 25 control workers and found a significant decrease in phagocytic activity in the exposed workers. Levels of chloroethane in the plant were not reported. This study was not used as the source of a LOAEL value because it did not contain an adequate description of either methods or results.

There were no reliable reports of immunological effects in animals after inhalation of chloroethane.

Rat spleen and thymus weight were not affected by exposure to 436 ppm chloroethane for 4 hours/day for 8 days (Schmidt et al. 1972). White blood cell counts were also unaffected in this study (Schmidt et al. 1972). Histological changes in the thymus, spleen, and lymph nodes were not observed in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987,1989). There were no compoundrelated effects on organs or tissues of the immune system after exposure to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or dogs (Landry et al. 1982), 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or mice (NTP 1989), 19,000 ppm 6 hours/day, 5 days/week for 13 weeks, in rats or mice (NTP 1989), or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years, in rats or mice (NTP 1989).

Slightly congested or anemic spleens were observed in guinea pigs exposed to 40,000 ppm chloroethane for 90 minutes (Sayers et al. 1929). Reduced leukocyte phagocytic activity was reported in rats following both 60-day exposure to 5,305 ppm chloroethane and 6-month exposure to 2 16 ppm (Troshina 1966). These concentrations were not used as levels of significant exposure, however, because no experimental details were provided.

The highest NOAEL values for immunological effects from each reliable study in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.4 Neurological Effects

There are numerous reports of neurological effects in humans exposed to chloroethane by inhalation. Marked dizziness was reported in volunteers who were given 3 breaths of 20,000 ppm chloroethane (Sayers et al. (1929). A subjective feeling of intoxication and decreased reaction times were reported in persons during exposure to 13,000 ppm for 12 minutes (Davidson 1925). At 19,000 ppm, slight intoxication was recorded within 1 minute of exposure. This effect progressed to distinct intoxication and mild analgesia within 12 minutes. At higher concentrations, more pronounced effects appeared, such as slight incoordination within 15 minutes at 25,000 ppm and marked incoordination within 8 minutes at 33,600 ppm. Inhalation of 33,600 ppm chloroethane in oxygen produced unconsciousness in 13-17 minutes (Davidson 1925). The number of subjects exposed at each concentration was not clearly stated in this study, and there was no discussion regarding how long it took for the subjects to recover fully from the effects of chloroethane.

Chloroethane, combined with nitrous oxide and oxygen, was used to maintain anesthesia in patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Anesthesia could be maintained up to an hour using chloroethane in this manner. In a similar study using 36,000 ppm chloroethane, the length of time required to recover from anesthesia varied from 3 to 15 minutes in 33 subjects (Cole 1967). This result was not used as a level of significant exposure because chloroethane was administered in combination with other anesthetic agents.

Unconsciousness is not the only neurological effect reported in humans following exposure to anesthetic concentrations of chloroethane. Anesthetic concentrations of chloroethane also produced vagus nerve stimulation leading to cardiac depression in subjects studied by Bush et al. (1952). A LOAEL was not taken from this study because the effective concentration of chloroethane was not reported. As indicated in Section 2.2.1.2, gastrointestinal effects (nausea, vomiting, mild abdominal cramps) have been reported in people recovering from chloroethane anesthesia (Cole 1967). Because these effects are thought to have a neurological basis, the NOAEL and LOAEL associated with the gastrointestinal effects in humans in the Davidson (1925) study are also presented in Table 2-l and plotted in Figure 2-l under neurological effects.

A woman who inhaled chloroethane daily as a narcotic for 4 months had several signs and symptoms indicating cerebellar dysfunction. A neurological examination revealed ataxia, nystagmus (rapid eye movement), scanning dysarthria (imperfect speech articulation), dysdiadochokinesia (inability to perform alternating movements) of the arm, and sluggish lower limb reflexes (Hes et al. 1979). After 1 month without chloroethane, her neurological condition returned to normal. The woman had previously used other drugs but was reported to be free of addiction for 2 years before starting to use chloroethane (Hes et al. 1979). In a second case of chloroethane abuse, neurological signs and symptoms observed during the withdrawal period included a grand mal seizure, ataxia, difficulties in walking, disorientation, short-term memory impairment, and visual hallucinations (Nordin et al. 1988). Electroneurography indicated neuropathy of motor and sensory neurons (Nordin et al. 1988). Because it provided a euphoric effect, this male subject had abused chloroethane for about 30 years, and during the 4 months before he was admitted to the hospital, inhaled at least 100 ml/day. This subject also had a history of alcohol and sedative abuse, although no ethanol was in his breath on hospital admission. After approximately 6 weeks, the neurological and mental changes regressed without any residual symptoms. The study authors indicated that it was not possible to determine if the nervous system effects were toxic effects of chloroethane or withdrawal

symptoms. Levels of significant exposure were not based on these reports because the effective concentration of chloroethane was not reported.

Only one study of chloroethane exposure in an industrial setting was found. Seventy-six workers in a butyl rubber plant possibly exposed to chloroethane vapors for 2 months to 3 years were examined; approximately half had autonomic nervous system dysfunction in the form of intensified parasympathetic tonus (Troshina 1966). The study author indicated that autonomous nervous system function was measured with a battery of tests, including Ashner's test, a synapse test, and a white spot test, but additional details were not provided. Concentrations of chloroethane in the plant were not reported.

Neurological effects of chloroethane inhalation have also been studied in animals. Guinea pigs exposed to 20,000 ppm chloroethane were unsteady, sluggish, and dizzy during a 9-hour exposure (Sayers et al. 1929). Those exposed to 40,000 ppm were unsteady and dizzy after 3 minutes of exposure. At higher concentrations (>51,000 ppm), these effects were seen after shorter exposure durations, and more severe effects were found such as inability to stand, lying on the side, convulsions, and unconsciousness. Two-hour inhalation of 54,948 ppm produced nervous excitation and convulsions followed by narcosis in mice and rats (Troshina 1966). Respiratory paralysis also occurred in some cases, leading to death. Histopathological examination revealed degeneration of nerve cells in the medulla oblongata and subcortical stratum of the brain (Troshina 1966). In dogs, concentrations of chloroethane that produced anesthesia also produced stimulation of the vagus nerve and, consequently, cardiac depression (Bush et al. 1952). Premeditation with anticholinergic drugs inhibited vagal stimulation (Bush et al. 1952). Muscle twitching and tremors have also been observed in dogs during chloroethane anesthesia (Morris et al. 1953). LOAELs were not taken from these studies because the effective concentrations of chloroethane were not reported.

There were few reports of neurological effects in studies of longer duration. Brain histopathology and weight in the rat were unaffected by eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). Slight lethargy was observed in rats, and hyperactivity was observed in 1 of 2 dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Brain weight and brain or peripheral nerve histopathology were not affected. Evaluation of the dogs for gait, posture, cranial nerve reflexes, postural reactions, spinal cord reflexes, muscle tone, and pain perception also did not reveal any chloroethane-related effects (Landry et al. 1982). When mice received 11 days of near-continuous exposure to 4,843 ppm chloroethane, no neurological effects were found by function testing or histopathological examination (Landry et al. 1987, 1989). No compound-related neurological effects were

found in histopathological examinations of rats and mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 or 13 weeks (NTP 1989). No increase in the occurrence of non-neoplastic lesions was found in nervous system organs or tissues following exposure of rats and mice to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). This study did, however, report hyperactivity of female mice during the daily exposure period. A temporary increase in the threshold of electrodermal excitability occurred in rats after 60 days of exposure to 5,305 ppm, but not after 6 months of exposure to 216 ppm (Troshina 1966).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. The results of the study by Troshina (1966) were not used as levels of significant exposure because experimental methods and results were not described in sufficient detail.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to chloroethane.

Several studies investigated reproductive endpoints in animals. In dogs anesthetized with chloroethane, high concentrations resulted in decreased uterine motility and muscle tonus (Van Liere et al. 1966). This study was not used as the basis for a LOAEL because the effective concentration of chloroethane was not reported. In addition, the relevance of this endpoint to other reproductive effects is unclear. No effects on uterine weights were observed in rats exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Compared to unexposed controls, absolute and relative uterine weights were decreased by approximately 35% in mice exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels were observed in both rats and mice (Fedtke et al. 1994b). The decreases in glutathione in the uterus were greater than the decreases in glutathione observed in the liver, lungs, and kidneys. A small increase in the average duration of the estrous cycle was observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Before the exposure, estrous cycle duration was 5.15±0.15 days, while during the exposure, estrous cycle duration was 5.52±0.19 days. Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure.

Testes weights were not affected in rats exposed to 436 ppm chloroethane 4 hours/day for 8 days during a l0-day time period (Schmidt et al. 1972). Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). At 22.7 ppm, the effect subsided after the exposure period ended, but at 216 ppm no recovery occurred during the month after exposure. Methods and results were inadequately reported in this study, so it was not used for a LOAEL.

Histopathological changes in reproductive organs were not observed in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989), or in rats and dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Microscopic examination of the reproductive organs of 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l or Figure 2-l for reproductive effects. No compound-related histopathological changes were found in the reproductive organs of rats or mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

No effects on the number of live and dead fetuses or on the number and position of resorption sites were observed in mice exposed to 4,946 ppm chloroethane 6 hours/day on gestation days 6-15 (Scortichini et al. 1986). Additional studies of reproductive outcome in animals following inhalation exposure to chloroethane were not identified.

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

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to chloroethane.

Only one study of the developmental effects of chloroethane in animals was found. In mice, 6-hour inhalation exposure to 4,946 ppm chloroethane on gestation days 6-15 resulted in minimal evidence of fetotoxicity (Scortichini et al. 1986). A small, statistically significant ($p=0.05$) increase in the incidence of foramina of the skull bones (small centers of unossified bone) was observed. This effect was observed in 5,4,4, and

23% of the litters at 0, 491, 1,504, and 4,946 ppm, respectively. An increase in supernumerary ribs was also found, although this effect was not indicated as statistically significant. The incidences of litters with supernumerary ribs were 9,4, 19, and 18% at 0, 491, 1,504, and 4,946 ppm, respectively. No effects were observed on maternal body or liver weights, reproductive parameters, fetal body weight, or the incidence of external or visceral malformations in the fetuses The NOAEL and LOAEL for fetotoxic effects in mice are recorded in Table 2-l and plotted in Figure 2-l 0 Based on the NOAEL of 1,504 ppm for developmental effects in mice (Scortichini et al. 1986), an acute-duration inhalation MRL of 15 ppm was calculated, as described in the footnote to Table 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following inhalation exposure to chloroethane.

Chloroethane did not increase the number of micronuclei in bone marrow cells or affect DNA synthesis in mice exposed nose-only to 25,000 ppm chloroethane 6 hours/day for 3 days (Ebert et al. 1994). The investigators indicated that the exposure concentration used in this study was about 66% of the flammability limit and that it was the highest concentration that could be safely administered.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to chloroethane.

A study of the carcinogenicity of chloroethane vapor in animals has been completed. Inhalation exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks, produced evidence of carcinogenicity in both male and female rats (NTP 1989). The combined incidence of skin trichoepitheliomas, sebaceous gland adenomas, and basal cell carcinomas was 10% (5/50) in treated male rats and 0% (0/50) in concurrent controls. This increase was statistically significant when compared to the mean historical inhalation control incidence of 0.7% (n=300) and the historical untreated control incidence of 2% (n=1,936). It is reasonable to combine incidence data of these neoplasms because they are morphologically similar (all are epithelial tumors arising from the epidermis or associated structures). Malignant brain astrocytomas were found in 6% (3/50) of the treated female rats and 0% (0/50) of the concurrent controls. This increase was statistically significant

compared to the historical inhalation control incidence of 0.3% (n=297) and the historical untreated glial cell tumor incidence of 1.2% (n=l,969). All three affected rats died before the end of the study and it was suggested that the brain tumors may have been the cause of death. The NTP (1989) concluded that this study provides equivocal evidence of the carcinogenicity of chloroethane in both male and female rats. A CEL of 15,000 ppm for rats is reported in Table 2-1 and plotted in Figure 2-l.

There was a highly significant increase in the incidence of uterine carcinomas of endometrial origin in female mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 100 weeks (NTP 1989). These tumors, which were highly malignant and metastasized to a wide variety of organs, were found in 86% (43/50) of treated females and 0% (0/49) of concurrent controls. In addition, there was a significant increase in hepatocellular carcinomas, which occurred in treated female mice at an incidence of 15% (7/48) and concurrent controls at 6% (3/49). A significant increase in the occurrence of lymphomas in treated female mice was discounted because concurrent control values were abnormally low compared to historical control values. In males, the combined incidence of alveolar and bronchiolar adenomas was 17% (8/48), a significant increase compared to the 6% (3/50) incidence in concurrent controls. The combined incidence of adenomas and carcinomas was 21% (10/48) in exposed mice and 10% (5/50) in concurrent controls. The study authors concluded that this study provides clear evidence of the carcinogenicity of chloroethane in female mice but that the study was inadequate for male mice because of low survival. A CEL of 15,000 ppm for mice is reported in Table 2- 1 and plotted in Figure 2- 1.

2.2.2 Oral Exposure

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

2.2.2.1 Death

2.2.2.2 Systemic Effects

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.

2.2.2.6 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to chloroethane.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals following dermal exposure to chloroethane.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, or ocular effects in humans or animals following dermal exposure to chloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following dermal exposure to chloroethane.

One study investigated the musculoskeletal effects of dermally applied chloroethane in animals. Chloroethane sprayed onto a l-2-cm^2 area on the thighs of rats until the skin was blanched produced local infiltration and disintegration of muscle fibers (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

Dermal Effects. Dermally applied chloroethane is used as a local anesthetic in humans (Nielsen 1980; Noble 1979; Ott 1969; Van Ketel 1976). When sprayed on the skin, chloroethane rapidly evaporates and causes the skin to freeze, which produces a numbing sensation. It is used for procedures such as skin biopsy and ear piercing that require short periods of surface anesthesia in a small area (Ott 1969). It is also used topically to relieve pain in facial muscles during physical therapy for those suffering from temperomandibular pain and dysfunction syndrome (also known as temperomandibular joint syndrome, or TMJ) (Marbach 1996). When used as a topical anesthetic, chloroethane is usually applied for 30 seconds or less. Symptoms of frostbite can result from prolonged exposures. Three children who had their earlobes sprayed with chloroethane for several minutes all developed chemical frostbite on their ears and necks (Noble 1979). This report was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported. As discussed in Section 2.2.3.3, humans can develop dermal contact sensitivity reactions to chloroethane (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976).

Dermal effects have also been reported in animals Chloroethane has the same topical anesthetic qualities in animals as it does in humans (Dobkin and Byles 1971). Chloroethane applied to a l-2-cm^2 area on the thighs of rats until the skin was blanched produced edema in the subcutaneous tissue of the application site (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

2.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to chloroethane can result in contact sensitivity. Patch tests performed on two patients with eczema were strongly positive for chloroethane, while a third patient suffered an eczematous reaction after the use of chloroethane as a local anesthetic, indicating that allergy to chloroethane can occur. Patch tests on 15 control volunteers were negative (Van Ketel 1976). A punch biopsy taken from a woman with a positive patch test to chloroethane revealed observations consistent with a T-cell-mediated allergic reaction (Bircher et al. 1994). Microscopic examination showed marked spongiosis and a lymphohistocytic infiltrate. There was a marked dermal infiltrate of $CD3^+$ T cells (pan T cells), with a predominance of $CD4^+$ T cells (helper/suppressor cell subtypes). Most of the cells expressed lymphocyte function-associated antigen. A considerable number of CDI^+ Langerhans cells were also found in the epidermis.

No studies were located regarding immunological and lymphoreticular effects in animals following dermal exposure to chloroethane.

2.2.3.4 Neurological Effects

Mild pain was reported when chloroethane was sprayed on a small area of 1 hand each of 40 women (Selby and Bowles 1995). The chloroethane was sprayed for 10 seconds, from a height of 20 cm. This procedure was used as analgesia for venous cannulation, a procedure that was reported to be more painful without pretreatment with chloroethane.

There is one study of the neurological effects of dermally applied chloroethane in animals. Rats were sprayed with chloroethane until their skin was blanched, and examination of the nerve fibers at the site of application (a 1-2-cm^2 area of the thigh) revealed thickening of the fibers and swelling of the Schwann cell nuclei (Kenig 1956). These effects subsided within 10 days of application. This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

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

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.

2.2.3.8 Cancer

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

2 . 3 TOXICOKINETICS

Chloroethane is readily absorbed following inhalation exposure. Data regarding the absorption of chloroethane following oral exposure were not identified. Based on physical properties, a dermal flux rate of

0.99 mg/cm^2 hour has been estimated. Partition coefficients indicate that chloroethane, once absorbed, would have a greater affinity for fat than for muscle or the liver.

The metabolism of chloroethane has not been studied in humans. In rats and mice, the two major pathways of chloroethane metabolism are the production of acetaldehyde by cytochrome P450, and conjugation of chloroethane with glutathione to form *S*-ethyl-glutathione. Acetaldehyde is rapidly metabolized to acetic acid. The glutathione metabohtes are further metabolized to *S*-ethyl-L-cysteine in mice, and *S*-ethyl-*N*-acetyl-L-cysteine in both rats and mice. Glutathione conjugate metabolites of chloroethane are excreted in the urine, while unmetabolized chloroethane is exhaled.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Chloroethane is readily absorbed through the lungs in humans and animals (Konietzko 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). The rapidity of anesthesia in humans and animals following inhalation exposure supports this contention (Dobkin and B yles 197 1; Finer 1966; Lawson 1965). Human subjects were exposed to about 5 mg ^{38}Cl-labeled chloroethane for 30 seconds by taking 1 breath through the mouth and then holding it for 30 seconds (Morgan et al. 1970). Approximately 18% of the radioactivity was exhaled in the first 2 breaths indicating that about 82% was retained.

No data are available to indicate that absorption of chloroethane would be different in children as compared to adults. Exposure to chloroethane is most likely via inhalation. Since infants and adolescents breathe more air per kilogram than adults, it is possible that children could inhale more chloroethane relative to their body weight than adults. However, infants have less developed alveoli than adults, which may result in a smaller surface area for absorption (NRC 1993).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals following oral exposure to chloroethane.

2.3.1.3 Dermal Exposure

A dermal flux rate of 0.99 mg/cm^2/hour was estimated based on the physical properties of chloroethane (Fiserova-Bergerova et al. 1990). Based on physical properties, the study authors considered chloroethane to have no significant dermal absorption potential. No quantitative studies were located regarding absorption in humans or animals following dermal exposure to chloroethane.

2.3.2 Distribution

Partition coefficients for human blood and serum measured *in vitro* at 40 °C were 1.9 for blood/air and 1.2 for serum/air (Morgan et al. 1970). A blood/air partition coefficient for humans of 2.69±0.2 has also been determined in vitro at 37°C (Gargas et al. 1989). Rat tissue/air partition coefficients of 38.6±0.7, 4.08±0.39, 3.61±0.32, and 3.22±0.68 for fat, blood, liver, and muscle, respectively, suggest that chloroethane has a higher affinity for fat than for blood, liver, or muscle (Gargas et al. 1989). These partition coefficients were determined *in vitro* at 37 °C using tissues from F344 rats.

No concrete data are available to indicate that distribution of chloroethane is different in children. Physical-chemical properties of chloroethane indicate that it would be readily soluble in fat. In the newborn and young infant, fat tissue is relatively scarce (15% of body weight; Morselli et al. 1980) as compared to an adult, indicating that distribution of lipophilic chloroethane will differ in infants and young children relative to adults. In addition, infants and younger children have much more total body and extracellular water relative to body weight than adults (Altman and Dittmer 1974), indicating that distribution of water-soluble compounds, such as chloroethane metabolites, will differ in children as compared with adults (Morselli et a1.1980).

The brain of a child is much larger, relative to body weight, than in the adult (Guzelian et al. 1992). Further, cerebral blood flow is greater, relative to brain weight, in the child than in the adult (Guzelian et al. 1992). Therefore, chloroethane present in the blood after exposures (such as inhalation) will more readily reach the brain of a child due to this increased blood flow. Since the central nervous system is the target organ for chloroethane's narcotic effects, the larger relative brain size of the child indicates that a child might experience a much larger exposure dose relative to body weight than an adult.

It is unknown if chloroethane can reach and cross the placenta or its precursors. However, based on physical-chemical characteristics of the compound, it is likely that it can. In addition, it is known that some chloroethane metabolites such as ethanol (Guzelian et al. 1992), can cross the placental barrier.

One study to date (Pellizari et al. 1982) determined that chloroethane does enter the milk of a lactating woman and can be detected. However, this study did not qluantify the chloroethane in milk, few women were tested, and the route of exposure to chloroethane was not determined. Therefore, it is impossible to estimate what percentage of exposed nursing mothers would be expected to excrete the compound in milk and what the significance of the compound in mother's milk would be for a nursing infant.

No data are available to indicate that females store chloroethane or its metabolites in their tissues. Data indicate that chloroethane is rapidly cleared within the body; therefore, it is unlikely that any of the compoundwould be stored in tissues, and it would not likely be available to be mobilized at a later time during pregnancy or lactation.

No data are available concerning the possibility of chloroethane entering into and adversely affecting parental germ cells.

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to chloroethane. Reviews of the effects of chloroethane (Konietzko 1984; Lehman and Flury 1943) provide some general information about the distribution of chloroethane. The species in which the information was obtained was not stated. In the blood, approximately 75% of the chloroethane is bound to red blood cells, and 25% is in the plasma (Konietzko 1984). The highest concentration of chloroethane in the animal body was found in fatty tissue around the kidney, and the lowest was found in the cerebrospinal fluid (Konietzko 1984). The brain was said to accumulate a concentration two times that of the blood. Lehman and Flury (1943) reported that chloroethane content in the brain and medulla oblongata was especially high.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of chloroethane in humans or animals following oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of chloroethane in humans or animals following dermal exposure.

2.3.3 Metabolism

No studies were located regarding metabolism of chloroethane by humans. A review indicates that a small amount of chloroethane was metabolized to ethanol via dechlorination in animals following administration of high anesthetic doses (Konietzko 1984). The species was not identified.
Less than 0.5% of the dose was dechlorinated by rat liver microsomes in vitro (Van Dyke and Wineman 1971).

The metabolic rates for chloroethane were estimated for male F344 rats using a gas uptake method (Gargas et al. 1990). The rats were exposed to an initial concentration of 100, 535, 1,200, or 2,350 ppm, and the disappearance of the gas was studied for about 5 hours. A physiologically based pharmacokinetic (PBPK) model that assumed metabolism occurred exclusively in the liver was used to analyze the data. The metabolism of chloroethane was best described by a combination of a saturable pathway and a first-order pathway. The V_{maxc} which is the maximum velocity (V_{max}) scaled for a 1-kg animal, was determined to be 4 mg/hour (to calculate a V_{max} for an animal of any body weight [body weight in kg] use $V_{max} = V_{maxc}[BW]^{0.7}$). The rate constant for the saturable pathway (K_m was estimated to be 0.1 mgL. The first-order rate constant, k_{fc} which is the rate constant (K_f scaled for a l-kg animal, was 1 hr^{-1} (to calculate a k_f for any body weight use $k_f = k_{fc}[BW]^{-0.3}$).

The proposed metabolic pathways for chloroethane in rats and mice (Fedtke et al. 1994b) are shown in Figure 2-2. The two major pathways are the production of acetaldehyde by cytochrome P450, and conjugation of chloroethane with glutathione to form S-ethyl-glutathione. The metabolism of chloroethane to acetaldehyde was studied *in vitro* using livers from rats and mice exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). The amounts of acetaldehyde detected ranged from 26.9 to 49.3% of the chloroethane metabolized, depending on pre-exposure to chloroethane, for the individual microsome preparations from rats and mice. The investigators found that exposure to chloroethane induced its own metabolism by approximately 100% in mice and female rats, with no effect in male rats. Based on

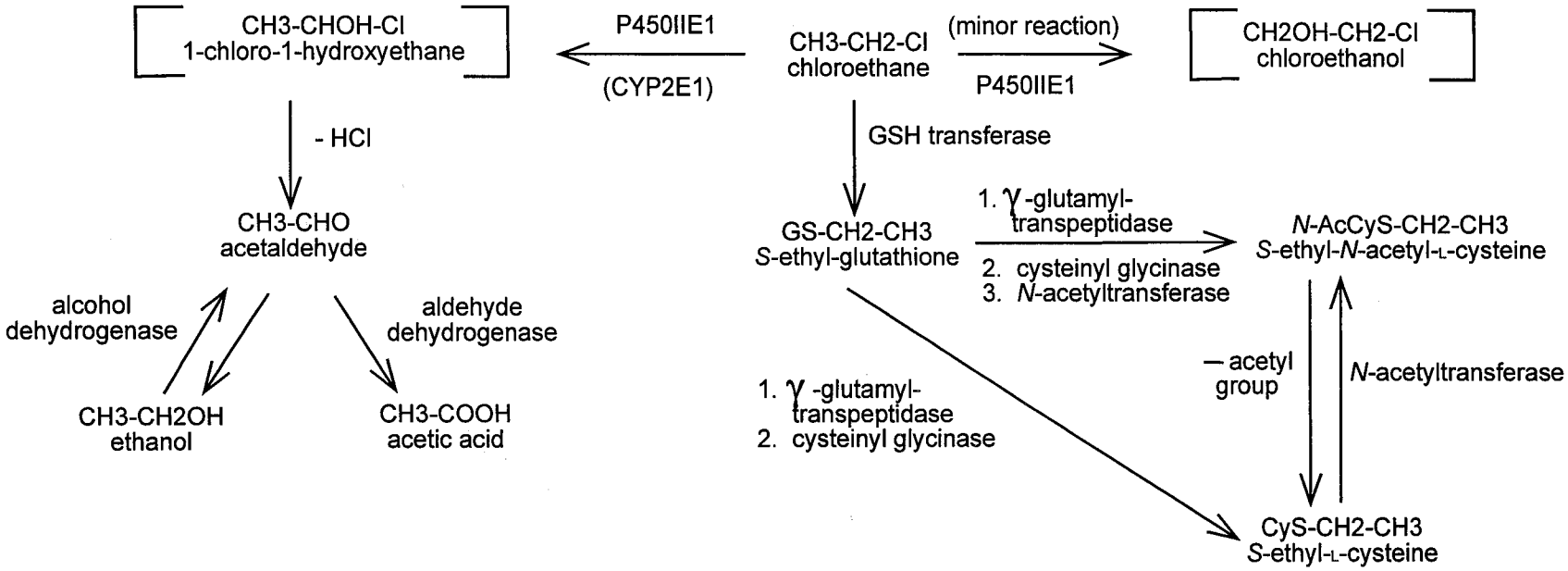
studies using specific P450 enzyme inducers and inhibitors, the investigators concluded that the P450 enzyme DE1 (CYP2El) was responsible for chloroethane metabolism. CYP2E1 also metabolizes alcohols, aldehydes, and ketones, and plays a role in gluconeogenesis within the body (Vieira et al. 1996).

Acetaldehyde is rapidly metabolized to acetic acid by aldehyde dehydrogenase. Therefore, increased acetaldehyde relative to normal levels was not detected in the serum of chloroethane-exposed rats or mice (15,000 ppm), or in the urine of exposed rats (Fedtke et al. 1994a). Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice. Acetaldehyde concentrations in the urine of male and female mice were 7.9-20.3 and 0-l 8.1 µmol/L, respectively, in unexposed mice, and 15.4-70.1 and 11.6-17 µmol/L, respectively, in chloroethane-exposed mice. Except for the approximately threefold greater metabolism of chloroethane in mice compared to rats, there was little difference between the species. The study authors concluded that the production of acetaldehyde from chloroethane was unlikely to have a role in the induction of uterine carcinomas in mice.

Glutathione levels were studied in rats and mice exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994b). The animals were sacrificed immediately after the last exposure. Compared to controls, glutathione concentrations were significantly ($p<0.05$) decreased in the livers of male rats, in the kidneys of female rats, in the lungs of both sexes of rats and mice, and in the uteri of both rats and mice. The decreases in glutathione levels were most dramatic in the uterus, in which levels were approximately two-thirds lower than in controls. *In vitro* studies of chloroethane conjugation to glutathione, using liver cytosolic fractions from control and chloroethane-exposed rats and mice, indicated that the conjugation was catalyzed by glutathione-*S*-transferase enzymes (Fedtke et al. 1994b). Glutathione conjugation rates, in nmol chloroethane conjugated/minute mg protein, were greater in mice (0.71±0.19 in males; 1.01±0.19 in females) than in rats (0.17±0.19 in males; 0.16±0.03 in females). Chloroethane exposure had no effect on these rates in rats and slightly decreased the rates in mice. When urine was analyzed for glutathione metabolites, *S*-ethyl-*N*-acety-L-cysteine was detected in both rats and mice. *S*-Ethyl-L-cysteine was detected only in the urine of mice. The total amount of glutathione metabolites excreted during the 5-day exposure period was about fivefold higher in mice than in rats. The study authors concluded that rats completely metabolize *S*-ethyl-L-cysteine to more hydrophilic metabolites before urinary excretion, while these metabolic pathways were not available to the same extent in mice under the conditions of this study.

No data are currently available to indicate that the metabolism of chloroethane is different in children when compared to adults; however, some of the enzymes in the chloroethane metabolism scheme belong to enzyme

Figure 2-2. Metabolic Pathways of Chloroethane Biotransformation*



*Modified from Fedtke et al. 1994b
GSH = glutathione
[ ] = known metabolites that were not detected in the referenced study

families that are developmentally regulated to some extent either in humans or animals. Chloroethane is metabolized by both cytochrome P450 and by glutathione *S*-transferase. Studies have shown that liver glutathione *S*-transferase activities are low in prepubertal male and female rats, but as the rats reach sexual maturity (at around 30-50 days of age), glutathione-conjugating activity toward dichloronitrobenzene is two to threefold higher in males than females (Lamartiniere and Lucier 1983). The difference in glutathione *S*-transferase activity was dependent on pituitary secretions. Further research on hypophysectomized male and female rats revealed that growth hormones may contribute to the establishment of glutathione *S*-transferase activities (Lamartiniere 1981). No data are available to indicate that glutathione *S*-transferase activity is developmentally or sexually expressed in humans.

After glutathione conjugation of chloroethane, three other enzymes convert the conjugate to a more hydrophilic form to be excreted by the body. These enzymes are γ-glutamyltranspeptidase, cysteinyl glycinase, and *N*-acetyltransferase, NAT (Amdur et al. 1991). These three enzymes convert elatively hydrophobic glutathione conjugates to their respective mercapturic acids, which can be excreted more readily. There are two *N*-acetyltransferase enzyme families, NAT1 and NAT2. Of these enzymes, only NAT2 is developmentally regulated. It is unknown which NAT enzyme metabolizes chloroethane; therefore, it is unknown whether chloroethane is developmentally regulated by this metabolic pathway.

Studies have shown that the other enzyme metabolizing chloroethane, cytochrome P45OIIEl (CYP2El), is developmentally regulated in humans (Vieira et al. 1996). This enzyme is not detectable from livers of fetuses at 14-40 gestational weeks. However, the level of the protein rises sharply in the first day after birth (1 unit/mg protein) and continues to increase until it reaches adult values in children from 1 to 10 years of age, approximately 5 units/mg protein (Vieira et al. 1996).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Excretion of chloroethane by the lungs is rapid in humans and animals (Adriani 1986; Konietzko 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). In humans exposed briefly by inhalation to chloroethane, 30% of the retained dose was excreted in the breath within 1 hour (Morgan et al. 1970). Excretion over a longer period of time could not be measured because of the short half-life of the ^{38}Cl

radioisotope used in this study. Morgan et al. (1970) found that the rate of excretion of radioactivity in the urine of humans was very slow (i.e., <0.01% per minute) I hour after inhalation.

Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice but not rats (Fedtke et al. 1994a). Acetaldehyde concentrations in the urine of male and female mice were 7.9-20.3 and 0-l 8.1 µmol/L, respectively, in unexposed mice, and 15.4-70.1 and 11.6-17 µmol/L,respectively, in chloroethane-exposed mice. Acetaldehyde is rapidly metabolized to acetic acid; therefore it would be difficult to detect in whole animal studies. Glutathione conjugates have also been detected in the urine of rats and mice exposed to chloroethane (Fedtke et al. 1994b). Rats excreted the more hydrophilic *S*-ethyl-*N*-acetyl-L-cysteine, while mice excreted both *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine. During the 5 days that rats and mice were exposed to chloroethane at 15,000 ppm for 6 hours/day, the total amount of glutathione metabolites excreted in the urine was about fivefold higher in mice than in rats.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of chloroethane and metabolites in humans or animals following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of chloroethane and metabolites in humans or animals following dermal exposure.

No data are available to indicate that excretion of chloroethane is different in children,

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.

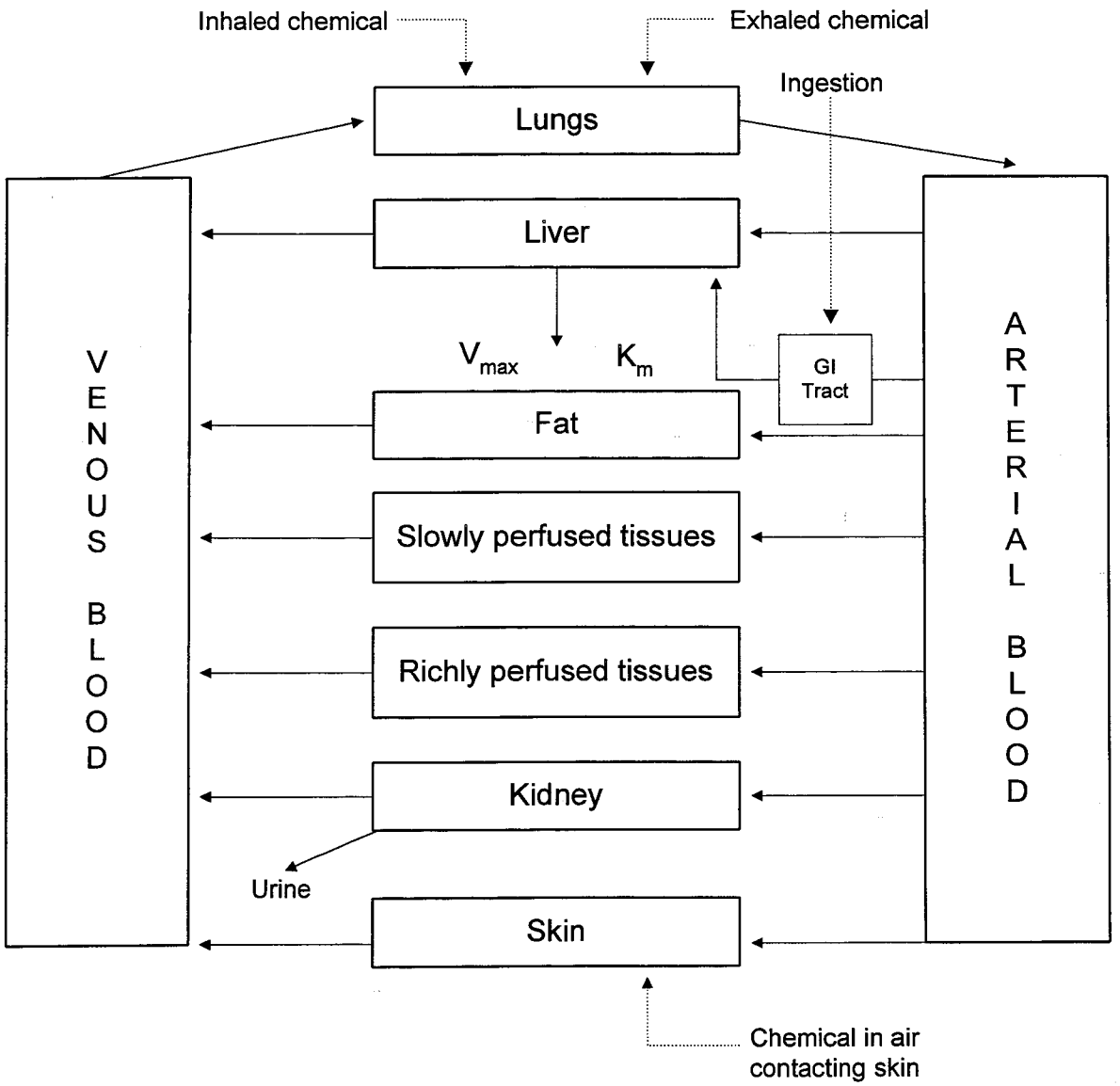
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). 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 substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. 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 2-3 shows a conceptualized representation of a PBPK model.

Figure 2-3. Conceptual Representation of a Physiologically-Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

If PBPK models for chloroethane 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.

See Section 2.3.3 for discussion of a study that used a PBPK model to estimate the metabolic parameters for chloroethane in rats (Gargas et al. 1990). This study was not used for risk assessment, tissue dosimetry, or dose, route, or species extrapolation. Therefore, it is not discussed in this section.

There are no PBPK models for children, fetuses, pregnant women, infants or lactating women, or any other appropriate age group with which to make predictions concerning the pharmacokinetics of chloroethane in humans. In addition, these models are lacking in animals.

2.4 MECHANISMS OF ACTION

The exact mechanism of action for chloroethane toxicity has not been defined. It is generally accepted that chloroethane's ability to target the central nervous system and the heart is based on its physicalchemical characteristics and similarity to other volatile halogenated organics with anesthetic properties. These currently accepted beliefs do not suggest that differences exist between children and adults in regards to the mechanism of toxicity of chloroethane.

2.4.1 Pharmacokinetic Mechanisms

Because chloroethane is a small lipophilic compound, simple diffusion accounts for its absorption across membranes, and its higher affinity for lipids determines its distribution. A review regarding the kinetics of chloroethane indicates that 75% of the compound in blood is bound to red blood cells, and 25% is in plasma (Konietzko 1984). This is consistent with the lipophilic nature of chloroethane. The metabolism of chloroethane has been studied *in vitro* using liver microsomal preparations from rats and mice (Fedtke et al. 1994a). The observations that inhibitors of the P450 enzyme IlEI reduce chloroethane metabolism, and that inducers of P450 IIEI enhance metabolism of the compound to acetaldehyde, provide evidence that P450 IIEI is the principal P450 enzyme involved in the metabolism of chloroethane. In vitro studies using hepatic cytosolic fractions from the livers of rats and mice have shown that the conjugation of chloroethane with glutathione is catalyzed by glutathione -*S*-transferase enzymes (Fedtke et al. 1994b). In mice, both *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine are formed and excreted in the urine, while in rats, only *S*-ethyl-*N*-acetyl-L-cysteine is formed and excreted in the urine.

2.4.2 Mechanisms of Toxicity

Chloroethane has a general anesthetic effect when inhaled at high concentrations by humans and animals. The anesthetic effect is thought to be produced by the compound itself. Although the specific mechanism of action is unknown, it is generally believed that chloroetbane's ability to induce anesthesia is related to the solubility of the compound in oils or fats. The lipophilicity of the nonpolar compound suggests that chloroethane is dissolved within and acts upon the lipid layer of cellular membrane or the hydrophobic areas of specific membrane-bound cellular proteins (Goodman and Gilman 1993). This hypothesis is supported by the findings of Balasubramanian and Wetlaufer (1966) who showed that chloroethane and other volatile anesthetics produced reversible structural changes in globular proteins *in vitro*. They proposed that the anesthetic activity of these compounds may be a result of their ability to produce structural changes in protein or lipoprotein structures.

Volatile anesthetics affect voltage-gated calcium channels (Langmoen et al. 1995). Using a guinea pig heartlung preparation, Doring (1975) found that volatile general anesthetics including chloroethane interfere with the calcium-mediated process of excitation-contraction coupling leading to a reduction in high energy phosphate (ATP) utilization. Extra calcium, cardiac glycosides, or β-adrenergic catecholamines did not reverse the effects. Doring (1975) indicated that, because of their lipophilic nature, volatile anesthetics may alter the lipid arrangement of the transverse tubule walls, resulting in permanent impairment of excitationcontraction coupling. In studies using chloroform, Doring (1975) was able to show ultrastructural changes in the transverse tubules, especially vacuolization and dilatation Electron microscopic examinations of hearts similarly exposed to chloroethane were not presented, but chloroethane would be expected to act in a manner similar to chloroform.

Chloroethane has been shown to have cardiotoxic effects in several studies (Bush et al. 1952; Cole 1967; Haid et al. 1954; Morris et al. 1953). At levels adequate to induce anesthesia, chloroethane sensitizes the heart to the effects of catecholamines (Haid et al. 1954; Morris et al. 1953). Catecholamine release can be induced by euphoria and excitement resulting from the effects of chloroethane on the central nervous system (Benowitz 1992). The myocardium can be sensitized to the effects of the catecholamines. This sensitization, along with asphyxia and hypoxia, which can also result from high concentrations of inhaled chloroethane, can cause arrhythmias, which can result in death (Benowitz 1992). It is possible that chloroethane and similar solvents may depress atrioventricular nodal conduction, causing atrioventricular block. Bradyarrhythmias

(abnormally slow hearth rhythms) may then occur to prevent ventricular arrhythmias, or asystole (lack of electrical or mechanical activity in the heart) may result.

Analysis of structure-activity relationships predicts that chloroethane is carcinogenic. The alerting substructure is the Cl-CH_2 group, which results in chloroethane being an alkylating agent and a mutagen to *Salmonella* (Tennant and Ashby 1991). It is not known why chloroethane does not cause respiratory cancers following inhalation exposure, or why it acts as a selective carcinogen resulting in uterine tumors in mice. Based on a lack of differences in P450 metabolism of chloroethane between rats and mice, decreased uterine glutathione levels in rats and mice following chloroethane exposure, and the urinary excretion of *S*-ethyl-Lcysteine in mice but not rats, Fedtke et al. (1994b) suggested that uterine tumor production is a result of the glutathione conjugation pathway, rather than a result of chloroethane metabolism by P450 enzymes. The study authors did not state which compound in the glutathione conjugation pathway was responsible for the carcinogenic effect of chloroethane.

2.4.3 Animal-to-Human Extrapolations

The metabolism of chloroethane has not been studied in humans. Therefore, it is not possible to determine which species of animal is the most appropriate model for humans exposed to chloroethane. Studies by Fedtke et al. (1994a, 1994b) indicate that compared to rats, mice have a greater capacity to metabolize chloroethane by both the P450 and glutathione conjugation pathways.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Overview

Although chloroethane has been used as a general anesthetic in humans, very little is known about the effects of inhalation exposure to lower concentrations. The concentrations required to produce anesthesia, approximately 40,000 ppm, are near the explosion limit of this compound. Chloroethane is also used as a local anesthetic in humans. When chloroethane is sprayed on the skin, it rapidly evaporates and causes the skin to freeze, producing a numbing sensation. Oral exposure of humans to chloroethane has not been

studied. Because chloroethane is a gas, substantial oral exposure of humans to this compound is not expected.

Animal studies regarding the effects of chloroethane are predominantly focused on the inhalation route of exposure. At high concentrations for short periods of time, chloroethane clearly results in neurological effects producing unsteadiness followed by unconsciousness. A number of toxicity studies have not clearly identified a target organ of toxicity for chloroethane (Eandry et al. 1982, 1987,1989; NTP 1989).

One target of chloroethane toxicity in animals exposed to high concentrations is the uterus. Chloroethane has been shown to decrease uterine weight by 35% in mice exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels were also observed in both rats and r-nice (Fedtke et al. 1994b). Chloroethane has also been shown to produce uterine cancer in mice but not rats exposed to 15,000 ppm chloroethane for approximately 2 years (NTP 1989). The relevance of these uterine effects in animals to humans is not known.

In addition to uterine effects, limited studies of reproduction and development in mice have shown effects. A small increase in the average duration of the estrous cycle was observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Before the exposure, estrous cycle duration was 5.15±0.15 days, while during the exposure, estrous cycle duration was 5.52±0.19 days. Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Evidence of fetotoxicity, a statistically significant increase in small centers of unossified bones of the skull, was observed in the offspring of mice exposed to 4,946 ppm chloroethane during gestation days 6-15 (Scortichini et al. 1986). Further studies are needed to confirm the reproductive and developmental toxicity of chloroethane and to determine that the effects are observed in another species in addition to mice.

Chloroethane is an alkylating agent and is mutagenic to *Samonella* (NTP 1989). Chloroethane has not been shown to cause genotoxic effects in *in vivo* assays in mice (Ebert et al. 1994). In a single high-concentration (15,000 ppm) study, chloroethane clearly caused uterine cancer in female mice, with equivocal evidence of carcinogenicity in rats (increased skin tumors in male rats and astrocytomas in the brains of female rats) (NTP 1989). Because only one concentration was tested, it cannot be determined whether or not the carcinogenic effect of chloroethane is a high-concentration phenomenon.

Minimal Risk Levels for Chloroethane

Inhalation MRLS

- An MRL of 15 ppm has been derived for acute-duration inhalation exposure (14 days or less) to chloroethane.

  This MRL is based on the developmental study by Scortichini et al. (1986) in which minimal fetotoxicity (a significant increase in the incidence of foramina of the skull bones) was observed in the offspring of mice exposed to 4,946 ppm chloroethane during gestation days 6-15. Fetotoxicity was not observed at 1,504 ppm, the NOAEL concentration that serves as the basis of the MRL. No additional developmental studies of chloroethane were identified.

Intermediate- and chronic-duration inhalation MRLs were not derived. The only concentration that resulted in adverse effects in longer duration studies was 15,000 ppm (NTP 1989). At this concentration in studies of about 2 years in duration, hyperactivity, renal effects, and decreased survival were observed in mice. In 13-week studies, no adverse effects were observed in rats or mice at 19,000 ppm (NTP 1989). Since the acuteduration inhalation MRL is based on a concentration much lower than those resulting in effects in longer duration studies, it should also be protective for intermediate- and chronic-duration inhalation exposure.

Oral MRLS

Oral data concerning the effects of chloroethane were not identified. Therefore, no oral MRLs were derived.

Death. Acute inhalation of high concentrations of chloroethane vapor is lethal to humans (Dawkins 1964; Konietzko 1984; Kuschinsky 1970; Lawson 1965; Lehman and Flury 1943; Yacoub et al. 1993) and animals (Lazarew 1929; Sayers et al. 1929; Troshina 1966). Death appears to be caused by asphyxiation, as well as effects on the heart and nervous system. The nervous system seems to be involved because neurological effects such as unsteadiness, loss of muscle coordination, and unconsciousness precede death in animals. Similar effects are seen in humans exposed to chloroethane. In addition, effects such as respiratory paralysis and cardiac depression, which have been reported during chloroethane exposure in both humans and animals, are at least partly neurological in origin. For example, cardiac depression can be caused by stimulation of the vagus nerve or by direct effect on the cardiac tissue. Bush et al. (1952) found that in dogs anesthetized with chloroethane, cardiac depression occurred first by vagal stimulation and then by direct effect on the heart. Upon overdose, the dogs died from cardiac arrest. Most human deaths caused by chloroethane were the result of overdose while under anesthesia. There is also one report of a death following abuse of chloroethane

(Yacoub et al. 1993). The specific level of exposure that causes death in humans is not known, but it probably exceeds 40,000 ppm, which is the concentration that was typically used to produce clinical anesthesia. Chloroethane is no longer used as a general anesthetic in the United States.

The long-term survival of mice was reduced by chronic exposure to 15,000 ppm chloroethane vapor (NTP 1989). An ascending urinary tract infection may have contributed to the reduced survival in male mice. The decreased survival in female mice was attributed to uterine cancer. Decreased survival was not observed in rats, but control survival was abnormally low for this species which obscured the results (NTP 1989). There is no evidence that humans would respond to chronic chloroethane exposure in a manner similar to the mouse, but these data suggest the possibility that sub-anesthetic concentrations of chloroethane may be potentially hazardous to humans if inhaled for an extended period of time.

Reliable information regarding death of humans or animals following oral consumption of chloroethane was not found. Because chloroethane is a gas, accidental oral exposure to doses of chloroethane large enough to result in deaths is highly unlikely. Although no studies of the acute lethality of dermally-applied chloroethane were located, it is unlikely that brief dermal exposure is lethal to humans since chloroethane is in widespread use as a topical anesthetic, and reports of accidental death from this use were not found. Further, as previously discussed, chloroethane is expected to evaporate quickly from the skin since its standard state is a gas. Therefore, it is unlikely to remain on the skin long enough to be absorbed at a dose that would result in death.

Systemic Effects. The systemic effects of chloroethane, which is a gas, have not been studied by the oral route of exposure. Few studies regarding dermal exposure to chloroethane were identified. Therefore, in the following discussion, unless stated otherwise, exposure is via inhalation.

Respiratory Effects. When used as a general anesthetic, chloroethane sometimes increases the respiratory rate of humans (Cole 1956, 1967). Respiratory paralysis was reported to be the cause of death of a 14-year old who died during anesthesia (Kuschinsky 1970). Mild lung effects have also been reported in animals exposed to very high concentrations of chloroethane for short periods of time (Gohlke and Schmidt 1972; Sayers et al. 1929). Histopathological changes in the lungs of animals were not observed in studies of longer duration (Landry et al. 1982, 1987,1989; NTP 1989).

The exposure concentrations (up to 19,000 ppm) used in the inhalation studies are much higher than one is likely to encounter in occupational settings or in the vicinity of hazardous waste sites. Therefore, respiratory effects resulting from chloroethane exposure are highly unlikely.

Cardiovascular Effects. Chloroethane has been shown to interfere with cardiac function in animals when inhaled at anesthetic concentrations. Cardiac depression, ventricular tachycardia, ventricular fibrillation, asystole, and sensitization to endogenous and exogenous epinephrine have all been observed in dogsanesthetized with chloroethane (Bush et al. 1952; Haid et al. 1954; Morris et al. 1953). Severe, irreversible, contractile failure of the heart occurred in a guinea pig heart-lung preparation after exposure to chloroethane vapor, and elevated ratios of ATP/ADP and creatine-P/inorganic-P were found in the heart, indicating that a reduction in high-energy phosphate utilization had taken place (Doring 1975). These results, together with the previously reported finding of cardiac depression in humans exposed briefly to high concentrations of chloroethane (Bush et al. 1952), suggest that high levels of chloroethane vapor in the air may be potentially hazardous to humans because of effects on the heart. Longer studies at lower concentrations have not reported any histopathological changes in the heart (Landry et al. 1982, 1987,1989; NTP 1989). Cardiovascular effects are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Gastrointestinal Effects. Abdominal cramps and nausea have been reported by persons exposed to chloroethane at very high concentrations for short periods of time (Davidson 1925; Sayers et al. 1929). Vomiting has also been reported in patients as they recovered from chloroethane anesthesia (Cole 1967). It is not clear if gastrointestinal effects are a direct irritant effect of chloroethane or if they are secondary to nervous system effects. Histopathological changes in the gastrointestinal tract of animals were not observed in longer studies (Landry et al. 1982, 1987, 1989; NTP 1989). Gastrointestinal tract effects are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Hematological Effects. Cyanosis has been reported in humans following inhalation exposure to chloroethane at very high concentrations (Davidson 1925). Since this effect was observed when chloroethane was not mixed with oxygen, it is very likely that it was the result of a lack of oxygen rather than a direct effect of chloroethane. Hematological effects were not observed in mice exposed to chloroethane for 11 days (Landry et al. 1987, 1989) or in rats or dogs exposed to chloroethane for 2 weeks (Landry et al. 1982).

Based on the available animal data, hematological effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following exposure to chloroethane. Histopathological changes in the muscle and bone have not been observed in animals following inhalation exposure (Landry et al. 1982, 1987, 1989; NTP 1989). Disintegration of muscle fibers has been observed in rats after chloroethane was applied dermally until the skin was blanched (Kenig 1956). This study suggests that improper use of chloroethane as a topical anesthetic could result in adverse effects on the underlying muscle. Musculoskeletal effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Hepatic Effects. An enlarged liver and mild transient disturbance of liver function were reported in a woman who sniffed chloroethane for 4 months (Hes et al. 1979). Moderately elevated serum alanine aminotransferase was observed in a man who abused chloroethane for 30 years (Nordin et al. 1988). Liver effects reported in animals exposed to high concentrations of chloroethane include an increase in the liver ATP/ADP ratio (Oura et al. 1966), decreased liver glutathione (Fedtke et al. 1994b), and decreased liver non-protein sulfhydryl concentrations (Landry et al. 1982). Increased liver weights have also been reported (Landry et al. 1982,1987, 1989). These mild liver effects may be considered an adaptive response to chloroethane exposure rather than a toxicologic effect. Other studies have not reported liver weight changes or histopathological changes in the liver (Bucher et al. 1995; NTP 1989). Based on the available data, hepatic effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Renal Effects. No studies were located regarding renal effects in humans following exposure to chloroethane. Mild signs of nephrotoxicity were observed in mice exposed to relatively high concentrations for 100 weeks (NTP 1989), while no renal effects were observed in rats exposed at the same concentrations for 102 weeks (NTP 1989). Additional acute- and intermediate-duration studies have not reported significant renal effects in animals (Fedtke et al. 1994a; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Based on the available animal data, renal effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Endocrine Effects. No studies were located regarding endocrine effects in humans following exposure to chloroethane. Endocrine gland effects have not been observed in animals exposed to chloroethane (Gohlke and Schmidt 1972; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Based on the available animal data, endocrine effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure to chloroethane. Following inhalation exposure of animals to chloroethane, dermal effects have not been reported (Landry et al. 1982, 1987, 1989; NTP 1989). Chloroethane has a local anesthetic effect in humans and animals following dermal application. It rapidly evaporates and draws heat from the skin, causing the skin to freeze. Application for too long a time can result in frostbite. Noble (1979) reported frostbite in three children sprayed with chloroethane for several minutes. Contact dermal sensitivity has also been reported in persons exposed to chloroethane (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976). Chloroethane applied to rats until the skin was blanched caused edema in the subcutaneous tissue at the site of application (Kenig 1956). Because chloroethane is used as a topical anesthetic, many people may be at risk of developing sensitivity to chloroethane or of the hazard of freezing of the skin if chloroethane is used incorrectly. Sensitized individuals may react to chloroethane in the environment or at hazardous waste sites.

Ocular Effects. Mild eye irritation has been reported in volunteers exposed briefly to very high concentrations of chloroethane (Sayers et al. 1929). Effects on the eyes have not been reported in animals exposed to chloroethane (Landry et al. 1982, 1987,1989). Based on the available data, ocular effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Body Weight Effects. Body weight effects have not been reported in animals exposed to chloroethane (Fedtke et al. 1994a; Landry et al. 1982,1987,1989; NTP 1989; Schmidt et al. 1972; Scortichini et al. 1986). Based on the available animal data, body weight effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Immunological and Lymphoreticular Effects. No immunological effects were reported in humans (Troshina 1966) or animals (Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972) after inhalation exposure to chloroethane, but contact dermatitis has been found in humans treated dermally with chloroethane (Bircher et al. 1994; Van Ketel 1976). This effect is notable because of the widespread use of chloroethane as a topical anesthetic. Sensitized individuals may react to chloroethane in the environment or at hazardous waste sites.

Neurological Effects. Chloroethane has a general anesthetic effect when inhaled at high concentrations by humans and animals. The severity of the effect increases with the concentration of chloroethane and the duration of exposure. In humans, unconsciousness was produced by inhalation of 33,600 ppm chloroethane for approximately 15 minutes (Davidson 1925). Cbloroethaue is no longer used as a general anesthetic in the United States, but in the past, concentrations of approximately 40,000 ppm were used clinically to produce anesthesia (Lawson 1965). The gastrointestinal effects reported in patients as they recovered from chloroethane anesthesia (Cole 1967; Davidson 1925; Sayers et al. 1929) may be secondary to the neurological effects. In animals, clinically effective anesthetic concentrations range from 30,000 to 45,000 ppm (Dobkin and Byles 1971). Induction of anesthesia using chloroethane is rapid, and so is recovery. The anesthetic effect is thought to be produced by the compound itself; however, its mechanism of action is unknown. Balasubramanian and Wetlaufer (1966) showed that the vapors produced from pure liquid chloroethane and other volatile anesthetics produced reversible structural changes in globular proteins *in vitro*. They proposed that the anesthetic activity of these compounds might be due to their ability to produce structural changes in protein or lipoprotein structures in cell membranes. Following abuse of chloroethane, ataxia, nystagmus, scanning dysarthria, dysdiadochokinesia of the arm, and sluggish lower limb reflexes were reported (Hes et al. 1979). These effects were reversible after 1 month without chloroethane exposure. In a second case of chloroethane abuse, neurological and mental changes (grand ma1 seizure, ataxia, difficulties in walking, disorientation, short-term memory impairment, visual hallucinations) were observed following recovery after 30 years of chloroethane abuse (Nordin et al. 1988). The study authors indicate that it was not possible to determine whether the nervous system effects were toxic effects of chloroethane or withdrawal symptoms.

Animal studies examining the histology of nervous system tissue have not revealed any adverse effects following inhalation exposure (Gohlke and Schmidt 1972; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Except for observations during exposure, neurological function has not been studied in animals following intermediate or chronic inhalation exposure.

Chloroethane is still used as a local anesthetic It is applied to the skin, and its rapid evaporation results in cooling. Mild pain has been reported during the dermal application of chloroethane to the skin of humans (Selby and Bowles 1995). Application of chloroethane to the skin of rats has been reported to result in thickening of nerve fibers and swelling of Schwann cell nuclei (Kenig 1956).

The nervous system is a target of chloroethane exposure, and functional effects of chloroethane exposure have not been well studied. Therefore, it is not known if neurological effects may occur in humans at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Reproductive Effects. Studies of reproductive effects in humans exposed to chloroethane were not identified. Several studies investigated reproductive endpoints in animals. In dogs anesthetized with chloroethane, high concentrations resulted in decreased uterine motility and muscle tone (Van Liere et al. 1966). Uterine weight was decreased by approximately 35% in mice exposed to high concentrations of chloroethane (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels have also been reported in rats and mice exposed to chloroethane (Fedtke et al. 1994b). The decreases in glutathione in the uterus were greater than the decreases in glutathione observed in the liver, lungs, and kidneys. A small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane 6 hours/day for 2 1 days (Bucher et al. 1995). Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). Histopathological effects have not been observed in reproductive organs of animals exposed to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989). No effects on the number of live and dead fetuses or the number and position of resorption sites were observed in mice exposed to chloroethane during gestation days 6-15 (Scortichini et al. 1986). Additional studies of reproductive outcome in animals following inhalation exposure to chloroethane were not identified.

Based on decreases in uterine glutathione in rats and mice, decreases in uterine weight in mice, and the development of uterine cancer in mice exposed to chloroethane (NTP 1989) (see Cancer discussion in Section 2.5), the uterus appears to be a target of chloroethane exposure in mice; rats are apparently less sensitive to these effects. Further studies are required to determine the mechanism of uterine toxicity in mice and to determine the relevance of these effects to humans exposed to chloroethane at concentrations normally found at occupational settings and in the environment, including hazardous waste sites.

Developmental Effects. No studies were located regarding developmental effects in humans following exposure to chloroethane. Only one study of the developmental effects of chloroethane in animals was found. In this mouse study, minimal evidence of fetotoxicity (increase in small centers of unossified bones of the skull) was observed at the highest concentration tested (Scortichini et al. 1986). This study serves as the basis for the acute-duration inhalation MRL. Further study is required to determine the relevance of developmental effects in animals to humans exposed to chloroethane at concentrations normally found at occupational settings and in the environment, including hazardous waste sites.

Genotoxic Effects. Results of mutagenicity tests performed *in* vivo and *in vitro* are shown in Tables 2-2 and 2-3, respectively. Chloroethane did not increase the number of micronuclei in bone marrow cells or affect DNA synthesis in mice exposed nose-only to 25,000 ppm chloroethane 6 hours/day for 3 days (Ebert et al. 1994). The investigators indicated that the exposure concentration used in this study was about 66% of the flammability limit and that it was the highest concentration that could be safely administered. Using a desiccator for exposure to the gas, positive rest&s in reverse mutation assays using *Salmonella typhimurium* strain TA1535 with and without activation were reported by NTP (1989). In strain TAl00, the results were positive only with metabolic activation, while the results were negative in strain TA98 both with and without metabolic activation. NTP (1989) indicated that the mutagenic activity of chloroethane in *S. typhimurium* was consistent with an alkylating agent. Chloroethane was positive for gene mutation in Chinese hamster ovary cells exposed *in vitro* (Ebert et al. 1994). Negative results were reported for chloroethane in a cell transformation assay using mouse BALB/c-3T3 cells (Tu et al. 1985). Although chloroethane is mutagenic in *in vitro* assays, negative results were observed in *in vivo* studies, and the data are insufficient to predict that chloroethane poses a genotoxic threat to humans.

Existing data are inconclusive concerning the genotoxicity of chloroethane. Despite this lack of data, the volatility of chloroethane, its rapid clearance from the body, and its quick metabolism within the body indicate it is unlikely that it would reach germ cells to result in any potential genotoxic effect.

Cancer. No studies were located regarding the carcinogenicity of chloroethane in humans, but chloroethane has been shown to be carcinogenic in animals. In a study by the NTP (1989), 86% of female mice chronically exposed to chloroethane vapor developed highly malignant uterine carcinomas. Uterine tumors were not observed in any of the control mice. The incidence of hepatocellular carcinomas also increased significantly in female mice. Male mice had an increased incidence of alveolar and bronchiolar adenomas, but because male survival was substantially reduced toward the end of the study these results are not conclusive. Male

TABLE 2-2. Genotoxicity of Chloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Mouse	Micronuclei	–	Ebert et al. 1994
Mouse	Unscheduled DNA synthesis	–	Ebert et al. 1994

– = negative result; DNA = deoxyribonucleic acid

TABLE 2-3. Genotoxicity of Chloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium[a]				
Strain TA1535	Gene mutation	+	+	NTP 1989
Strain TA100	Gene mutation	+	–	NTP 1989
Strain TA98 (desiccator test for exposure to gases)	Gene mutation	–	–	NTP 1989
Strains TA1535, TA100	Gene mutation	+	+	Milman et al. 1988
Eukaryotic organisms:				
Mammalian cells				
Mouse BALB/c-3T3 cells	Cell transformation	No data	–	Milman et al. 1988; Tu et al. 1985
Chinese hamster ovary cells	Gene mutation	+	+	Ebert et al. 1994
Mouse B6C3F$_1$ hepatocyte primary culture	DNA repair	No data	–	Milman et al. 1988

[a]Mutagenic activity consistent with an alkylating agent - positive in base substitution strains

+ = positive result; – = negative result; DNA = deoxyribonucleic acid

rats had marginally increased incidences of skin tumors, and female rats had marginally increased incidences of brain astrocytomas, providing equivocal evidence that chloroethane is carcinogenic in rats (NTP 1989). The fact that chloroethane is carcinogenic in mice and may be carcinogenic in rats as well suggests the possibility that this compound may also be carcinogenic in humans. Based on limited evidence of carcinogenicity in animals and no human data, IARC (1991) considers chloroethane to be in Group 3, not classifiable as to its carcinogenicity to humans. The carcinogenicity of chloroethane has not been classified by EPA (IRIS 1997) or NTP (DHHS 1994). The data are not sufficient to predict whether chloroethane is carcinogenic at concentrations that occur in the environment or at hazardous waste sites. OSHA has recommended that ethyl chloride be treated in the workplace with caution because of the structural similarity to the four confirmed halogenated animal carcinogens: ethylene dichloride; hexachloroethane; 1,1,2,2-tetrachloroethane; and 1,1,2-trichloroethane (NIOSH 1997).

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 (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). 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 (Leeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend 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; West et al. 1948; NRC 1993). 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.

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).

Children have infrequently been observed for health effects following exposure to chloroethane. Effects observed in humans exposed to chloroethane have resulted primarily from inhalation exposure. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970); however, the concentration of chloroethane administered was not known. Another study reported vagal stimulation, followed by depression of cardiac tissues in children exposed briefly to reportedly high concentrations of chloroethane; the specific levels were not indicated (Bush et al. 1952).

Chloroethane has also been used and sometimes misused as a topical anesthetic in both children and adults (Nielsen 1980; Noble 1979; Ott 1969; Van Ketel 1976). Misuse occurs when excessive amounts of chloroethane are sprayed on the skin for long periods of time. Three children suffered frostbite on the

exposed skin of their ears and necks after having their earlobes sprayed with chloroethane for several minutes (Noble 1979).

Effects seen in adults exposed to chloroethane are also expected in children. In particular, the nervous system is likely to be a sensitive target of chloroethane, as it is in adults. Since infants and young children have a larger proportion of their bodies as brain mass, and since blood flow is greater to this organ in children, one might predict on pharmacokinetic grounds that these ages of children would be more susceptible to the anesthetic effects of chloroethane than adults In addition, chloroethane distribution may be very different in children relative to adults due to the difference in fat and water content and lean body mass in children.

No studies were identified that reported effects caused by chloroethane in adults exposed as children and there is no information on the health effects of exposures in immature animals. There are no data concerning the effects of chloroethane exposure on human development and there is only one developmental study in animals. This study (Scortichini et al. 1986) reported that at the highest concentration administered to mice, delayed ossification of skull bones occurred. However, no other developmental parameters were affected, and no maternal toxicity was reported.

There are no data available concerning the pharmacokinetics of chloroethane in children. There are no human or animal studies available concerning the ability of chloroethane or its metabolites to reach and cross the placenta. One study determined that chloroethane can be detected in the breast milk of nursing mothers (Pelizzari et al. 1982), but the study was not quantitative and did not offer data concerning the percentage of nursing mothers that might excrete the compound in milk after exposure, nor did it provide a range of concentrations of the compound in this medium. No studies were identified that determined if chloroethane was stored in maternal tissues. However, the rapid clearance of chloroethane, as well as its volatility, suggest that it would not be stored within the body for an extended period of time, so pre-conception maternal exposure is not likely to result in exposure to children during gestation or lactation. See Section 2.3 for further information.

No data are currently available to indicate that the metabolism of chloroethane is different in children when compared to adults; however, some of the enzymes in the chloroethane metabolism scheme belong to enzyme families that are developmentally regulated to some extent either in humans or animals. Chloroethane is metabolized by both cytochrome P450 and by glutathione *S*-transferase. Studies have shown that liver glutathione S-transferase activities are low in prepubertal male and female rats, but as the rats reach sexual

maturity (at around 30-50 days of age), glutathione-conjugating activity toward dichloronitrobenzene is two to threefold higher in males than females (Lamartiniere and Lucier 1983). The difference in glutathione *S*-transferase activity was dependent on pituitary secretions. Further research on hypophysectomized male and female rats revealed that growth hormones may contribute to the establishment of glutathione S-transferase activities (Lamartiniere 198 1). No data are available to indicate that glutathione *S*-transferase activity is also developmentally or sexually expressed in humans.

After glutathione conjugation of chloroethane, three other enzymes convert the conjugate to a more hydrophilic form to be excreted by the body. These enzymes are γ-glutamyltranspeptidase, cysteinyl glycinase, and *N*-acetyltransferase, NAT (Amdur et al. 1991). These three enzymes convert relatively hydrophobic glutathione conjugates to their respective mercapturic acids, which can be excreted more readily. There are two *N*-acetyltransferase enzyme families, NAT 1 and NAT2. Of these enzymes, only NAT2 is developmentally regulated. It is unknown which NAT enzyme metabolizes chloroethane; therefore, it is unknown whether chloroethane is developmentally regulated by this pathway.

Studies have shown that cytochrome P450 IIEl is developmentally expressed in humans (Vieira et al. 1996). This enzyme is not detectable from livers of fetuses at 14-40 gestational weeks. However, the level of the protein rises sharply in the first day after birth (1 unit/mg protein), and continues to increase until it reaches adult values of approximately 5 units/mg protein, in children from 1 to 10 years of age (Vieira et al 1996).

It is unknown whether children differ from adults in their susceptibility to chloroethane, despite the theoretical reasons for which they might potentially differ, as discussed above.

There are no data concerning parental exposure affecting children, including pre-conception exposure. There are no data concerning pre-conception exposure of either parent to germ line mutations, developmental defects, childhood cancer, or other health effects. Chloroethane is positive in *in vitro* mutagenicity studies in bacterial and mammalian cells, but is negative in *in vivo* mammalian cell tests. These inconclusive results do not allow the prediction of chloroethane genotoxicity in humans.

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 chloroethane 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 chloroethane are discussed in Section 2.7.2.

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

There are no known biomarkers of exposure or effect that have been validated in children or adults exposed as children. There are no known biomarkers of exposure and effect that are unique to children. Further, there are no known biomarkers of exposure and effect in adults that could identify childhood exposure. Since

chloroethane is rapidly metabolized in the body, biomarkers for adults or children would be limited to current exposures.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Chloroethane

Studies of the association of environmental concentrations of chloroethane with levels of chloroethane in the breath, fluids, and body tissues were not identified. Because a portion of the chloroethane inhaled is exhaled, measurement of chloroethane in breath may serve as a useful biomarker of exposure. In rats and mice, chloroethane is metabolized to acetaldehyde and the glutathione conjugates, *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine (Fedtke et al. 1994a, 1994b). Further research is required to determine if urinary excretion of glutathione conjugates would serve as a useful biomarker following exposure of humans to chloroethane. The glutathione conjugates *S*-ethyl-*N*-acetyl-E-cysteine and *S*-ethyl-L-cysteine would not be biomarkers unique to chloroethane exposure. Acetaldehyde forms adducts with plasma proteins. Because ethanol is also metabolized to acetaldehyde, it has been suggested that the measurement of these adducts, or of antibodies produced in response to these adducts, may serve as a biomarker of ethanol exposure (Won-all et al. 1994). The measurement of acetaldehyde protein adducts, or the associated antibodies, may also serve as a biomarker of chloroethane exposure. It should be noted that formation of antibodies to these compounds can result from exposure to chemicals other than chloroethane.

2.7.2 Biomarkers Used to Characterize Effects Caused by Chloroethane

Anesthesia is rapidly produced in humans by inhalation of chloroethane at a concentration of approximately 40,000 ppm. Other effects reported at anesthetic concentrations include cardiac irregularities, respiratory paralysis, and nausea. A blood concentration of 20-30 mg percent was reported for this exposure level (Adriani 194 1). No other studies were located regarding levels of chloroethane in human tissues and fluids associated with effects. Because these effects occur following exposure to many chemicals, they would not serve as useful biomarkers for chloroethane exposure.

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

The interaction between chloroethane and ethanol was studied by Schmidt et al. (1972) and Gohlke and Schmidt (1972), who found that chloroethane enhanced the effects of ethanol in rats. Inhalation of chloroethane 4 hours/day for 8 of 10 days in conjunction with ethanol treatment led to greater changes in liver enzyme levels (decreased succinate dehydrogenase and nonspecific esterase and increased acid phosphatase) than were produced by ethanol alone. In addition, inflammation of the liver and fatty degeneration of hepatocytes were most prominent in rats given chloroethane in addition to ethanol. These results, although limited, are interesting because both ethanol and chloroethane are metabolized by CYP2El to acetaldehyde. Therefore, one compound could compete for active sites in CYP2E1, resulting in delayed metabolism of the other compound. However, ethanol, as well as chloroethane, induces CYP2El to expression, so more enzyme should be produced to handle a metabolic challenge (Leeder and Kearns 1997).

A study in cats demonstrated that the extent of methemoglobinemia induced by intravenous administration of aniline was significantly reduced in cats anesthetized with chloroethane compared to unanesthetized cats (McLean et al. 1967). The rate at which the methemoglobin disappeared, however, was also significantly reduced in the anesthetized cats compared with unanesthetized cats. The results suggest that concurrent exposure to aniline and chloroethane may induce less methemoglobin than exposure to aniline alone, but the methemoglobin induced by the combined exposure would persist longer than that induced by exposure to aniline alone. A similar effect was not observed when cats were anesthetized with chloralose and treated with phenylhydroxylamine, the aniline metabolite that results in methemoglobin formation. Therefore, the study authors concluded that chloralose acts by inhibiting the metabolism of aniline. It is not known if chloroethane acts in the same manner.

No studies were available investigating the interactions of chloroethane with other chemicals in children or in adults.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chloroethane than will most persons exposed to the same level of chloroethane 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 chloroethane, or compromised function of

target organs affected by chloroethane. Populations who are at greater risk due to their unusually high exposure to chloroethane are discussed in Section 5.7, Populations with Potentially High Exposure.

Persons with prior exposure to ethanol may be at higher risk from chloroethane exposure because chloroethane has been shown to enhance the effects of ethanol in rats (Gohlke and Schmidt 1972; Schmidt et al. 1972). Because chloroethane is metabolized by the liver (Fedtke et al. 1994a, 1994b), and minimal liver effects have been observed in animals following inhalation exposure (Landry et al. 1987, 1989; Oura et al. 1966; Sayers et al. 1929; Troshina 1966), persons with compromised liver function may be at greater risk following exposure to chloroethane.

It is unknown whether children differ in their susceptibility to chloroethane from adults. This is discussed in detail in 2.6 Children's Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chloroethane. 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 chloroethane. 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 chloroethane: Bronstein AC, Currance PL. 1988. Emergency Care for Hazardous Materials Exposure; Haddad LM, Winchester H. 1990. Clinical Management of Poisoning and Drug Overdose; Stutz DR, Ulin S. 1992. Hazardous Materials Injuries.

There are no known pediatric-specific methods for reducing peak absorption following exposure or reducing body burden. None of the methods for reducing peak absorption or body burden are contraindicated in children. No data were available to indicate that the methods used in adults have been validated in children.

2.10.1 Reducing Peak Absorption Following Exposure

Because chloroethane is a gas, human exposure is most likely to occur by inhalation. Moving the subject to fresh air is the best way to reduce absorption of chloroethane following inhalation exposure (Haddad and Winchester 1990).

2.10.2 Reducing Body Burden

Animal studies suggest that the body does not retain significant amounts of chloroethane (Fedtke et al. 1994a, l994b). Because some of the absorbed chloroethane is exhaled, increasing the ventilation rate once the subject is removed from exposure may help to enhance elimination.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

No methods for interfering with the mechanism of action of chloroethane were identified.

2.11 ADEQUACY OF THE DATABASE

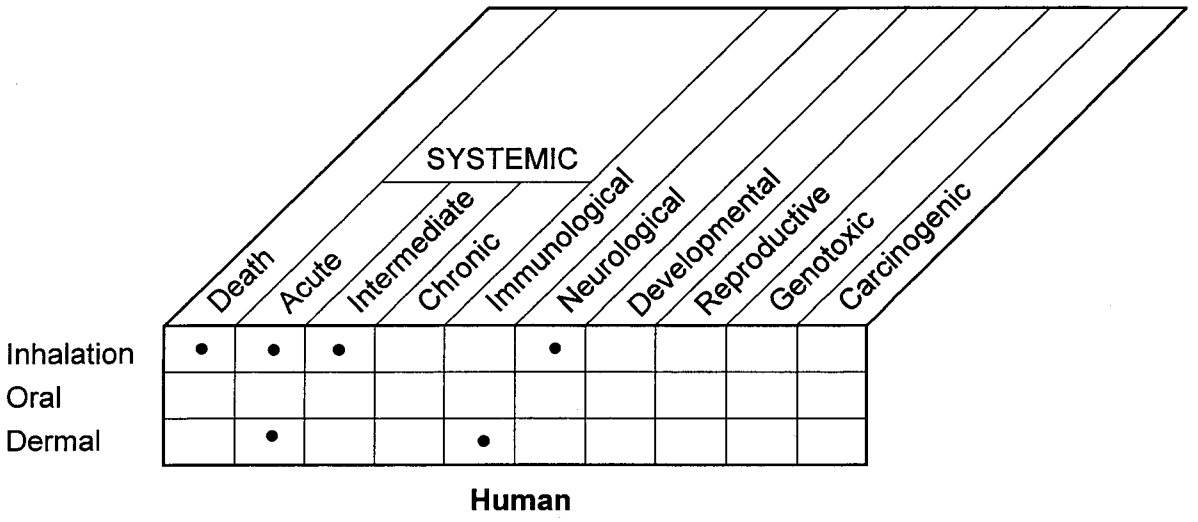
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloroethane is available. Where adequate information is not 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 chloroethane.

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.

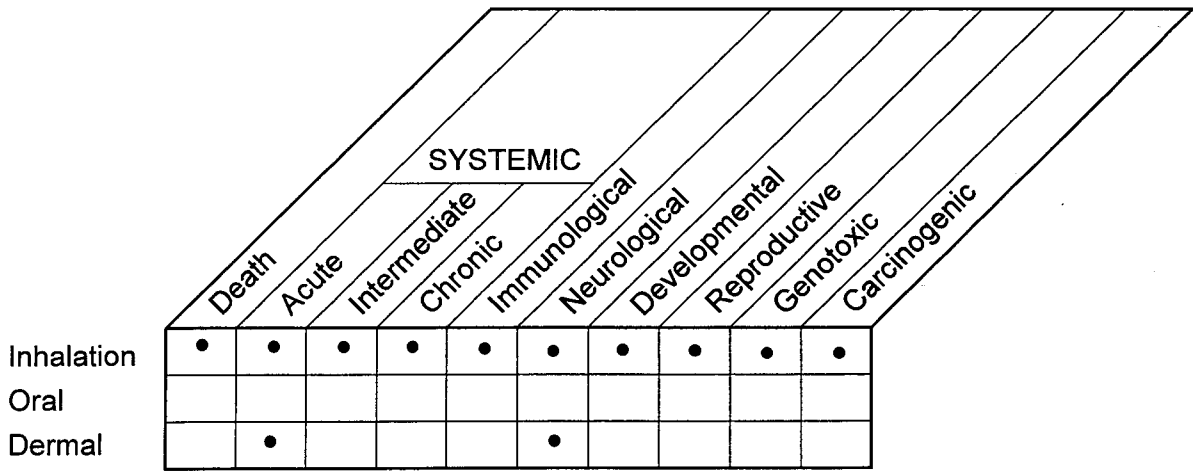
2.11.1 Existing Information on Health Effects of Chloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chloroethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of chloroethane. 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*

FIGURE 2-4. Existing Information on Health Effects of Chloroethane



Human



Animal

• Existing Studies

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 can be seen from the figure, chloroethane exposure by the inhalation route in animals has been well studied; however, there are few studies of the health effects of chloroethane exposure by other routes. The lack of studies of oral and dermal exposure is consistent with the fact that chloroethane is a gas at room temperature.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Tests of the acute toxicity of chloroethane by inhalation exposure have provided information on the levels of chloroethane that produce neurological effects in humans (Davidson 1925; Sayers et al. 1929) and animals (Landry et al. 1982; Sayers et al. 1929) and the levels that produce death in animals (Sayers et al. 1929). Other toxic effects, such as those on the heart, have been reported (Bush et al. 1952; Haid et al. 1954), but the precise levels at which they occur have not been identified. Studies that carefully examine tissues histologically and look for other subtle effects are needed. They might provide information on the mechanisms of chloroethane lethality and neurotoxicity and provide further information on other toxic effects. The acute-duration inhalation MRL is based on an acute-duration developmental study in which minimal fetotoxicity was observed in the offspring of mice exposed to chloroethane on gestation days 6-15 (Scortichini et al. 1986).

No reliable studies of the oral or dermal toxicity of chloroethane were located. Reliable oral exposure studies are needed. Many people are exposed to chloroethane through its use as a topical anesthetic. Frostbite has occurred following prolonged skin application (Noble 1979). Studies of the acute dermal toxicity of chloroethane are needed to estimate safe application times. There is one report of eye irritation in humans caused by exposure to high concentrations of chloroethane vapor (Sayers et al. 1929), but skin irritation has not been studied for any exposure route.

Intermediate-Duration Exposure. Repeated-dose studies of the toxicity of chloroethane by inhalation exposure have been performed in rats (Landry et al. 1982; NTP 1989), mice (Landry et al. 1987, 1989; NTP 1989), and dogs (Landry et al. 1982) at several dosage levels and for several durations of exposure. Reports indicate that inhalation abuse of chloroethane by adults and children may be increasing (Hersh 199 1; Walker 1993). Human studies involving chloroethane abusers or animal studies using doses comparable to those sniffed from household products are needed to help elucidate the systemic effects caused by the compound.

Reliable studies of repeated-dose exposure to chloroethane are not available for other routes of exposure. Reliable oral exposure studies are needed. Chloroethane is also repeatedly used as a local anesthetic to treat sports injuries and in the treatment of musculoskeletal facial pain (Marbach 1996). Repeated-dose dermal studies are needed to provide information on whether repeated dermal exposure of humans is hazardous.

Chronic-Duration Exposure and Cancer. A 2-year bioassay on inhaled chloroethane was performed in rats and mice by the National Toxicology Program (NTP 1989). Survival of mice was reduced compared to controls as a result of ascending urinary tract infections in males and uterine cancer in females. The only systemic effects noted were in the kidney (scattered foci of tubular regeneration, minimal glomerulosclerosis) in female mice. Female mice were also hyperactive during the exposures.

Chloroethane was carcinogenic in female mice resulting in uterine cancer (NTP 1989). Because of reduced survival of male mice, the study was considered inadequate, although there was an increased incidence of alveolar/bronchiolar neoplasms of the lungs. In exposed rats, there was equivocal evidence of carcinogenicity based on skin trichoepitheliomas, sebaceous gland adenomas, or basal cell carcinomas in males, and malignant astrocytomas in the brain of females. A chronic study in which several exposure levels are tested is needed to provide more information on the danger to humans at lower exposure levels. Studies of chronic toxicity and carcinogenicity do not exist for other routes of exposure. Therefore, studies on chronic oral exposure to chloroethane are needed.

Genotoxicity. The available genotoxicity studies indicate that chloroethane is mutagenic in bacteria (NTP 1989) and in mammalian cells *in vitro* (Ebert et al. 1994) but not clastogenic in mammalian cells *in vivo* (Ebert et al. 1994). Additional genotoxicity tests are needed to determine whether it is possible that chloroethane is genotoxic in humans.

Reproductive Toxicity. Several studies investigated reproductive endpoints in animals. Uterine weight was decreased by approximately 35% in mice exposed to high concentrations of chloroethane (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels have also been reported in rats and mice exposed to chloroethane (Fedtke et al. 1994b). A small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane (Bucher et al. 1995). Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). Histopathological effects have not been observed in reproductive organs of animals

exposed to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989). No effects on the number of live and dead fetuses or on the number and position of resorption sites were observed in mice exposed to chloroethane on gestation days 6-15 (Scortichini et al. 1986).

Based on decreases in uterine glutathione in rats and mice (Fedtke et al. 1994b), decreases in uterine weight in mice (Fedtke et al. 1994a), and the development of uterine cancer in mice exposed to chloroethane (NTP 1989) (see Cancer discussion in this Section 2.11.2), the uterus appears to be a target of chloroethane exposure in mice; rats are apparently less sensitive to these effects. The relevance of uterine effects in animals to human chloroethane exposure is not known, and further studies to examine the mechanisms of uterine effects observed in chloroethane-exposed mice are needed. A multigeneration study to determine if uterine effects, estrous cycle effects, and effects on sperm motility impact reproductive performance is also needed.

Developmental Toxicity. Only one study of the developmental effects of chloroethane in mice was
found. In this study, minimal evidence of fetotoxicity (increase in small centers of unossified bones of the skull) was observed at the highest concentration tested (Scortichini et al. 1986). This study serves as the basis for the acute-duration inhalation MRL. Additional developmental studies in other species are needed Because chloroethane is a neurotoxin, studies of the developmental neurotoxicity of chloroethane are also needed to assess the potential risk to humans.

Immunotoxicity. Several studies included histopathological examinations of immunological organs and tissues following inhalation exposure to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989) but found no effects. Studies in which tests of immune function were performed are needed to provide more useful information on the immunotoxicity of chloroethane. Three reports on sensitization produced by dermally applied chloroethane in humans (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976) were found. Because many people are dermally exposed to chloroethane as a topical anesthetic, studies of this phenomenon are needed.

Neurotoxicity. Studies of chloroethane inhalation in humans and animals have provided information on the neurological effects produced by acute exposure to chloroethane and the levels at which they occur. Most repeated-exposure studies involved only behavioral observations and histopathological examinations of neurological organs and tissues; one case report involved a neurological examination of an adult male, which revealed marked nystagmus, ataxia and vertigo, but nothing abnormal upon evaluation of the brain, brain

stem, or spine upon MRI (Walker 1993). In addition, two studies in mice (Landry et al. 1987, 1989) and one in dogs (Landry et al. 1982) were identified, neither of which reported signs of neurotoxicity. Reliable studies of neurotoxicity following exposure by other routes do not exist. Controlled studies regarding the neurological effects of chloroethane are needed.

Epidemiological and Human Dosimetry Studies. No epidemiological or human dosimetry studies of chloroethane have been performed. High inhalation concentrations of chloroethane are anesthetic in humans and overdose can be lethal because of cardiovascular or respiratory effects. Chronic inhalation exposure has produced cancer in animals (NTP 1989). The general population might be exposed to chloroethane by inhalation of contaminated ambient air or intentional use as a topical anesthetic. Occupational exposure may occur by inhalation or dermal contact. Epidemiological studies of people who live near industries releasing chloroethane or near hazardous waste sites, of people who use chloroethane as a topical anesthetic, and of people who are occupationally exposed to chloroethane are needed to provide information on whether chloroethane is carcinogenic or has other toxic effects in humans at environmentally relevant concentrations. If such effects are identified, human dosimetry studies may be able to correlate levels of chloroethane in human tissues or fluids with health effects.

Biomarkers of Exposure and Effect

Exposure. Studies of the association of environmental concentrations of chloroethane with levels of chloroethane in the breath, fluids, and body tissues were not identified. Studies examining the association between air and breath levels of chloroethane are needed. Further research is required to determine if urinary excretion of glutathione conjugate metabolites or acetaldehyde-protein adducts (Worrall et al. 1994) would serve as a useful biomarker following exposure of humans to chloroethane.

Effect. Unique biomarkers of effect have not been identified for exposure to chloroethane. Further research regarding the biochemical effects of chloroethane is needed to identify biomarkers of effect for chloroethane.

Absorption, Distribution, Metabolism, and Excretion. A single breath absorption study (Morgan et al. 1970) is the only quantitative study regarding the absorption, distribution, metabolism, and excretion of chloroethane in humans. Studies in rats and mice indicate that chloroethane is readily absorbed following inhalation exposure and metabolized to acetaldehyde and glutathione conjugates (Fedtke et al. 1994a, 1994b). Additional quantitative studies of the pharmacokinetics of chloroethane are needed.

Comparative Toxicokinetics. A study that compares the metabolism of chloroethane in rats and miceindicates that mice have a greater capacity to metabolize chloroethane than rats (Fedtke et al. 1994a, 1994b). An *in vitro* study using human liver preparations to study the metabolism of chloroethane is needed to determine which species is the most appropriate model for the metabolism of chloroethane.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure (Haddad and Winchester 1990) and increasing ventilation rate to enhance elimination after the subject is removed from exposure, methods for reducing toxic effects were not identified. As more information is learned regarding the mechanism of chloroethane toxicity, methods for reducing the toxic effects of chloroethane can be developed.

Children's Susceptibility. No studies involving exposure of children or immature animals to chloroethane have provided quantitative doses. There are two very qualitative studies in children associated with the use of chloroethane as an anesthetic (Nielsen 1980; Noble 1979). There currently exists a need for studies with children or immature animals exposed to the compound to investigate any differences in dose absorption, metabolism, excretion, and presence and severity of effects, Current knowledge of differences in physiology and biochemistry between children and adults indicate that distribution and metabolism mightdiffer between children and adults. However, experiments evaluating qualitative and quantitative differences in these processes would greatly facilitate the understanding of adverse effects of chloroethane in the developing human.

Definitive studies do not exist evaluating whether pharmacokinetics of chloroethane are different in children as compared with adults. Furthermore, no PBPK models exist on any age of children or adults that might inform the public as to the pharmacokinetics of the compound.

Studies are needed to determine whether chloroethane or its metabolites cross the placenta and no studies have evaluated placental or cord blood concentrations of chloroethane or its metabolites in humans or animals. It is unknown whether the delayed bone development seen in the Scortichini et al. (1986) study was due to chloroethane or its metabolites crossing the placenta or to some indirect effect on the fetus. Experiments evaluating these parameters are needed, as well as experiments to determine whether chloroethane significantly accumulates in breast milk. One study detected the compound in breast milk (Pellizari et al, 1982), but neither route of exposure of the mother nor concentration of chloroethane in the milk was identified. In addition, studies determining whether chloroethane would be stored in maternal

tissues would be informative, although the volatility of the compound, as well as data indicating its rapid clearance from the body following inhalation exposure (Morgan et al. 1970), indicate that tissue storage is not expected.

Adequate data do not exist on the effect, if any, chloroethane exposure has on fetal development. The one available prenatal developmental study and data needs on this topic are discussed above in the Developmental Effects subsection. Reliable studies of this type are needed in determining the fetotoxicity of chloroethane, as well as the potential of the compound for disrupting normal child development. Studies on postnatal exposures and their influence on development in immature animals would also be useful.

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

Data Needs for Modeling

Studies which provide information on the physiological biochemical parameters specific to chloroethane in human and animal tissues are needed. For instance, there are no data on organ volumes, alveolar ventilation,cardiac output, or organ perfusion rates, among other parameters, in humans and animals. A PBPK model in rats exposed to chloroethane via inhalation was developed with the assumption that metabolism of the compound occurred exclusively in the liver (Gargas et al. 1990). The authors determined a V_{maxc} which is the maximum velocity (V_{max}) scaled for a 1 -kg animal, the K_m (rate constant for the saturable pathway), and the first-order rate constant, K_{fc}, which is the rate constant (K_f) scaled for a l-kg animal.

Other biochemical parameters that affect metabolism and clearance have not been investigated. Waller et al. (1996) modeled the cytochrome P450-mediated metabolism of chloroethane using three-dimensional quantitative structure-activity relationships (3D-QSAR). Their models have predicted a metabolic clearance rate for chloroethane. Other studies, involving the experimental or modeled estimation of other biochemical parameters, such as excretory clearance, binding and reactivity, absorption constants, inhibition rate constants, first pass effects, and other parameters that may influence the rate of elimination and bioavailability were not available. Studies investigating these parameters using human or animal tissues would provide much-needed information concerning the metabolism of chloroethane.

2.11.3 Ongoing Studies

Ongoing studies regarding chloroethane were not identified in the CRISP (1996), FEDRIP (1998), or CRIS/USDA (1998) databases.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chhloroethane is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

TABLE 3-1. Chemical Identity of Chloroethane

Characteristic	Information	Reference
Chemical name	Ethyl chloride; chloroethane	Lide 1993
Synonym(s)	Aethylis chloridum; chlorethyl; ether chloratus; ether hydrochloric; ether muriatic; ethyl chloride; monochloro-ethane, chloroethane	HSDB 1997
Registered trade name(s)	Anadynon; Chelen; Chlorylanesthetic; Kelene; Narcotile	HSDB 1997
Chemical formula	C_2H_5Cl	Budavari 1989
Chemical structure	$CH_3–CH_2–Cl$	Lide 1993
Identification numbers:		
CAS registry	75-00-3	OHM/TADS 1998
NIOSH RTECS	KH7525000	RTECS 1998
EPA hazardous waste	C266	Mitre Corp. 1987
OHM/TADS	7216712	OHM/TADS 1998
DOT/UN/NA/IMO shipping	UN 1037; IMO 2.3	HSDB 1997
HSDB	533	HSDB 1997
NCI	CO6224	RTECS 1998

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

TABLE 3-2. Physical and Chemical Properties of Chloroethane

Property	Information	Reference
Molecular weight	64.52	Budavari 1989
Color	Colorless	Morris and Tasto 1979
Physical state	Gas	Budavari 1989
Melting point	-138.7°C	Budavari 1989
Boiling point	32.5°C at 2 atm	Budavari 1989
Specific gravity	0.9214@O°C/4°C	HSDB 1997
Vapor density	0.8970 (20/4°C)	Morris and Tasto 1979
Odor	Ethereal, pungent	HSDB 1997
Odor threshold:		
Water	0.019 ppm (w/v)	Amoore and Hautala 1983
Air	4.2 ppm (v/v) (11.3 g/L)	Amoore and Hautala 1983
Solubility:		
Water at 20°C	0.574 g/100 mL	Budavari 1989
Organic solvent(s)	Alcohol: 48.3 g/100 mL; miscible with ether	Budavari 1989
Partition coefficients:		
Log K_{ow}	1.43	Hansch and Leo 1985; HSBD 1997
Log K_{oc}	1.52 (estimated using equation 4-7)	Lyman 1982
K_{oc}	143; 33 (using Log K_{oc} of 1.52)	Lyman 1982
Vapor pressure:		
At 20°C	1,008 mmHg	Daubert and Danner 1985
Henry's law constant:		
At 25°C	1.11×10^{-2} atm•m^3/mole (24.8 °C)	Gossett 1987
Autoignition temperature	519°C	Morris and Tasto 1979
Flashpoint:		
Open cup	-43°C	Budavari 1989
Closed cup	-50°C	Budavari 1989
Explosive limits in air	3.6–14.8 volume %	Budavari 1989
Conversion factors:		Budavari 1989
ppm (v/v) to mg/m^3 in air (20°C)	ppm (v/v) × 2.68 = mg/m^3	
mg/m^3 to ppm in air (20°C)	mg/m^3 × 0.373 = ppm (v/v)	

v = volume; w = weight

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

4.1 PRODUCTION

Table 4-l lists the facilities in each state that manufacture or process chloroethane, the intended use, and the range of maximum amounts of chloroethane that are stored on site. There are currently 50 facilities that produce or process chloroethane in the United States. The data listed in Table 4-l are derived from theToxics Release Inventory (TRI) (TR196 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

The production of chloroethane in the United States has decreased as the use of leaded gasoline has been regulated. In 1960, approximately 247,000 metric tons (1 metric ton = 1,000 kg) of chloroethane were produced, while in 1988 production of chloroethane was approximately 69,000 metric tons (IARC 1991).

Companies on the TRI listed as producers of chloroethane include: Degussa Corporation and Huls America, Inc., in Theodore, AL; Monsanto Company in Muscatine, IA, and Bridgeport, NJ; Westlake Monomers Corporation in Calvert City, KY; BASF Corporation in Geismar, LA; Condea Vista Company in Westlake, LA; Dow Chemical Company in Plaquemine, LA, and Freeport, TX; Formosa Plastics Corporation in Baton Rouge, LA, and Point Comfort, TX; Georgia Gulf Corporation in Plaquemine, LA; PPG Industries in Lake Charles, LA; Vulcan Materials Company in Geismar, LA; Dow Chemical USA in Midland, MI; Dow Corning Corporation in Midland, MI; Akzo Nobel Chemicals, Inc., in Edison, NJ; Cyanamid Agricultural in Manati, PR; Lobeco Prods., Inc., in Lobeco, SC; Zeneca Specialties in Mount Pleasant, TN; Eastman Chemical Company in Longview, TX; Hoechst-Celanese in Bay City, TX; Occidental Chemical Corporation in Deer Park, TX, and Gregory, TX; Specialtychem Prods. Corporation in Marinette, WI; and OS1 Specialties, Inc., in Friendly, WV (TR196 1998).

4.2 IMPORT/EXPORT

From 1979 to 1988, chloroethane imports were significant only in 1980, 1981, and 1982. During those years, imported quantities were 1,270,5,030, and 2,325 metric tons, respectively (IARC 1991). From 1990 to 1994, US. imports of chloroethane in kilograms were 3,011,432 in 1990,4,103,072 in 1991, 14,260 in 1992,24 in 1993, and 0 in 1994 (NTDB 1996).

Table 4-1. Facilities that Manufacture or Process Chloroethane

State[a]	Number of Facilities	Range of Maximum Amounts on Site in Pounds[b]	Activities and Uses[c]
AL	2	0–999	1, 5, 6
CA	1	100,000–999,999	8
CT	2	10,000–999,999	7, 8
GA	2	10,000–999,999	7, 8
IA	1	100–999	1, 5
IL	2	100,000–999,999	7, 11
KY	1	100,000–999,999	1, 3, 7
LA	10	1,000–49,999,999	1, 3, 4, 5, 6, 7, 8, 11
MI	2	10,000–999,999	1, 5, 7, 13
MO	2	1,000–999,999	2, 4, 8, 10
NJ	4	0–999,999	1, 5, 7, 13
OH	2	10,000–999,999	10, 12
PA	1	100,000–999,999	10
PR	1	0–99	1, 5
SC	2	10,000–99,999	1, 5, 7
TN	1	0–99	1, 5, 7
TX	11	0–999,999	1, 5, 6, 7, 11, 13
VA	2	10,000–999,999	7, 8
WI	1	1,000–9,999	1, 5
WV	1	100–999	1, 5

Source: TRI96 1998

a Post office state abbreviations used

b Range represents maximum amounts on site reported by facilities in each state

c Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

From 1979 to 1988, the United States exported 8,562-13,868 metric tons, with the maximum occurring in 1986 and the minimum occurring in 1988 (IARC 1991). From 1991 to 1995, U.S. exports of chloroethane in metric tons were 11.3 in 1991, 16.8 in 1992, 15.1 in 1993,38.1 in 1994, and 5.4 in 1995 (NTDB 1996).

4.3 USE

In the past, the single largest use of chloroethane was in the production of tetraethyl lead. As recently as 1984, 80% of the chloroethane consumed in the United States was used in domestic production of tetraethyl lead, 15% was used in the production of ethyl cellulose, and 5% was used for miscellaneous applications including use as a solvent, refrigerant, and topical anesthetic, and use in the manufacture of dyes, chemicals, and pharmaceuticals (HSDB 1997; Morris and Tasto 1979). Government-mandated reduction in the amount of lead additives used in gasoline in the United States and a shift to the use of unleaded gasoline caused a drastic reduction in the amount of chloroethane required for the production of tetraethyl lead (CMR 1982; EPA 1985; IARC 1991).

Chloroethane has been used as a pulp vitality tester in dentistry, as a medication to alleviate pain associated with insect bums, stings, and sports injuries, as an adjunct in the treatment of tinea lesions and creeping eruptions, as a test for regional anesthesia before Caesarean section, and as a counterirritant and anesthetic for relief of myofacial and visceral pain syndromes (Adriani 1986; Boume et al. 1997; Brown 1972; Ehrmann 1977; Marbach 1996; Ott 1969). Chloroethane has recently been used as a freezing agent to relieve spasms in recipient arteries in microvascular transfer (Cavadas 1996).

Chloroethane is also used as a recreational inhalant, desired for its narcotic effects. The compound is manufactured in pressurized canisters and sold specifically for inhalant abuse under names such as Ethyl Gaz, Ethyl Four Star, Black Jac, and Maximum Impact (Hersh 199 1; Walker 1993).

4.4 DISPOSAL

Chloroethane is listed as a toxic substance under Section 3 13 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1998c). Disposal of wastes containing chloroethane is controlled by a number of federal regulations (see Chapter 7).

Chloroethane may be disposed of by controlled incineration. It is recommended that chloroethane be mixed with another combustible fuel prior to incineration; however, sufficient oxygen and an adequate operating temperature are mandatory to avoid incomplete combustion resulting in the formation of phosgene. Incinerators for this compound are typically equipped with an acid scrubber to remove halo acids from the effluent gas (HSDB 1997; OHM/TADS 1998). In a study of the thermal destruction of chloroethane, the minimum temperature required for 99.99% destruction with a 1 -second residence time was 727 °C (Fisher and Koshland 1990). Among the chlorinated methanes and ethanes studied, chloroethane had the lowest temperature required for destruction. Chloroethane is also a constituent of some waste-water streams; it is susceptible to removal by air stripping (HSDB 1997). Placing chloroethane in a landfill is not recommended (HSDB 1997).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

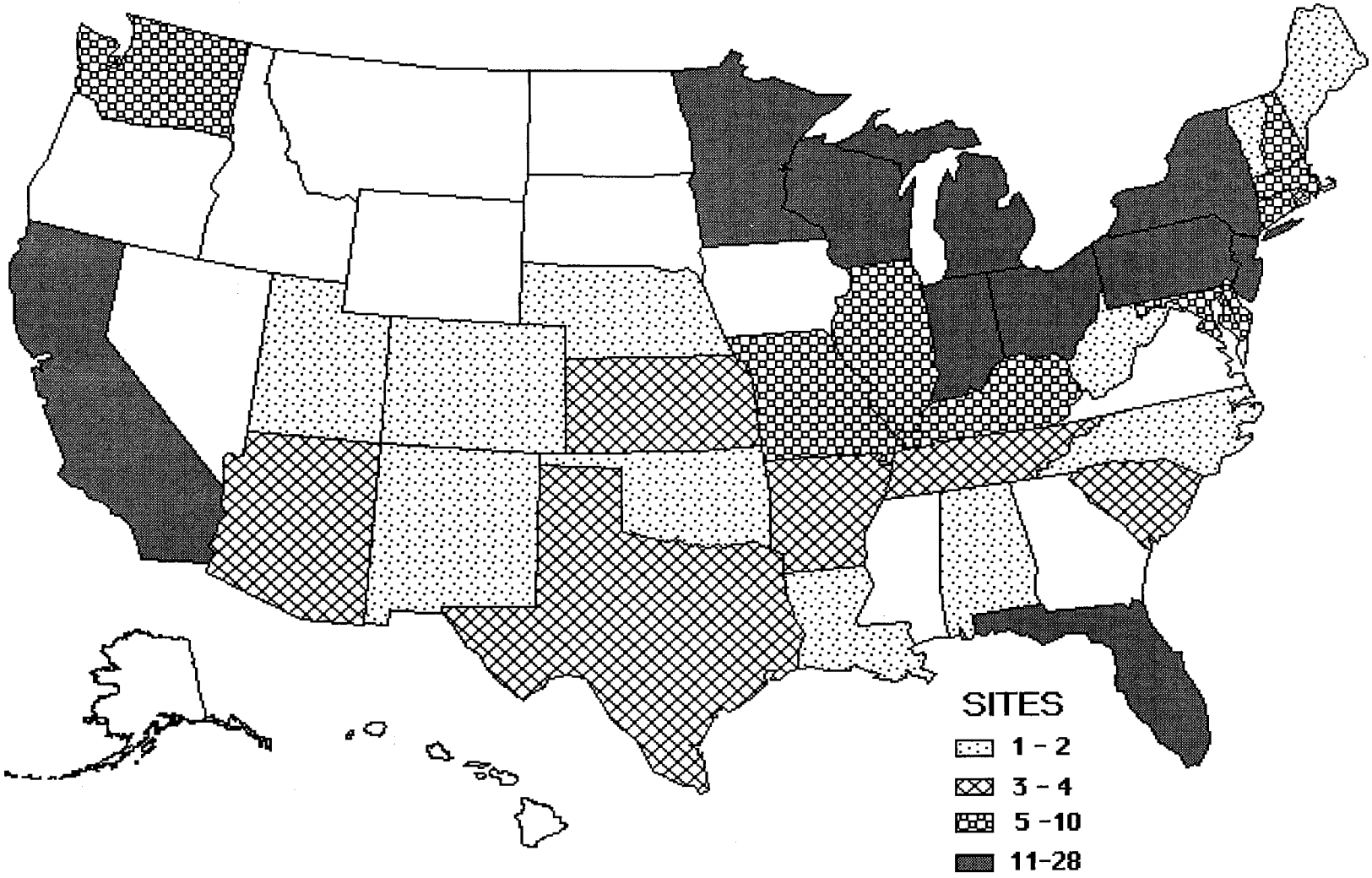
Chloroethane has been ientified in at least 282 of the 1,467 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1998). However, the number of sites evaluated for chloroethane is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

Chloroethane is a compound that occurs in the euviroument as the result of anthropogenic activity. Sources of chloroethane exposure include process and fugitive emissions from its production and use as a chemical intermediate; evaporation from waste-water streams, landfills, solvents, refrigerants, and anesthetics; emissions from plastics, refuse, and biomass combustion; formation during water chlorination; formation via anaerobic biodegradation of some chlorinated solvents; and evaporation and leaching from landfills. Most chloroethane released in the environment eventually enters the atmosphere.

When released to the atmosphere, the dominant removal mechanism is expected to be reaction with photochemically-generated hydroxyl radicals (half-life of 40 days). Potential exists for removal from the atmosphere in precipitation; however, most chloroethane removed by this mechanism is likely to reenter the atmosphere by volatilization. When released to surface water, volatilization is expected to be the primary fate process (half-life of 2.4 hours in a model river). When released to soil, chloroethane either volatilizes rapidly from soil surfaces or leaches through subsurface soil where it becomes a potential groundwater contaminant. In groundwater, chloroethane would probably be subject to chemical hydrolysis. Sufficient data are not available to establish the rate of chloroethane degradation in groundwater.

The general population may be exposed to low (ppt) levels of chloroethane through inhalation of contaminated ambient air and consumption of contaminated drinking water. Dermal contact can occur as a result of the intentional use of chloroethane as a topical anesthetic. Occupational exposure may occur by inhalation and/or dermal contact. According to a 1981-1983 NIOSH survey, an estimated 49,212 workers in the United States are potentially exposed to chloroethane in the workplace (NIOSH 1991).

Figure 5-1. Frequency of NPL Sites with Chloroethane Contamination*



* Derived from HazDat 1998
282 of 1,467 Sites

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxics Release Inventory (TRI), in 1996, a total of 3,242,710 pounds (1,470,617 kg) of chloroethane was released to the environment from 50 large processing facilities (TR196 1998). Table 5-l lists amounts released from these facilities. In addition, an estimated 762 pounds (346 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 688,311 pounds (312,159 kg) were transferred offsite (TR196 1998). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Chloroethane has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 282 of the 1,467 NPL hazardous waste sites.

5.2.1 Air

According to the Toxics Release Inventory (TRI), in 1996, the estimated releases of chloroethane of 2553,260 pounds (1,157,941 kg) to air from 50 large processing facilities accounted for about 79% of total environmental releases (TR196 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Chloroethane may be released to the environment through process and fugitive emissions related to its production and use as a chemical intermediate; through evaporative losses from waste-water streams, landfills, solvents, refrigerants, and anesthetics; and through emissions from combustion of plastics, refuse, and biomass (Graedel et al. 1986; Liepins et al. 1977; Vogt and Walsh 1985; Young and Parker 1984). Based on 1980 air monitoring data, it was estimated that 20 million pounds of chloroethane per year were being released into the atmosphere in the United States (Singh et al. 1981). Between 1980 and 1988, production levels of chloroethane in the United States decreased by approximately 62% (IARC 1991), and a proportional decrease in emissions related to its production and use as a chemical intermediate probably occurred.

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Chloroethane

State[b]	Number of Facilities	Total of reported amounts in pounds per year[a]						
		Air[c]	Water	Land	Underground Injection	POTW Transfer	Off-Site Waste Transfer	Total Environment[d]
AL	2	257	0	0	0	0	250	507
CA	1	122,000	0	0	0	0	0	122,000
CT	2	198,010	0	0	0	750	0	198,760
GA	2	180,300	0	0	0	0	0	180,300
IA	1	6,700	0	0	0	0	0	6,700
IL	2	199,356	0	0	0	0	0	199,356
KY	1	1	0	0	0	0	156,414	156,415
LA	10	106,691	4	0	0	0	4,705	111,400
MI	2	226,602	0	0	0	0	48,066	274,668
MO	2	345,106	0	0	0	0	0	345,106
NJ	4	30,875	27	0	0	2	24,620	55,524
OH	2	445,611	0	0	0	0	1,926	447,537
PA	1	1,895	0	0	0	0	0	1,895
PR	1	136,460	0	0	0	5	1,300	137,765
SC	2	8,473	0	0	0	0	447,430	455,903
TN	1	302	0	0	0	0	0	302
TX	10	126,408	0	0	92	0	0	126,500
VA	2	363,839	0	0	0	5	0	363,844
WI	1	314	0	0	0	0	3,600	3,914
WV	1	54,060	254	0	0	0	0	54,314

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

5.2.2 Water

According to the Toxics Release Inventory (TRI), in 1996, the estimated releases of chloroethane of 285 pounds (129 kg) to water from 50 large processing facilities accounted for about 0.01% of total environmental releases (TR196 1998). Table 5-l lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Limited data are available regarding the release of chloroethane to water. This compound may be released to the environment as a constituent of waste-water streams from various industries, particularly those that use chloroethane as an intermediate. The following industries have been identified as potential sources of release of chloroethane: electroplating, organic chemicals, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint and ink formulating, gum and wood, and carbon black (EPA 1988a). It is possible that chloroethane forms in some waste-water streams as a result of disinfection bychlorination (Gould et al. 1983; Liepins et al. 1977; Otson 1987). Because of its volatility, the majority of chloroethane released to surface water is expected to enter the atmosphere. This compound can leach into groundwater from waste disposal sites, and it may form in groundwater as an anaerobic biodegradation product of chlorinated solvents (e.g., 1,l ,l -trichloroethane and cis-1 ,1 -dichloroethylene) (Barrio-Lage et al. 1986; Vogel and McCarty 1987).

5.2.3 Soil

According to the Toxics Release Inventory (TRI), in 1996, there were no releases to soil from the 50 large processing facilities required to report (TR196 1998).

Chloroethane can occur in soil as a result of the disposal of waste products that contain this compound and as a result of formation as an anaerobic biodegradation product of various chlorinated compounds (e.g., 1 ,l ,ltrichloroethane and *cis*- 1,2-dichloroethylene) (Barrio-Lage et al. 1986; Vogel and McCarty 1987).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The relatively high water solubility of chloroethane suggests that potential exists for removal of this compound from the atmosphere via washout. However, most chloroethane removed by this mechanism is likely to reenter the atmosphere by volatilization.

The dominant removal process for chloroethane in surface water is expected to be volatilization. Based on a measured Henry's Law constant of 1 .11x10^{-2} atm-m^3/mole at 24.8 °C, the volatilization half-life of chloroethane from a model river 1 m deep, flowing 1 m/second with a wind speed of 3 m/second was estimated to be 2.4 hours (Gessett 1987; Thomas 1982).

Bioconcentration factors (BCF) of 7 and 5 have been estimated for chloroethane using linear regression equations based on a log of the octanol-water partition coefficient (K_{ow}) of 1.43 and a water solubility of 5,678 mg/L at 20°C, respectively (Bysshe 1982; Hansch and Leo 1985; Horvath 1982). These BCF values indicate that this compound would not bioconcentrate significantly in aquatic organisms.

Adsorption coefficients (K_{oc}) of 143 and 33 were estimated for chloroethane using linear regression equations based on log K_{ow} and water solubility data, respectively (Lyman 1982). These &, values suggest that adsorption of chloroethane to suspended solids and sediments in water would not be a significant fate process.

The likely insignificant sorption of chloroethane to soil, indicated by the relatively low K_{oc} value for the compound, suggests that it would be highly mobile in soil and might undergo significant leaching (Swann et al. 1983). The relatively high vapor pressure of chloroethane and its volatility from water suggest that it would evaporate rapidly from soil surfaces, and that volatilization would probably be a major removal process. Washington (1996) has calculated a K_c value for chloroethane. This value is the ratio of the concentration of the compound in the gas phase relative to the water phase and indicates the mobility of the compound from water in saturated soils to vapor. The calculated value of K_c, 0.347 at 17.5 °C, indicates that chloroethane in soil has a propensity to become dissolved in soil water and will then enter soil gas. The concentrations of chloroethane in soil water and the vapor phase will approach equilibrium (Washington 1996).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The dominant atmospheric removal process for chloroethane is predicted to be removal by reaction with photochemically-generated hydroxyl radicals in the troposphere. This reaction is believed to proceed via hydrogen abstraction (Atkinson 1985; Howard and Evenson 1976). The half-life for this reaction has been estimated to be 40 days based on a reaction rate constant of $4.0x10^{-13}$ m^3/molecule-second at 25 °C and a typical hydroxyl radical concentration of $5.0x10^5$ molecules/m^3 (Atkinson 1985; Howard and Evenson 1976). This tropospheric half-life suggests that less than 1% of the chloroethane released to the atmosphere would diffuse into the stratosphere, where it would be destroyed by photolysis (Callahan et al. 1979). Chloroethane is not expected to photolyze in the atmosphere below the ozone layer since it contains no chromophores that absorb light in the visible part of the spectrum (wavelengths about 400-700 nm) (Hubrich and Stuhl l980; Jaffe and Orchin 1962; Mabey et al. 1981).

5.3.2.2 Water

Chloroethane is susceptible to slow chemical hydrolysis and forms ethanol and hydrochloric acid as reaction products. The hydrochloric acid formed dissociates at the neutral pH of most natural waters and forms a chloride salt. The hydrolytic half-life of chloroethane is not known with certainty. The hydrolytic half-life in water at 25 °C and pH 7 was estimated to be 38 days based on a reaction rate constant extrapolated from experimental data at 100°C (Laughton and Robertson 1959; Mabey and Mill 1978). However, in another study, the hydrolytic half-life was estimated to be approximately 1.9 years based on an estimated first-order rate constant of 1 .18x10m^{-8} s^{-1} obtained from the analysis of chloroethane in a batch fermented at 20°C (Vogel and McCarty 1987). Both the neutral and alkaline reaction rates for the hydrolysis of chloroethane were determined by Jeffers and Wolf (1996). The neutral reaction measured in 0.01 M hydrochloric acid at 25 °C was found to predominate, with a rate constant of 5.1 x 10^{-7}, resulting in an estimated half-life for chloroethane of 2.6 years. Despite these conflicting data, chemical hydrolysis may be an important fate process in groundwater when losses from other degradation and transport processes are expected to be negligible.

The high volatility of chloroethane indicates that this compound will volatilize from groundwater and enter soil as a gas. In addition, chloroethane is susceptible to biodegradation in groundwater and other media. Vogel and McCarty (1987) have shown that chloroethane, formed by the anaerobic biodegradation of

trichloroethylene in a batch fermenter, was further dechlorinated by methanogenic bacteria. This study, however, provided no rate constant for this reaction that could be compared to the rate for hydrolysis. Oxidation of chloroethane in water via reaction with singlet oxygen or peroxy radicals is too slow to be environmentally relevant (Mabey et al. 198 1). Direct photolysis in surface waters is not expected to be an environmentally relevant fate process (Mabey et al 1981).

5.3.2.3 Sediment and Soil

In moist subsurface soils, chloroethane is expected to be susceptible to chemical hydrolysis. However, this pathway is expected to be slow and other fate and transport processes may predominate. A large body of data exists on the biodegradation of chlorinated alkenes and alkanes under anaerobic or aerobic conditions. The majority of this data, however, deals with polycblorinated compounds that are biodegraded to chloroethane or a structurally similar alkane or alkene (Ahlert and Enzminger 1992; Barrio-Lage et al. 1986; Chang and Alvarez-Cohen 1996; Tabak et al. I98 1; Vogel and McCarty 1987).

Chloroethane can undergo reductive dehalogenation by methanogenic bacteria in an anaerobic cell suspension or packed column environment (Baek et al. 1990; Holliger et al. 1990). Ethane and hydrochloric acid are formed by the reductive dechlorination of chloroethane (Holliger et al. 1990). In addition, chloroethane can be oxidized by aerobic nitrifying bacteria (Rasche et al. 1990). Both acetaldehyde and 2-chloroethanol are produced from the oxidation of chloroethane, with acetaldehyde predominating at more than 98% of the total product (Rasche et al. 1990).

Although these studies provided maximum product formation rates, first-order rate constants were not estimated; therefore, no comparisons could be made to determine which biodegradation pathway would more rapidly clear chloroethane from a contaminated environment. The pathways do not directly compete, because they occur in different environments, one in an oxygen-deficient environment and the other in an oxygen-rich environment. For example, methanogenic environments are found at landfills and deep aquifers rich in carbohydrate-like compounds. Denitrifying environments are common to agricultural land use as well as areas that have on-site wastewater treatment systems (Ahlert and Enzminger 1992).

Further, optimal biodegradation of chloroethane in aquifers or saturated sediments or soils is highly dependent on the presence of appropriate metabolizing bacteria, the migration of the contaminant to the bacteria, and the availability and concentration of necessary reactants such as carbon sources, reducers,

and/or oxidizers. While laboratory studies indicate that biodegradation can be a significant pathway for clearance of chloroethane and other contaminants from affected media, the importance of this pathway in the environment is still unknown.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chloroethane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on chloroethane 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

Limited data are available regarding the detection of chloroethane in air. Monitoring data from the early 1980s indicate that levels of chloroethane in ambient air at various urban/suburban locations in the United States ranged from 10 to 1,248 ppt with average concentrations ranging from 41 to 140 ppt (Shepson et al. 1987; Singh et al. 198 1). Marine air samples collected in the Northern Hemisphere during 198 1 contained an average concentration of 19 ppt (Singh et al. 1983). Rural air samples collected in 1974-1975 in the northwest United States contained less than 5 ppt chloroethane (Grimsrud and Rasmussen 1975). Current ambient levels of chloroethane are believed to be markedly lower than levels found during the mid 1970s and early 1980s because of a substantial decrease in the production of chloroethane in the United States. Chloroethane has been detected in the air samples of landfill gas collected from a municipal/industrial landfill in the United Kingdom and a municipal landfill simulator (Young and Parker 1984; Vogt and Walsh 1985). These data indicate that chloroethane may be found in the air above some landfills. However, sufficient data are not available to determine whether elevated levels of chloroethane typically occur at or in the vicinity of
waste disposal sites.

5.4.2 Water

Limited data are available regarding the detection of chloroethane in surface water, groundwater, drinking water, and waste water. Analysis of data input into the EPA STORET database during the early 1980s indicates that chloroethane is not a common surface water pollutant and that levels in unfiltered surface water samples typically fall below the detection limit (<10 mg/L) (Staples et al. 1985). Chloroethane

contamination of groundwater has occurred at various waste disposal sites throughout the United States (ATSDR 1989,199l; Cline and Viste 1985; EPA 1986a, 1987; Myers 1983; Sabel and Clark 1984). Groundwater and landfill leachate were the media in which chloroethane was most frequently found at NPL hazardous waste sites (HazDat 1998). Chloroethane was found in groundwater at 218 sites and in leachate at 43 NPL sites. Results of a 1982-1983 survey of 10 Canadian drinking water supplies suggest that trace levels (<0.1 mg/L) of chloroethane may occur in some finished drinking water supplies as a result of formation during the chlorination process (Otson 1987). During the 1975 EPA National Organics Reconnaissance Survey (NORS), chloroethane was qualitatively identified in drinking water samples from three of five finished drinking water supplies in the United States (EPA 1975). Without more recent or comprehensive data, the average daily intake of chloroethane by ingestion of drinking water cannot be estimated. Chloroethane is not a common constituent of treated waste water (EPA 198 1; Perry et al. 1979; Staples et al. 1985; Young et al. 1983). The maximum reported concentration for chloroethane in a waste stream was 10 mg/L in treated waste water from a paint and ink formulation industry (EPA 1981). A survey of storm water runoff samples collected from 15 cities located across the United States revealed that chloroethane is not a typical contaminant of stormwater runoff (Cole et al. 1984).

5.4.3 Sediment and Soil

Chloroethane was found in sediment at 10 NPL sites and in soil at 42 NPL sites (HazDat 1998). In a survey of U.S. waste-water treatment plants receiving both municipal and industrial waste streams, chloroethane was found in undigested sewage sludge from 2 of 13 plants at concentrations ranging from 14.5 to 24 mg/kg dry weight. Assuming that the sludge was disposed of by land application, the application rate of chloroethane to soil was projected to be 0.16-0.17 kg/hectare (dry weight), and the resulting concentration of chloroethane in the top 15 cm of soil was predicted to be 0.08-0.085 mg/kg (Naylor and Loehr 1982).

5.4.4 Other Environmental Media

Few reports are available concerning the identification of chloroethane in other media. Traces of chloroethane were found in two of eight human milk samples taken from women in four urban areas of the United States (Pellizzari et al. 1982). Chloroethane at a mean concentration of 7.6 ng/g was found in oysters collected from Lake Pontchartrain, LA (Ferrario et al. 1985).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

According to a National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, an estimated 49,212 workers in the United States are potentially exposed to chloroethane (NIOSH 1991). This was a tentative estimate and extrapolating to the present, such estimates are subject to change depending upon whether further information on trade name compounds containing chloroethane becomes available. Workers may be exposed to chloroethane by inhalation and/or dermal exposure. Chloroethane exposure can occur in several occupational environments including: chemical manufacturing industries; medical and health facilities; automotive dealerships and service stations; wholesale trade, electric, gas and sanitary services; companies manufacturing or using machinery (except electrical); metal production facilities; printing and publishing companies; paint manufacturers and painting companies; companies manufacturing rubber and plastic products not elsewhere classified; and companies manufacturing food and kindred products (Fidler et al. 1987; Parker et al. 1979). Workers who may potentially be exposed include physicians, nurses, and other medical workers, automobile mechanics, office machine mechanics, household appliance and accessory installers, assemblers, professional painters, heavy-equipment mechanics (including diesel mechanics), and plumbers and pipe fitters (Fidler et al. 1987; Parker et al. 1979). Limited data indicate that the general population is exposed to very low (ppt) levels of chloroethane by inhalation of contaminated air and ingestion of contaminated drinking water. Apparently, people residing in urban/suburban areas are exposed to somewhat higher levels of chloroethane in air than people living in rural areas (Grimsrud and Rasmussen 1975; Shepson et al. 1987; Singh et al. 1983). Medical use of chloroethane as a topical anesthetic results in direct dermal exposure of the general population to this compound. The general population is also exposed to chloroethane by dermal contact with consumer products that contain this compound (i.e., various paints, solvents, refrigerants) (HSDB 1997).

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 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 humans 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 can be exposed inadvertently to chloroethane via household products such as paints, solvents, air fresheners, and refrigerants. However, children are unlikely to be exposed to a significant amount of chloroethane during normal use of these products by adults. Children can be exposed to chloroethane by intentionally sniffing household products containing the compound or sniffing packaged chloroethane that is sold specifically for misuse as an inhalant (Hersh 1991; Walker 1993).

Children can also be exposed to chloroethane via contaminated drinking water or foods. Chloroethane concentrations in drinking water are expected to be low. One study was identified that reported chloroethane in small amounts (7.6 ng/g) in oysters in Lake Pontchartrain, LA (Ferrario et al. 1985). Because children drink more fluids and eat more food per kilogram of body weight than adults, they are expected to be disproportionately affected by exposure to chloroethane. However, because of the low concentrations of chloroethane detected in food and water, dietary exposures are not expected to be significant in children.

Chloroethane has been detected in human breast milk (Pellizari et al. 1982). However, the concentrations of chloroethane were not determined, nor was the exposure dose. Therefore, it is not possible to determine how much of an absorbed chloroethane dose would be excreted in the milk and ingested by a nursing infant. In addition, the number of women with detectable levels of chloroethane in their milk was low; data do not exist that could indicate what percentage of an exposed female population could be expected to excrete chloroethane in their breast milk.

Parents' work clothes, skin, hair, tools, or other objects removed from the workplace are not likely to be a source of exposure to children. Chloroethane is a gas at room temperature and pressure; thus, it will not remain on parents' clothes, hair, skin or other items, even for those who work with liquid chloroethane. Therefore, secondary exposure to children is unlikely.

It is unknown whether children are different in their weight-adjusted intake of chloroethane.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Humans are typically exposed to very low levels of chloroethane. Nonetheless, potentially high levels could result from occupational exposure, exposure at or near hazardous waste sites, and frequent contact with consumer products that contain chloroethane (i.e., solvents, paints, refrigerants). Inhalation and dermal contact are expected to be the primary routes of exposure, although ingestion via indirect contact (e.g., eating foods that come in contact with contaminated surfaces or swallowing mucus that becomes contaminated as the result of breathing air containing chloroethane) is also possible.

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 chloroethane 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 chloroethane.

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 on the physical and chemical properties of chloroethane are available (Budavari 1989; HSDB 1997). A K_{oc} value provides a means for predicting whether a compound will partition significantly into suspended solids and sediments in water or adsorb strongly to soil. A K_{oc} for chloroethane was estimated using regression equations based on log K_{ow} and water solubility data (Lyman 1982). This estimation technique is believed to provide a reasonable approximation of K_{oc}. However, additional studies are needed in which the soil adsorption coefficient of chloroethane is measured in order to remove any doubt concerning the reliability of the K_{oc}.

Production, Import/Export, Use, Release, and Disposal. 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.

Data are adequate for the production and disposal of chloroethane (IARC 199 1; TR196 1998). Information on the pattern of use of chloroethane is not available after 1988. Information would have to be supplied by the chemical industry in order to establish the percentage breakdown of the current chloroethane uses. This type of information is needed to establish the sources of chloroethane release and the potential for general population and occupational exposure.

Environmental Fate. Conflicting data are available concerning the hydrolytic half-life of chloroethane in water (Jeffers and Wolf 1996; Laughton and Robertson 1959; Mabey and Mill 1978; Vogel and McCarty 1987). Experimental data obtained from a hydrolysis study carried out in distilled water under environmental conditions (at 25 °C and pH 5-9) are needed to predict the half-life of chloroethane (Haider 1980; Kobayashi and Rittmann 1982) in natural water and moist soil. Available data regarding biodegradation of chloroethane are insufficient for predicting the importance of biodegradation as a removal process for chloroethane. Natural water grab sample biodegradation studies and soil metabolism studies carried out under both aerobic and anaerobic conditions are needed to estimate the biodegradation half-life of chloroethane. Although volatilization from soil is expected to be an important fate process (Washington 1996), data pertaining to the rate of volatilization from soil surfaces were not located in the available literature. Studies involving the measurement of the volatilization rate of chloroethane from soil surfaces are needed to evaluate the persistence of this compound upon release to soil. The dominant removal mechanism for chloroethane in air is expected to be reaction with photochemically-generated hydroxyl radicals (Atkinson 1985; Howard and Evenson 1976). However, no data are available concerning the products of this reaction. These data are needed to understand the mechanism by which this compound degrades in the atmosphere.

Bioavailability from Environmental Media. Chloroethane is readily absorbed following inhalation exposure, the major route of exposure (Konietzto 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). Data regarding the bioavailability of chloroethane from different media for other routes of exposure were not identified. Studies examining the absorption of chloroethane from various media following oral and dermal exposure are needed to predict exposure to chloroethane at hazardous waste sites.

Food Chain Bioaccumuiation. Based on bioconcentration factors of 7 and 5 estimated from log K_{ow} and water solubility (Bysshe 1982; Hansch and Leo 1985; Horvath 1982), chloroethane is not expected to bioconcentrate significantly in aquatic organisms. Studies in which chloroethane is measured in biota and environmental media are needed to determine if the predictions are correct.

Exposure Levels in Environmental Media. Relatively large amounts of chloroethane are released to the environment on an annual basis (TR196 1998). However, limited data were available concerning the detection of chloroethane in the environment, particularly in ambient air (Shepson et al. 1987; Singh et al. 198 1), air in the vicinity of waste disposal sites (Vogt and Walsh 1985; Young and Parker 1984), drinking water, groundwater downgradient from waste disposal sites (HazDat 1998), and soil at waste disposal sites (HazDat 1998; Otson 1987). Reliable monitoring data for the levels of chloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chloroethane in the environment can be used in combination with the known body burdens of chloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Despite the fact that chloroethane is a fairly large volume commercial compound, limited data are available concerning occupational exposure. Tentative results of the National Occupational Exposure Survey are indicative of the number of workers potentially exposed to chloroethane in industry (NIOSH 1991). However, there are no quantitative data relating type of occupation to level and route of exposure. Available data indicate that the general population may be exposed to chloroethane by inhalation, ingestion of drinking water, and dermal contact (HSDB 1997). However, data were insufficient for estimating average daily intake by these routes. Up-to-date comprehensive monitoring data for air, water, and soil are needed to determine the typical amount of chloroethane to which the general population is exposed.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to chloroethane via many different exposure pathways. However, to date no studies have provided information on adverse effects observed in children as a result of exposure to a specific dose of the compound. Reliable exposure and body burden studies in children are needed to relieve this data gap. In addition, because many older children may be exposed to chloroethane through sniffing the compound directly, there is a need to explore the prevalence of this behavior, the frequency of the abuse, and resulting exposure doses.

It is currently unknown whether children differ from adults in their weight-adjusted intake of chloroethane. Therefore, studies investigating this issue are needed.

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

5.8.2 Ongoing Studies

Ongoing studies regarding the environmental fate of chloroethane were not identified in the CRISP (1996), PEDRIP (1998), or CRIS/USDA (1998) databases.

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 chloroethane, its metabolites, and other biomarkers of exposure and effect to chloroethane. 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

The analytical methods for the determination of chloroethane in biological matrices are given in Table 6-1. The purge and trap method used for environmental samples is also commonly used for biological samples. The discussion regarding the methods that may be most sensitive for determining chloroethane levels in environmental samples and the advantages and disadvantages of the commonly used methods as given in Section 6.2 are also applicable for biological samples.

6.2 ENVIRONMENTAL SAMPLES

Analytical methods for the determination of chloroethane in environmental samples are presented in Table 6-2. The two common methods used for preconcentrating chloroethane in air samples are adsorption on a sorbent column and collection in a cryogenically cooled trap. The disadvantages of cryogenic cooling are that the method is cumbersome and condensation of moisture in air may block the passage of further air through the trap. The disadvantages of the sorption tubes are that the sorption and desorption efficiencies may not be 100% and that the background impurities in the sorbent tubes may interfere with the detection of samples containing low concentrations of chloroethane (Cox 1983). The most common method for determining chloroethane levels in water, sediment, soil, and aqluatic species is purging chloroethane vapor from the sample or its solution in water using an inert gas and then trapping the desorbed vapors in a sorbent

TABLE 6-1. Analytical Methods for Determining Chloroethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air[a]	Exhaled air collected by valved Teflon spirometer mouthpieces into Tedlar bag, content adsorbed in Tenax, thermal desorption	Cryofocus-sing HRGC-FID/MS	No data	No data	Pellizzari et al. 1987
Human milk	Purged at 70°C and trapped in Tenax, thermal desorption	Cryofocus-sing HRGC-FID/MS	No data	No data	Michael et al. 1980; Pellizzari et al. 1982
Blood and urine	Mixed with water and antifoaming agent, purged at 50°C, trapped in Tenax, thermal desorption	Cryofocus-sing HRGC-FID/MS	3 µg/L (blood); 3 µg/L (urine)	>80%	Michael et al. 1980[b]; Pellizzari et al. 1979[b]
Urine	Add NaH_2PO_4 to dried sample and add acylase solution. Incubate, deproteinize. Separate by cation exchange.	HPLC 340 nm	7 µg/L	94.2	Eškinja et al. 1997
Adipose tissue	Tissue homogenized, purged at 50°C, trapped in Tenax, thermal desorption	Cryofocus-sing HRGC-FID/MS	No data	No data	Michael et al. 1980; Pellizzari et al. 1979

[a]The method was not used for the quantification of chloroethane, but other halogenated hydrocarbons were quantified.

[b]The methods in these studies were not used for the quantification of chloroethane, but structurally-similar chlorinated organics were analyzed. Although not previously tested, these methods should work for chloroethane. Detection limits and recovery percentages are provided for purposes of comparison only.

FID = flame ionization detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; HPLC = high performance liquid chromatography

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

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Ambient air	Collected in electropolished stainless steel canister and preconcentrated in a liquid oxygen-cooled trap	GC-EC	$<5.0\times10^{-6}$ ppm	No data	Singh et al. 1983
	Direct injection	Subambient GC-MS	$<5.0\times10^{-6}$ ppm	No data	Grimsrud and Rasmussen 1975
	Collected in cryogenically cooled trap, vaporized and adsorbed onto Tenax, thermal desorption	GC-MS	$>1.4\times10^{-5}$ ppm[a]	100% (assumed by study author)	Shepson et al. 1987
	Collect air in sorbent trap. Heat trap, desorb gas and vapor. Purge with helium.	GC-MS (ion trap)	810 ppm	---	Oliver et al. 1996
Air	Adsorbed on charcoal tubes, desorbed by carbon disulfide	GC-FID (NIOSH Method 2519)	0.01 mg per sample	≈101% at 485–1940 ppm (1300–5200 mg/m^3)	NIOSH 1994a NIOSH 1994a
Air from contaminated site	Adsorbed on Tenax, thermal desorption	Cryofocussing HRGC-MS	No data	No data	Hauser and Bromberg 1982
Air from landfill	Adsorbed on Tenax-silica gel, thermal desorption	Cryofocussing HRGC-MS	10^5 ppm	No data	Vogt and Walsh 1985
Raw/treated water	Purge and trap, and thermal desorption	GC-MS	<1 µg/L	90%	Otson 1987

TABLE 6-2. Analytical Methods for Determining Chloroethane in Environmental Samples (*continued*)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Finished drinking/raw source water	Purge at ambient temperature, trap in Tenax/silica gel/charcoal and thermal desorption	GC-HECD (EPA Method 502.1)	0.008 µg/L	93% at 0.4 µg/L	EPA 1986b
Finished drinking/raw source water	Purge at ambient temperature, trap in Tenax/silica gel/charcoal and thermal desorption	Subambient GC-MS (EPA Method 524.1)	No data	No data	EPA 1986b EPA 1986b
Water	Purge at ambient temperature, trap in Tenax/silica gel/charcoal, thermal desorption	Cryofocussing HRGC-MS (EPA Method 524.2)	0.10 µg/L (wide-bore column); 0.02 µg/L (narrow bore column)	89% (wide bore) at 0.5–10 µg/L; 100% (narrow bore) at 0.1 µg/L	EPA 1986b
	Purge at ambient temperature, whole column cryotrapping	HRGC (wide bore capillary) - MS	No data	No data	Pankow and Rosen 1988
	Purge at 35°C, trap in Tenax/ Ambersorb 340/silica/charcoal, thermal desorption	Cryofocussing HRGC-MS	0.4 µg/L	42% at 32.9 µg/L	Otson and Chan 1987
Water/waste water	Purge at ambient temperature, trap in Tenax/silica gel/charcoal, thermal desorption	GC-HECD (EPA Method 601)	0.52 µg/L	91.5%	EPA 1988a
Waste water	Purge at ambient	GS-MS (EPA	No data	97–103%	EPA 1988b

TABLE 6-2. Analytical Methods for Determining Chloroethane in Environmental Samples (*continued*)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
	temperature, trap in Tenax/silica gel, thermal desorption	Method 624)			
Groundwater	Purge at ambient temperature, trap in Tenax/silica gel, thermal desorption	GC-MS	10 µg/L	No data	EPA 1986b
Water/fish	Dry purge and trap (water); sonicated slurry subjected to dry purge and trap (fish)	Cryofocussing HRGC-HECD/PID in series	No data	No data	Driscoll et al. 1987
Fish	Homogenized in blender, mix in water, purge at 80°C, trap in Tenax, thermal desorption	GC-MS	<0.3 µg/kg (wet weight)	60–90%	Young et al. 1983
Fish	Vacuum distillation	Cryofocussing HRGC-MS	No data	No data	Hiatt 1983
Marine biota/ sediment	Homogenize biota ultra-sonically, mix with water, purge at 70°C, trap in Tenax/silica gel, thermal desorption	Subambient focussing HRGC-MS	No data	No data	Ferrario et al. 1985
Soil and sediment	Purge suspension in water at 50°C, trap in Tenax/silica, thermal desorption	GC-MS	10 µg/kg	No data	EPA 1986b

TABLE 6-2. Analytical Methods for Determining Chloroethane in Environmental Samples (*continued*)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Liquid and liquid waste	Disperse sample in glycol, purge at ambient temperature, trap in Tenax/silica gel/charcoal, thermal desorption	GC-HECD (EPA Methods 5030 and 8010)	0.008 µg/L (method detection limit)	No data	EPA 1994
Solid and liquid waste	Disperse sample in glycol, purge at ambient temperature, trap in Tenax/silica gel/charcoal, thermal desorption	GC-HECD/PID in series	1000–5000 µg/kg (soil)	No data	Lopez-Avila et al. 1987

[a]Estimated value from the impurity in blank tube, a sampling volume of 50 L and the detection limit being twice the blank level.

EC = electron capture detector; EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; HECD = Hall electrolyte conductivity detector; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; PID = photoionization detector; GC/MS = gas chromatography/mass spectrometry

trap. Subsequent thermal desorption is used for the quantification of its concentration. The two analytical instruments that provide the lowest detection limits are the halide-specific detectors (e.g., Hall electrolytic conductivity detector) and the mass spectrometer (see Table 6-2). The advantages of halide-specific detectors are that they are not only very sensitive, but they are also specific for halide compounds. The mass spectrometer, however, provides an additional confirmation of the presence of a compound through the ionization patterns and is desirable when a variety of compounds are to be quantified. High-resolution gas chromatography with capillary columns is a better method for volatile compounds than chromatography with packed columns because capillary columns provide better resolution of closely eluting compounds and increase the sensitivity of detection. In addition, purge and whole column cryotrapping eliminates the need for the conventional purge and trap unit and reduces the time of analysis (Pankow and Rosen 1988). The plugging of the trap by the condensation of moisture during cryotrapping may be avoided by using a wide bore capillary column, although the chromatographic resolution of such a column is inferior to narrow bore capillary columns (Mosesman et al. 1987; Pankow and Rosen 1988).

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 chloroethane 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 chloroethane.

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 Parent Compounds and Metabolites in Biological Materials. There is a relative paucity of data on the analytical methods for the determination of chloroethane levels, as well as levels of its metabolites, in biological matrices. Most of the limited number of publications that discuss the methods for the determination of organic volatiles in biological matrices (Michael et al. 1989; Pellizzari et al. 1979) are not specific for chloroethane. These studies analyze other structurally-similar chlorinated hydrocarbons and discuss the applicability of the techniques for measuring other hydrocarbons. Therefore, it is believed that these techniques would be useful for the detection of chloroethane in certain biological matrices. However, recovery data and detection limits have not been conclusively determined for chloroethane at this time. Further studies to develop analytical methodologies for the determination of chloroethane in biological matrices are needed.

One study was identified which described the assay of a chloroethane metabolite in human urine (ESkinja et al. 1997). This study measured the concentration of ethylmercapturic acid (EMA), a metabolite of glutathione conjugation of chloroethane, in urine from subjects presumably exposed to chloroethane. Themethod is fairly sensitive, with detection limits in the ppb range.

Methods for Determining Biomarkers of Exposure and Effect. No known biomarker for this chemical in human tissue or body fluids has been identified. Ethylmercapturic acid, a metabolite of glutathione conjugation of chloroethane, can be detected in human urine. However, this metabolite can be formed by glutathione conjugation to other structurally-similar compounds and is not specific to chloroethane exposure. The potential usefulness of this compound as an indicator of exposure needs to be investigated further. Additional studies to identify specific biomarkers and to develop analytical monitoring methodologies for the determination of chloroethane exposure are needed. One breath absorption study using inhaled radiolabeled chloroethane quantitatively measured absorption of the compound (Morgan et al. 1970). However, the analytical technique used is not applicable for widespread use because it involved quantitative analysis of the radiolabel, not the compound itself.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods with adequate sensitivity and specificity are available for the quantification of chloroethane in environmental samples (Driscoll et al. 1987; EPA 1982a, 1986b; Ferrario et al. 1985; Hiatt 1983; Lopez-Avila et al. 1987; Otson and Ghan 1987; Shepson et al. 1987; Vogt and Walsh 1985). The degradation products of chloroethane are ethanol and chloride salts (the hydrochloric acid initially formed dissociates to form chloride salts at the neutral pH values in most environmental media). Analysis for these compounds in environmental media would provide little or no information about chloroethane.

6.3.2 Ongoing Studies

No significant ongoing studies are in progress for the development of analytical methodologies for chloroethane and its metabolites in biological media or for chloroethane and its degradation products in environmental media.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chloroethane in air and water are summarized in Table 7-l.

IARC considers chloroethane to be a Group 3 carcinogen, not classifiable (IARC 1991). A carcinogenic assessment of chloroethane has not been completed by the EPA (IRIS 1997). ACGIH considers chloroethane to be an animal carcinogen of unknown relevance to humans (ACGIH 1998).

Toxicity data for chloroethane are limited to inhalation data. Therefore, estimates of safe exposure concentrations are only available for air. The QSHA permissible exposure limit (PEL) for chloroethane is 1,000 ppm (OSHA 1998). ACGIH recommends an occupational exposure threshold limit value timeweighted average (TLV-TWA) of 100 ppm (skin) (ACGIH 1998).

ATSDR has derived an acute-duration inhalation MRL of 15 ppm with an uncertainty factor of 100, based on a NOAEL of 1,504 ppm for fetotoxicity in mice that was observed at 4,946 ppm (Scortichini et al. 1986). The EPA reference concentration (RfC) of 10 mg/m^3 (4 ppm) is based on the same study. EPA used uncertainty factors of 10 to account for sensitive populations, 3 for interspecies extrapolation with dosimetric adjustment of the inhaled concentration, and 10 for database deficiencies (the lack of a multigeneration study).

TABLE 7-1. Regulations and Guidelines Applicable to Chloroethane

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1991
NATIONAL			
Regulations:			
a. Air:			
OSHA	Permissible Exposure Limit–Time Weighted Average	1,000 ppm (2,600 mg/m^3)	OSHA 1998 (29 CFR 1910.1000)
b. Other:			
EPA	Reportable Quantity	45.4 kg (100 pounds)	EPA 1998b (40 CFR 302.4)
	Required Reporting Under Title III SARA	Yes	EPA 1998c (40 CFR) 372)
	Designated as a hazardous substance	No	EPA 1998a (40 CFR 116.4)
Guidelines:			
a. Air:			
ACGIH	TLV-TWA	100 ppm (skin) (264 mg/m^3)	ACGIH 1998
	Carcinogenic Classification	Group A3[b]	ACGIH 1998
EPA	RfC (inhalation)	10 mg/m^3 (4 ppm)	IRIS 1997
b. Water:			
EPA	MCLG	None listed	EPA 1998f
	MCL	None listed	EPA 1998f
	Health Advisories:		EPA 1998f
	1-day (child)	None listed	
	10-day (child)	None listed	
	Longer Term (child and adult)	None listed	
	Lifetime	None listed	
	DWEL	None listed	EPA 1998f
b. Other:			
ACGIH	Biological Exposure Index	None listed	ACGIH 1998
EPA	RfD (oral)	None listed	EPA 1998f

TABLE 7-1. Regulations and Guidelines Applicable to Chloroethane (*continued*)

Agency	Description	Information	References
STATE			
Regulations:			
a. Air:			
	Acceptable Ambient Air Concentrations		
Connecticut	(30 minute)	2.60×10^5 µg/m^3	CT DEP 1998
	(8 hour)	5.20×10^4 µg/m^3	
Florida	(8 hour)	5.20×10^4 µg/m^3	NATICH 1994
	(24 hour)	1.25×10^4 µg/m^3	
Idaho	(24-hour)	1.32×10^5 µg/m^3	ID DHW 1998
Louisiana	(8 hour)	6.29×10^4 µg/m^3	NATICH 1994
Massachusetts	(24 hour)	7.18×10^2 µg/m^3	NATICH 1994
	(1 year)	3.59×10^2 µg/m^3	
North Dakota	(8 hour)	2.64×10^4 µg/m^3	NATICH 1994
Nevada	(8 hour)	6.40×10^4 µg/m^3	NATICH 1994
New Hampshire	(24 hour)	1.00×10^4 µg/m^3	NH SDES 1998
	(1 year)	1.00×10^4 µg/m^3	
New York	(1 year)	5.20×10^4 µg/m^3	NATICH 1994
Oklahoma	(24 hour)	2.60×10^5 µg/m^3	NATICH 1994
South Carolina	(24-hour)	2.64×10^4 µg/m^3	SC DHEC 1998
Texas	(30 minute)	5.00×10^2 µg/m^3	NATICH 1994
	(20 minute)	2.60×10^4 µg/m^3	
	(1 year)	5.00×10^1 µg/m^3	
	(1 year)	2.60×10^3 µg/m^3	
Virginia	(24 hour)	4.40×10^4 µg/m^3	NATICH 1994
Washington	(24 hour)	1.00×10^4 µg/m^3	WA DE 1998
Wisconsin	(1 year)	1.00×10^4 µg/m^3	NATICH 1994

[a]IARC Group 3: not classifiable
[b]ACGIH Group A3: animal carcinogen of unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NATICH = OSHA = Occupational Safety and Health Administration; RfC = reference concentration; RfD = Reference Dose; SARA = Superfund Amendments and Reauthorization Act; TLV-TWA = Threshold Limit Value–Time-Weighted Average

8. REFERENCES

ACGIH. 1991. Documentation of the threshold limit values and biological exposure indices. 6th edition.

American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1998. TLVs and BEIs: Threshold limit values for chemical substances and physical agents-Biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH. 37.

*Adinolfi M. 1985. The development of the human blood-csf-brain barrier. Dev Med Child Neurol 27:532-537.

*Adriani J. 1941. The pharmacology of anesthetic drugs. Springfield, IL: Thomas, 33-34.

*Adriani J. 1986. Selection of anesthesia. Int Anesthesiol Clin 6:96 I - 1040.

*Ahlert RC, Enzminger JD. 1992. Anaerobic processes for the dechlorination of 1, I, 1 -trichloroethane. J Environ Sci Health A27: 1675- 1699.

*Altman PK, Dittmer DS. 1974. Biological handbooks: Biology data book. Volume III, 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008,204l.

*Amdur MO, Doull J, Klaassen CD, eds. 199 1. Casarett and Doull's toxicology: The basic science of poisons. 4th ed. New York, NY: Pergamon Press, 108.

*Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxico1 3:272-290.

*Andersen ME, Krishnan K. 1994. Relating in vitro to *in vivo* exposures with physiologically-based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives. Aberdeen Proving Ground, Maryland: U.S. Army Chemical Research Development and Engineering Center.

*Andersen ME, Clewell HJ,III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87: 185-205.

*Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 85:69-201.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, GA.

*ATSDR. 199 1. Health assessment for Beacon Heights Landfill Site, Beacon Falls, Connecticut, Region 1. Cerclis No. CTD072122062. Addendum. Agency for Toxic Substances and Disease Registry.PB91205666.

---

*Cited in text

8. REFERENCES

*ATSDIUCDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

*Baek NH, Jaffe PR, Shingal N. 1990. Simulating the degradation of TCE under methanogenesis. J Environ Sci Health A25:987-1005.

*Balasubramanian D, Wetlaufer DB. 1966. Reversible alteration of the structure of globular proteins by anesthetic agents. Proc Nat1 Acad Sci USA 55:762-765.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. U.S. Environmental Protection Agency. Regul Toxicol Pharmacol8:47 l-486.

*Barrio-Lage G, Parsons FZ, Nassar RS, et al. 1986. Sequential dehalogenation of chlorinated ethenes. Environ Sci Technol 20:96-99.

*Benowitz NL. 1992. Hazardous materials toxicity: Clinical principles of environmental health. In: Sullivan JB, Krieger GR, eds. Cardiac toxicity. Baltimore, MD: Williams & Wilkins, 168178.

*Bircher AJ, Hampl K, Hirsbrunner P, et al. 1994. Allergic contact dermatitis from ethyl chloride and sensitization to dichlorodifluoromethane. Contact Dermatitis 31:41-44.

*Bos SD, Buys GA. 1994. Treatment of priapism with ethyl chloride spray after failed intracavernous injection with adrenaline. Br J Urol 74:677-678.

*Bourne TM, deMelo AE, Bastianpillai BA, et al. 1997. A survey of how British obstetric anaesthetists test regional anaesthesia before Caesarean section. Anaesthesia 52:896-913.

*Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, 143- 144.

*Brown BR Jr. 1972. Office management of common musculoskeletal pain syndromes. Am Fam Physician 6:92-98.

*Bucher JR Morgan DL, Adkins B Jr, et al. 1995. Early changes in sex hormones are not evident in mice exposed to ;he uterine carcinogens chloroethane or bromoethane. Toxicol Appl Pharmacol 130: 169-l 73.

*Budavari S, O'Neil MJ, Smith A, et al., eds. 1989. The Merck Index: An encyclopedia of chemicals, drugs, and biologicals. Eleventh edition. Rahway, NJ: Merck & Co., Inc., 597.

*Bush OF, Bittenbender G, Adriani J. 1952. Electrocardiographic changes during ethyl chloride and vinyl ether anesthesia in the dog and man. Anesthesiology 13: 197-202.

*Bysshe SE. 1982. Bioconcentration factors in aquatic organisms. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York: McGraw-Hill Book Co., Chapter 5.

*Callahan MA, Slimak MW, Gavel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. II. EPA-440/4-79-029B. U.S. EPA Office of Water Planning and Standards, Washington, DC, 42-l to 42-49.

8. REFERENCES

*Cavadas PC. 1996. *In* viva vascular freezing in clinical microvascular transfer. Microsurgery 17: 121-2.

*Chang HL, Alvarez-Cohen L. 1996. Biodegradation of individual and multiple chlorinated aliphatic hydrocarbons by methane-oxidizing cultures. Appl Environ Microbial 62:337 1-3377.

C&EN. 1988. Production by the U.S. chemical industry. Chemical and Engineering News, June 20, 1988, 40.

*Clewell HJ, III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxico1 IndHealth 1:111-113.

*Cline PV, Viste DR. 1985. Migration and degradation patterns of volatile organic compounds. Waste Management Research 3:35 I-360.

*CMR. 1982. Chemical profile: Ethyl chloride. Chemical Marketing Reporter. August 2, 1982.

*Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. J Water Pollut Control Fed 56:898-908.
*Cole WH. 1956. Ethyl chloride as a gaseous anesthetic. Anesthesia 11:156-l 59.

*Cole WH. 1967. A re-evaluation of the pharmacology of ethyl chloride. Med J Aust 1:853-855.

*Cox RD. 1983. Sample collection and analytical techniques for volatile organics in air. Special Conference on Measurement and Monitoring of Non-Criteria (Toxic) Contamination in Air, Knickerbocker Hotel, Chicago, IL, March 22-24, 1983. Chicago, IL: Air Pollution Conrol Association, 10l- 112.

*CRIS/USDA. 1998. Current Research Information System/United States Department of Agriculture. Beltsville, MD. May 13, 1998.

*CRISP. 1996. Computer Retrieval of Information on Science Projects. National Library of Medicine, National Institutes of Health, Bethesda, MD.

*CT DEP. 1998. Hazardous limiting values for hazardous air pollutants, Connecticut Department of Environmental Protection, Bureau of Air Management. 22a-174-29.

*Daubert TE, Danner RP. 1985. Data compilation tables of properties of pure compounds. Design Institute for Physical Property Data. American Institute of Chemical Engineers, New York, NY.

*Davidson BM. 1925. Studies of intoxication: V. The action of ethyl chloride. J Pharmacol Exp Ther 26137-42.

*Dawkins CJM. 1964. Safety of vinyl ether. Br Med J 2:538.

*DHHS. 1994. Seventh annual report on carcinogens: Summary 1994. U.S. Department of Health and Human Services, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

8. REFERENCES

*Dobkin AB, Byles PH. 197 1. The pharmacodynamics of divinyl ether, ethylchloride, fluroxene, nitrous oxide and trichloroethylene. In: Soma LR ed. Textbook of veterinary anesthesia. Baltimore, MD: Williams & Wilkins, 94-104.

*Doring HJ. 1975. Reversible and irreversible forms of contractile failure caused by disturbances by general anesthetics in myocardia.! ATP utilization. Recent Adv Stud Cardiac Struct Metab 5:395-403.

*Driscoll JN, Duffy M, Pappas S, et al. 1987. Analysis of purgeable organics in water by capillary GC/PIDEICD. J Chromatogr Sci 25:369-375.

*Ebert R, Fedtke N, Certa H, et al. 1994. Genotoxicity studies with chloroethane.Mutat Res 322:33-44

*Ehrmann, EH. 1977. Pulp testers and pulp testing with particular reference to the use of dry ice. Aust Dent J 22:272-279.

*EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Interim report to Congress, June, 1975. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC., 9.

EPA. 1979. Chloroethane. In: Water-related environmental fate of 129 priority pollutants. Volume II: Halogenated aliphatic hydrocarbons, halogenated ethers, monocyclic aromatics, phthalate esters, polycyclic aromatic hydrocarbons, nitrosamines, and miscellaneous compounds. U.S. Environmental Protection Agency, Office of Water Planning and Standards, Washington, DC. EPA-440/4-79-029B.

*EPA. 1981. Treatability manual. Vol. 1. Treatability Data Revised Sept. 198 1. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC. 600/2-82-OOla. 1.12.5-l to 1.12.5-4.

*EPA. 1982a. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Purgeable halocarbon method 601 and EPA No. 60014-82-057. U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory, Cincinnati, OH. 601-2 to 601 - 10; 624-l to 624- 12.

*EPA. 1982b. Test methods for evaluating solid waste. Physical/chemical methods (SW-846). 2nd ed. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. l-l 4.

*EPA. 1985. Regulations of fuel and fuel additives, gasoline lead content. U.S. Environmental Protection Agency. Federal Register 50:9386-9399.

*EPA. 1986a. Superfund record of decisions (EPA Region 3): Tybouts Corner Landfill, New Castle County, Delaware, March 1986. Report. US. Environmental Protection Agency, Washington, DC. EPA/ROD/R03-86-019.

*EPA 1986b. Methods for the determination of organic compounds in finished drinking water and raw source water. Method Nos 502.1, 524.1 and 524.2. U.S. Environmental Protection Agency, Physical and Chemical Methods Branch, Environ Monitoring and Support Lab, Cincinnati, OH.

*EPA. 1986c. Test methods for evaluating solid waste. Vol. 1B. Laboratory manual: Physical/chemical methods. 3rd ed., SW-846. Method No. 8010. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. 8010-1 to 8010-13.

8. REFERENCES

*EPA. 1987. Superfund record of decision (EPA Region 3): Blosenski Landfill, West Cain Township, Chester County, Pennsylvania, September 1986. Report. U.S. Environmental Protection Agency, Washington, DC. EPA/RODIR03-86/029. l-34.

*EPA. 1988a. Analysis of Clean Water Act effluent guidelines pollutants. Summary of the chemicals regulated by industrial point source category. 40 CFR Parts 400-475. Draft. Prepared by the Industrial Technology Division (WH 552), Office of Water Regulations and Standards, Office of Water, U.S. Environmental Protection Agency, Washington, DC.

EPA. 1988b. Summary of emissions associated with sources of ethyl chloride. U.S. Environmental Protection Agency, Chemical and Petroleum Branch, Emissions Standards Div., Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA 450/3-88-005.

*EPA. 1990. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA-600/8-90/066A.

*EPA. 1998a. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4.

*EPA. 1998b. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.4.

*EPA. 1998c. Toxic chemical release reportin g: Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372.

*EPA. 1998d. Methods for organic chemical analysis of municipal and industrial wastewater, method 601. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 136 Appendix A.

*EPA. 1998e. Methods for organic chemical analysis of municipal and industrial wastewater, method 624 U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 136 Appendix A.

*EPA. 1998f. Drinking water regulations and health advisories. U.S. Environmental Protection Agency, Office of Water, Washington, DC.

*Eškinja M, Lamprecht G, Scherer G, et al. 1997. Assay of S-ethyl-N-acetyl-1-cysteine in urine by high-performance liquid chromatography using post-column reaction detection. J Chromatogr B 704: 159- 165.

*FEDRIP. 1998. Federal Research in Progress. National Technical Information Service, Springfield, VA. May 13, 1998.

*Fedtke N, Certa H, Ebert R, et al. 1994a. Species differences in the biotransformation of ethyl chloride: I.Cytochrome P450-dependent metabolism. Arch Toxicol 68: 158-l 66.

*Fedtke N, Certa H, Ebert R, et al. 1994b. Species differences in the biotransformation of ethyl chloride: II. GSH-dependent metabolism. Arch Toxicol 68:217-223.

*Ferrario JB, Lawler GC, Deleon IR, et al. 1985. Volatile organic pollutants in biota and sediments of Lake Pontchartrain. Bull Environ Contam Toxicol 34:246-255.

8. REFERENCES

*Fidler AT, Baker EL, Letz RE. 1987. Estimation of long term exposure to mixed solvents from questionnaire data: A tool for epidemiological investigations. Br J Ind Med 44: 133- 14 1.

*Finer B. 1966. Divinyl ether and ethyl chloride for outpatients. Acta Anaesthesiol Scand 25:410-412.

*Fiserova-Bergerova V, Pierce JT, Droz PO. 1990. Dermal absorption potential of industrial chemicals: Criteria for skin notation. Am J Ind Med 17:6 17-635.

*Fisher EM, Koshland CP. 1990. Numerical simulation of the thermal destruction of some chlorinated C_1 and C_2 hydrocarbons. J Air Waste Manage Assoc 40: 1384-l 390.

*Foman SJ. 1966. Body composition of the infant. Part I: The male reference infant. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fornan SJ, Haschke F, Ziegler EE, Nelson SE. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-l 175.

*Gargas ML, Burgess RJ, Voisard DE, et al. 1989. Partition coefficients of low-molecular weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98:87-99.

*Gargas ML, Clewell HJ III, Andersen ME. II 990. Gas uptake inhalation techniques and the rates of metabolism of chloromethanes, chloroethanes, and chloroethylenes in the rat. Inhal Toxicol 2:295-319.

*Gohlke R, Schmidt P. 1972. [Subacute action of low concentrations of chlorinated ethanes on rats with and without additional ethanol-treatment. II. Histological, histochemical and morphometrical studies.] Int Arch Arbeitsmed 30:298-3 12. (German)

*Goodman ES, Gilman A. 1993. The pharmacological basis of therapeutics. 8th ed. New York, NY: McGraw-Hill, Inc., Health Professions Division, 28 1.

*Gossett JM. 1987. Measurement of Henry's Law constants for C, and Cz chlorinated hydrocarbons. Environ Sci Technol21:202-208.

*Gould JP, Ramsey RE, Giabbai M, et al. 1983. Formation of volatile haloorganic compounds in the chlorination of municipal landfill leachates. Water Chlorin Environ Impact Health Eff 4:525-539.

*Graedel TE, Hawkins DT, Claxton LD. 1986. Atmospheric chemical compounds sources, occurrence and bioassay. New York: Academic Press, 461.

*Grimsrud EP, Rasmussen RA. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos Environ 9:1014- 1017.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose, 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1174-l 177.

8. REFERENCES

*Haid B, White JM, Morris LE. 1954. Observations of cardiac rhythm during ethyl chloride anesthesia in the dog. Curr Res Anesth Analg 33:3 1 S-325.

*Haider K. 1980. Degradation of chlorinated aliphatic and aromatic compounds by aerobic and anaerobic soil microorganisms. In: Comm Eur Communities (REP) Eur 1980 Eur 6388, Environmental Research Programme, 200-204.

*Hansch C, Leo AJ. 1985. Medchem Project Issue No. 26. Claremont, CA: Pomona College.

*Hauser TR, Bromberg SM. 1982. EPA monitoring program at Love Canal 1980. Environ Monit Assess 2:249-271.

*HazDat. 1996. Hazardous substances database. Agency for Toxic Substance and Disease Registry (ATSDR), Atlanta, GA.

*HazDat. 1998. Hazardous substances database. Agency for Toxic Substance and Disease Registry (ATSDR), Atlanta, GA.

*Hersh R. 199 1. Abuse of ethyl chloride [letter]. Am J Psychiatry 148:270-27 1.

*Hes JP, Cohn DF, Streifler M. 1979. Ethyl chloride sniffing and cerebellar dysfunction (case report). Isr Ann Psychiatr Relat Discip 17: 122- 125.

*Hiatt MH. 1983. Determination of volatile organic compounds in fish samples by vacuum distillation and fused silica capillary gas chromatography/mass spectrometry. Anal Chem 55:506-5 16.

*Hollinger C, Schraa G, Stupperich E, et al. 1992. Evidence for the involvement of corrinoids and factor F_{430} in the reductive dechlorination of 1,2-dichloroethane by *Methanosarcina barkeri*. J Bacterial 174:4427- 4434.

*Horvath AL. 1982. Halogenated hydrocarbons solubility-miscibility with water. New York: Marcel Dekker, Inc., 494-495.

*Howard CJ, Evenson KM. 1976. Rate constants for the reactions of OH with ethane and some halogen substituted ethanes at 296K. J Chem Phys 64:4303-4306.

*HSDB. 1997. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. May 11, 1998.

*Hubrich C, Stuhl F. 1980. The ultraviolet absorption of some halogenated methanes and ethanes of atmospheric interest. J Photochem 12:93-107.

*IARC. 1991. IARC monographs volume 52. Lyons, France: World Health Organization, International Agency for Research on Cancer. 3 15-335.

*ID DHW. 1998. Pollution control rules for control of air pollution in Idaho. Idaho Department of Health and Welfare, Division of Environmental Quality. Title 01, Chapter 01.585.

8. REFERENCES

*IRIS. 1997. Integrated Risk Information System. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. May 11, 1998.

*Jaffe HH, Orchin M. 1962. Theory and application of ultraviolet spectroscopy, New York: John Wiley and Sons, Inc., 173-l 74.

*Jeffers PM, Wolfe NL. 1996. Homogeneous hydrolysis rate constants-Part II: Additions, corrections, and halogen effects. Environ Toxicol Chem 15: 1066- 1070.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. Brain Res 190:3- 16.

*Kenig EE. 1956. [Changes in the peripheral nervous system through the effects of ethyl chloride.] [Abstract]. Biological Abstracts 35: 188 Il. (German)

*Kobayashi H, Rittmann BE. 1982. Microbial removal of hazardous organic compounds. Environ Sd Technol 16: 170a- 183a.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

*Konietzko H. 1984. Chlorinated ethanes: Sources, distribution, environmental impact and health effects. Hazard Assessment of Chemicals 3:401-448.

*Kriechbaumer N, Hemmer W, Focke M, et al. 1998. Sensitization to ethyl chloride in a handball player. Contact Dermatitis 38:227-228.

*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes W, ed. Principles and methods of toxicology. 3rd edition, New York, NY: Raven Press, Ltd.

*Krishnan K, Andersen ME, Clewell HJ, III, et al. 1994. Physiologically-based pharmacokinetic modeling of chemical mixtures. In: Yang RSA, ed. Toxicology of chemical mixtures, New York, NY: Academic Press.

*Kuschinsky G. 1970. [Death caused by general anesthesia with ethyl chloride.] Dtsch Med Wochenschr 95:2499. (German)

*Lamartiniere CA. 198 I. The hypothalamic-hypophyseal-gonadal regulation of hepatic glutathione Stransferases in the rat. Biochem J 198:21 l-217.

*Lamartiniere CA, Lucier GW. 1983. Endocrine regulation of xenobiotic conjugation enzymes. Basic Life Sci 24:295-3 12.

*Landry TD, Ayres JA, Johnson KA, et al. 1982. Ethyl chloride: A two-week inhalation toxicity study and effects on liver non-prc?in sulfhydryl concentrations. Fundam Appl Toxicol 2:230-234.

*Landry TD, Johnson KA, Momany-Pfruender JJ, et al. 1987. Ethyl chloride: 11 -day continuous exposure inhalation toxicity study in B6C3Fl mice. The Dow Chemical Company, Midland, MI. NTIS no.OTS05 17040. Doc # 86-870002250.

8. REFERENCES

*Landry TD, Johnson KA, Phillips JE, et al. 1989. Ethyl chloride (EtCl): 1 l-day continuous exposure inhalation toxicity study in B6C3Fl mice. Fundam Appl Toxicol 135 16-522.

*Langmoen IA, Larsen M, Berg-Johnsen J. 1995. Volatile anaesthetics: Cellular mechanisms of action. Eur J Anaesthesiol 125 l-59.

*Laughton PM, Robertson RE. 1959. Solvolysis in hydrogen and deuterium oxide. Can J Chem 37:1491-1497.

*Lawson JIM. 1965. Ethyl chloride. Brit J Anaesth 37:667-670.

*Lazarew NW. 1929. [Concerning the strength of the narcotic effects of the vapors of the chlorine derivatives of the methanes, ethanes and ethylenes.] Arch Exp Path01 Pharmakol 141: 19-24. (German)

*Leeder JS, Kearns, GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Ped Clin North America 44:55-77.

*Lehmann KB, Flury F. 1943. Toxicology and hygiene of industrial solvents. Baltimore, MD: William and Wilkins Co. 154- 157.

*Leung H. 1993. Physiologically-based pharmacokinetic modeling. In: Ballantyne B, Marrs T, Turner P,eds. General and applied toxicology. Vol. I. New York, NY: Stockton Press, 153-I 64.

*Lide DR, Frederikse HPR, eds. 1993. CRC handbook of chemistry and physics. 74th ed. Boca Raton, FL:CRC Press.

*Liepins R, Mixon F, Hudak C, et al. 1977. Industrial process profiles for environmental use: Chapter 6. The industrial organic chemical industry. U.S. EPA, Research Triangle Park, NC. EPA 600/2-77-023f. NTIS PB28 1478. 6-303 to 6-308.

*Lopez-Avila V, Heath N, Hu A. 1987. Determination of purgeable halocarbons and aromatics by photoionization and Hall electrolytic conductivity detectors connected in series. J Chromatogr Sci 25:356-363.

*Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York: McGraw-Hill Book Co., 4-l to 5-29.

*Mabey W, Mill T. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J Phys Chem Ref Data 7:383-415.

*Mabey WR, Smith JH, Pod011 RT, et al. 198 1. Aquatic fate process data for organic priority pollutants. U.S. Environmental Protection Agency, Office of Water Regulations and Standards, Washington, DC. EPA-440/4-81-014. 14 l-142.

*Marbach JJ. 1996. Temporomandibular pain and dysfunction syndrome: History, physical examination, and treatment. Rheum Dis Clin North Am 22:477-98.

8. REFERENCES

*McLean S, Robinson J, Starmer GA, et al. 1967. The influence of anaesthetic agents on the formation of methaemoglobin induced by aniline in cats. J Pharm Pharmac 19:803-809.

*Michael LC, Erickson MD, Parks SP, et al. 1980. Volatile environmental pollutants in biological matrices with a headspace purge technique. Anal Chem 52: 1836- 1841.

*Millnan AH, Story DL, Riccio ES, et al. 1988. Rat liver foci and *in vitro* assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann NY Acad Sci 53452 l-530.

*Mitre Corp. 1987. National Priority List Technical Data Base (& Base III Version). April, 1987. McLean, VA: Mitre Corp., Table 4.

*Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13:219-233.

*Morris LE, Noltensmeyer MH, White JM. 1953. Epinephrine induced cardiac irregularities in the dog during anesthesia with trichloroethylene, cyclopropane, ethyl chloride and chloroform. Anesthesiology 14:153-158.

*Morris TE, Tasto WD. 1979. Ethyl chloride. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. Vol. 5. New York, NY: John Wiley and Sons, 714-722.

*Morsehi PL, France-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clin Pharmacokin 5:485-527.

*Mosesman NH, Sidisky LM, Corman SD. 1987. Factors influencing capillary analysis of volatile pollutants. J Chromatogr Sci 25:35 l-355.

*Myers VB 1983. Remedial activity at the Miami Drum Site, Florida. In: National Conference Management of Uncontrolled Hazardous Waste Sites, October 3 1 -November 2, 1983. Silver Spring, MD: Hazardous Materials Control Research Institute, 354-357.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*NATICH. 1994. National Air Toxics Information Clearinghouse: Data base report on acceptable ambient air concentration guidelines/standards concentrations, units, and averaging times report. US Environmental Protection Agency, Office of Air Quality Planning and Standards, Washington, DC.

*Naylor LM, Loehr RC. 1982. Priority pollutants in municipal sewage sludge. Biocycle 23: 18-22.

*Nielsen AJ. 1980. Precautions about ethyl chloride [letter]. Phys Ther 60:474-475.

*NH SDES. 1998. Table containing the list naming all regulated toxic air pollutants. New Hampshire State Department of Environmental Services, Air Resources Division. Chapter Env-A 1400, Part Env-A 1450.01.

*NIOSH. 199 1. National Occupational Exposure Survey. U.S. Department of Health and Human Services,National Institute for Occupational Safety and Health, Cincinnati, OH.

8. REFERENCES

NIOSH. 1992. Recommendations for occupational safety and health. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. NIOSH publication no. 92- 100.

*NIOSH. 1994. NIOSH manual of analytical methods. 4th ed., NIOSH Publication No. 94-l 13, Method No. 2519. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH. 1997. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. NIOSH publication no. 94-l 16. 134-l 35.

*Noble DA. 1979. Another hazard of pierced ears [letter]. Br Med J 1: 125.

*Nordin C, Rosenqvist M, Hollstedt C. 1988. Sniffing of ethyl chloride - An uncommon form of abuse with serious mental and neurological symptoms. Int J Addict 23:623-627.

*NRC. 1993. Pesticides in the diets of infants and children. National Research Council, Washington DC: National Academy Press.

*NTDB. 1996. National Trade Data Bank: The export connection. U.S. Department of Commerce, Economics and Statistics Administration, Washington, DC. (CD-ROM).

*NTP. 1989. Toxicology and carcinogenesis studies of chloroethane (ethyl chloride) (CAS No. 75-00-3) in F344/N rats and B6C3Fl mice (inhalation studies). National Toxicology Program. Research Triangle Park, NC. NTP Technical Report Series No. 346. NTIS No. PB90-225053.

*OHM/TADS. 1998. Oil and Hazardous Materials Technical Assistance Data System. U.S. EPA-NIH (National Institute of Health). May 12, 1998.

*Oliver KD, Adams JR, Daughtrey EH Jr, et al. 1996. Technique for monitoring toxic VOCs in air: Sorbent preconcentration, closed-cycle cooler cryofocusing, and GC/MS analysis. Environ Sci Technol 30: 1939-l 945.

*OSHA. 1998. U.S. Department of Labor, Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 19 10.1000.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

*Otson R. 1987. Purgeable organics in Great Lakes raw and treated water. Int J Environ Anal Chem 31:41-53.

*Otson R, Chan C. 1987. Sample handling and analysis for 5 1 volatile organics by an adapted purge and trap GC-MS technique. Int J Environ Anal Chem 30:275-287.

*Ott RL. 1969. Local anesthesia in the dog. Fed Proc 28:1450-1455.

8. REFERENCES

*Oura E, Raiha NC, Suomalaimen H. 1966. Influence of some alcohols and narcotics on the adenosine phosphates in the liver of the mouse. Ann Med Exp Biol Fenn 45:57-62.

*Owen GM, Brozek J. 1966. Influence of age, sex, and nutrition on body composition during childhood and adolescence. In: Falkner, ed. Human development. Philadelphia, PA: Saunders, 222-238.

*Pankow JF, Rosen ME. 1988. Determination of volatile compounds in water by purging directly to a capillary column with whole column cryotrapping. Environ Sci Technol22:398-405.

*Parker JC, Casey GE, Bahlman LJ, et al. 1979. Chloroethanes: Review of toxicity. NIOSH Current Intelligence Bulletin #27. Am Ind Hyg Assoc J 40:46-60.

*Pellizzari ED, Erickson MD, Zweidinger RA. 1979. Analytical protocols for making a preliminary assessment of halogenated organic compounds in man and environmental media. EPA Report No, 560/13-79-010. NTIS PB 80109168. 115-137.

*Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28:322-328.

*Pellizzari ED, Perrith K, Hartwell TD, Michael LC, et al. 1987. The Total Exposure Assessment Methodology (TEAM) Study. Vol. II. Part I. EPA Report No. 600/6-87/002b, EPA, Office of Research and Development, Washington, DC. 145-153.

*Perry DL, Chuang CC, Jungclaus GA, et al. 1979. Identification of organic compounds in industrial effluent discharges. USEPA Office of Research and Development. Athens, GA: EPA-600/4-79-016. NTIS PB-294794. 40-41; 43.

*Rasche ME, Hicks RE, Ilyman MR, et al. 1990. Oxidation of monohalogenated ethanes and n-chlorinated alkanes by whole cells of *Nitrosomonas europaea.* J Bacterial 172:5368-5373.

*RTECS. 1998. Registry of Toxic Effects of Chemical Substances. National Technical Information Service (NTIS), US. Department of Commerce, Springfield, VA. May 11, 1998.

*Sahel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Management and Research 2: 119- 130.

*Sayers RR, Yant WP, Thomas BG, et al. 1929. Physiological response attending exposure to vapors of methyl bromide, methyl chloride, ethyl bromide and ethyl chloride. U.S. Public Health Bull No. 185: I-56.

*SC DHEC. 1998. Air pollution control standards, Toxic air pollutants. South Carolina Department of Health and Environmental Control, Bureau of Air Quality. 62.5, Standard No. 8.

*Schmidt P, Binnewies S, Gohlike R, et al. 1972. [Subacute action of low concentrations of chlorinatedethanes on rats with and without additional ethanol treatment. I. Subacute and chronic toxicity studies with 1 ,I ,2,2-tetrachloroethane.] Int Arch Arbeitsmed 38:283-298. (German)

*Scortichini BH, Johnson KA, Momany-Pfruenderd JJ, et al. 1986. Ethyl chloride: Inhalation teratology study in CF-1 mice. Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Midland, MI. NTIS no. OTS0001135.

8. REFERENCES

*Selby IR, Bowles BJM. 1995. Analgesia for venous cannulation: A comparison of EMLA (5 minute application), lignocaine, ethyl chloride, and nothing. J R Sot Med 88:264-267.

*Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, Greiger SR, eds.Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society.

*Shepson PB, Kleindiemst TE, Mcelhoe HB. 1987. A cryogenic trap/porous polymer sampling technique for the quantitative determination of ambient volatile organic compound concentrations. Atmos Environ 2 1:579-587.

*Singh HB, Salas LJ, Smith A, et al. 1981. Atmospheric measurements of selected hazardous organic chemicals. NTIS No. PB81-200628.

*Singh HB Salas LJ, Stiles RE. 1983. Selected man-made halogenated chemicals in the air and oceanic envirbonment. J Geophys Res [Sect] C 88:3675-3683.

*Staples CA, Werner A, Hoogheem T. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4: 13 l-l 42.

*Stutz DR, Ulin S. 1992. Hazardous materials injuries. Beltsville, MD: Bradford Communications Corporation, 286-287.

*Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res Rev 85: 17-28.

*Tabak HH, Quave SA. Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-l 5 18.

Takano T, Miyazaki Y. 1982. Effect of chlorinated ethanes and ethylenes on electron transport in rat liver mitochondria. J Toxicol Sci 7: 143- 149.

*Tennant RW, Ashby J. 1991. Classification according to chemical structure, mutagenicity to *Salmonella* and level of carcinogenicity of a further 39 chemicals tested for carcinogenicity by the U.S. National Toxicology Program. Mutat Res 257:209-227.

*Thomas R. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York: McGraw Hill Book Co., Chapter 15.

*Torkelson TR, Rowe VK. 198 1. Ethyl chloride. In: Clayton GD and Clayton FE, eds. Patty's industrial hygiene and toxicology Vol2B. 3rd ed. New York: John Wiley and Sons, Inc., 3480-3483.

*TRI96. 1998. Toxics Release Inventory for 1996. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC.

*Troshina MM. 1966. [Some materials for substantiation of the maximum admissible concentration of ethyl chloride in the air of work places.] Gig Tr Prof Zabol 10:37-42. (Russian)

8. REFERENCES

*Tu AS, Murray TA, Hatch KM, et al. 1985. In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28:85-92.

USITC. 1984. United States International Trade Commission. Synthetic organic chemicals United States production and sales, 11983. USITC Publication 1588. Washington, DC: USITC, 259.

USITC. 1985. United States International Trade Commission. Synthetic organic chemicals United Statesproduction and sales, 11984. USITC Publication 1745. Washington, DC: USITC, 258.

USITC. 1986. United States International Trade Commission. Synthetic organic chemicals United States production and sales, 11985. USITC Publication 1892. Washington, DC: USITC, 268.

USITC. 1987. United States International Trade Commission. Synthetic organic chemicals United States production and sales, 11986. USITC Publication 2009. Washington, DC: USITC, 2 12-213.

*Van Dyke RA, Wineman CG. 197 1. Enzymatic dechlorination: Dechlorination of chloroethanes and propanes *in vitro*. Biochem Pharmacol20:463-470.

*Van Ketel WG. 1976. Allergic contact dermatitis from propellants in deodorant sprays in combination with allergy to ethyl chloride. Contact Dermatitis 2: 115-l 19.

*Van Liere EJ, Mazzocco TR, Northup DW. 1966. The effect of cyclopropane, trichloroethylene and ethyl chloride on the uterus of the dog. Am J Obstet Gynecol994:861-867.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2El in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vogel TM, McCarty PL. metcanogenic conditions.1987. Abiotic and biotic transformations of 1,l ,l - trichloroethane under Environ Sci Technol2 1: 1208-l 2 13.

*Vogt WG Walsh JJ. 1985. Volatile organic compounds in gases from landfill simulators. Proc Air Pollttion Control Association Annu Meet 78:2- 17.

*WA DE. 1998. Toxic air pollutants and acceptable source impact levels. Washington Department of Ecology. WAC 173-460-l 60.

*Walker JS, Soult TA. 1993. Ethyl chloride intoxication [letter]. Am J Emerg Med 11:3 13-3 15.

*Wailer CL, Evans MV, McKinney JD. 1996. Modeling the cytochrome P450-mediated metabolism of chlorinated volatile organic compounds. Drug Metab Dispos 24:203-210.

*Washington JW. 1996. Gas partitioning of dissolved volatile organic compounds in the vadose zone: Principles, temperature effects and literature review. Ground Water 34:709-7 18.

*Watanabe Y. 1983. [Studies on the biologic effects of hydrocarbons (III)-chlorinated hydrocarbons.] Kanagawa-ken Taiki Osen Chosa Kenkyu Hokoku 25: 146- 152. (Japanese)

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Ped 32a: 10- 18.

8. REFERENCES

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise, volume II, The elements part A. New York, NY: Academic Press.

*Worrall S, De Jersey J, Wilce PA, et al. 1994. Studies on the usefulness of acetaldehyde-modified proteins and associated antibodies as markers of alcohol abuse. Alcohol Alcohol Suppl2:503-507.

*Yacoub I, Robinson CA, Simmons GT. 1993. Death attributed to ethyl chloride. J Anal Toxicol 17:384-385.

*Young DR, Gossett RW, Baird RB, et al. 1983. Wastewater inputs and marine bioaccumulation of priority pollutant organics off southern California. In: Jolley RL, ed. Proceedings of the Fourth Conference on Water Chlorination-Environmental Impacts and Health Effects, October 18-23, 198 1. Ann Arbor, MI: Ann Arbor Science, 87 1-884.

*Young P, Parker A. 1984. Vapors, odors and toxic gases from landfills. In: Jackson LP, Rohlik AR, Conway RA, eds. Hazardous and Industrial Waste Management and Testing: Third Symposium, March 7-10, 1983. Philadelphia, PA: ASTM Technical Publication, 24-41. ASTM Publication Code Number 04-851000-16.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

9. GLOSSARY

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

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

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

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

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

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.
Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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

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

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

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

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

9. GLOSSARY

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 Concentratioq$_{(LO)}$ (LC_{LO})-The lowest concentraGon 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$_{(50)}$ (LD_{50})-The lowest dose of a chemical introduced by a route other than inhalation that isexpected 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 Aowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

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

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

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

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

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

Octanol-Water Partition Coefficient (K_{ow}) -The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

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

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

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

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

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

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

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

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

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

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

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

APPENDIX A

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. 994991, 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 1eveVuncertainty 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.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chloroethane
CAS Number: 75-00-3
Date: November 1998
Profile Status: Post-Public
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [] Intermediate [ ] Chronic
Graph Key: 30
Species: Mice (CF-1)

Minimal Risk Level: 15 [ ] mg/day [x] ppm

Reference: Scortichini et al. 1986

Experimental design: Groups of 23-26 pregnant mice were exposed to 99.9% pure chloroethane at 0,49 1, 1504, or 4,946 ppm 6 hours/day on gestation days 6-15. Body weights were recorded on gestation days 6,9, 12, 15, and 18, and food and water intakes were measured. The animals were sacrificed on gestation day 18 and the following data were recorded: maternal liver weight; number and position of fetuses in utero; number of live and dead fetuses; number and position of resorption sites; weight and sex of each fetus; gross externalalterations. Half of each litter was examined for visceral alterations, half for skeletal alterations.

Effects noted in study and corresponding doses: No maternal toxicity (body weight, food and water intake,liver weight) was observed. There were no effects on reproductive parameters, fetal body weight, or malformations. A small increase in the incidence of foramina of the skull bones (small centers of unossified bone) was observed at the high dose that was statistically significant ($p = 0.05$) (percent of litters affected 5%, 4%, 4%, 23%; percent of fetuses affected l%, l%, l%, 4% at 0,491, 1,504, and 4,946 ppm, respectively). An increase in supernumerary ribs was also found, although the effect was not indicated as statistically significant. The incidence of fetuses with supernumerary ribs was 2/257 (1%) controls, and in increasing concentrations l/299 (0.3%), 6/311 (2%), and 2/242 (2%). The incidence in litters was 2/22 (9%) controls, l/25 (4%), 5/26 (19%), and 4/22 (18%). The authors indicate that the effect was “suggestive of, at most, very slight fetotoxicity” at the high dose.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

1,504 ppm

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

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

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If an inhalation study in animals. list the conversion factors used in determining human equivalent dose:

Because fetotoxic effects may result from peak concentrations rather than total duration of exposure, the NOAEL was not adjusted for intermittent exposure.

Because chloroethane is lipid soluble it is reasonable to assume that periodicity was attained. Therefore, a human equivalent concentration (HEC) could be calculated by multiplying the NOAEL by the ratio of the human/mouse blood gas partition coefficients. The value for humans is 2.69 (Gargas et al. 1989). The value for mice is not known. Since the human/mouse ratio is unknown, a default value of 1 is used.

Other additional studies or uertinent information which lend support to this MRL:

There are no additional developmental or reproductive studies of chloroethane. A study by Bucher et al. (1995) reported a small increase in the average duration of the estrous cycle in female mice exposed to chloroethane at 15,000 ppm 6 hours/day for 21 days. No consistent effects on estradiol or progesterone effects were noted. No other exposure concentrations were used in this study.

Other studies have not identified clear dose-related effects of chloroethane in animals at concentrations up to 19,000 ppm (Landry et al. 1982, 1987, 1989; NTP 1989). Because of an explosion hazard (chloroethane is explosive at 40,000 ppm), intermediate- and chronic duration toxicity studies have not examined higher concentrations.

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-l and Figure 2-l 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-l) 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 1.5 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. "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 18), 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 e 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_l *).

(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

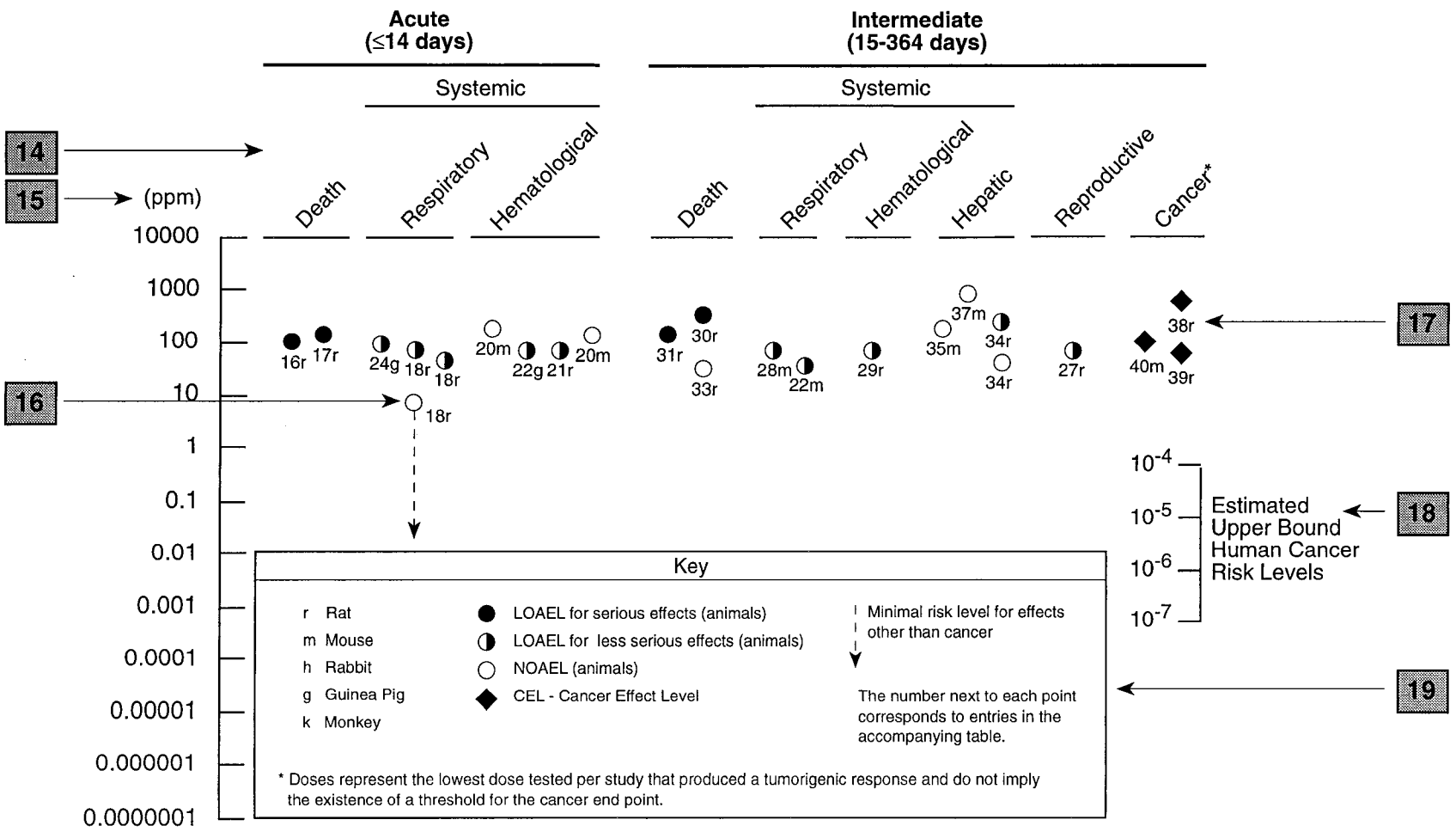
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
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] 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**



APPENDIX B

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).

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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
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
hr^{-1}	1/hour
IDLH	Immediately Dangerous to Life and Health

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IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
M	molar
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration

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PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

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

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