TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

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

September 2001

DISCLAIMER

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

UPDATE STATEMENT

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:

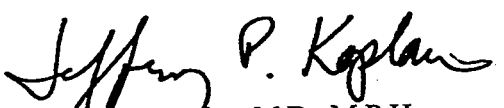
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

Disease Registry

*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 prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, 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 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 639-6357 ***Fax:*** (404) 639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

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.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Malcolm Williams, D.V.M., Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Stephen Bosch, M.S.
Mario Citra, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

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 1,2-dichloroethane. The panel consisted of the following members:

1. Dr. G.A. Shakeel Ansari, Department of Human Biological Chemistry & Genetics and Pathology, University of Texas Medical Branch, Galveston, TX;

2. Dr. John L. Egle, Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA;

3. Dr. F. Peter Guengerich, Center in Molecular Toxicology, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN; and

4. Mr. Lyman K. Skory, Skory Consulting, Inc., Health, Environmental and Regulatory Consulting, Midland, MI.

These experts collectively have knowledge of 1,2-dichloroethane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about 1,2-dichloroethane 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. 1,2-Dichloroethane has been found in at least 570 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for 1,2-dichloroethane is not known. As more sites are evaluated, the sites at which 1,2-dichloroethane is found may increase. This information is important because exposure to 1,2-dichloroethane 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 1,2-dichloroethane, 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 1,2-DICHLOROETHANE?

1,2-Dichloroethane is a clear, manufactured liquid that is not found naturally in the environment. It evaporates quickly at room temperature and has a pleasant smell and a sweet taste. 1,2-Dichloroethane burns with a smoky flame. At this time, the most common use of 1,2-dichloroethane is to make vinyl chloride, which is used to make a variety of plastic and vinyl products including polyvinyl chloride (PVC) pipes and other important construction materials, packaging materials, furniture and automobile upholstery, wall coverings, housewares, and automobile parts. 1,2-Dichloroethane is also used as a solvent and is added to leaded gasoline to

remove lead. In the past, it was also found in small amounts in products that industries used to clean cloth, remove grease from metal, and break down oils, fats, waxes, resins, and rubber. In the household, 1,2-dichloroethane was formerly a component of some cleaning solutions and pesticides; some adhesives, such as those used to glue wallpaper or carpeting; and some paint, varnish, and finish removers. Although large amounts of 1,2-dichloroethane are produced today, most is used to make other chemical products.

Small amounts of 1,2-dichloroethane that were released into water or soil evaporate into the air. 1,2-Dichloroethane that remains in soil from a spill or improper disposal can travel through the ground into water. The chemical may remain in water or soil for more than 40 days.

Chapter 4 contains more chemical and physical information about 1,2-dichloroethane. Chapter 5 has more information on its uses, and Chapter 6 tells about its presence in the environment.

1.2 WHAT HAPPENS TO 1,2-DICHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

1,2-Dichloroethane can enter the environment when it is made, packaged, shipped, or used. Most 1,2-dichloroethane is released to the air, although some is released to rivers or lakes. 1,2-Dichloroethane could also enter soil, water, or air in large amounts in an accidental spill.

1,2-Dichloroethane evaporates into the air very fast from soil and water. In the air, it breaks down by reacting with other compounds formed by the sunlight. 1,2-Dichloroethane will stay in the air for more than 5 months before it is broken down. It may also be removed from air in rain or snow. Since it stays in the air for a while, the wind may carry it over large distances.

In water, 1,2-dichloroethane breaks down very slowly and most of it will evaporate to the air. Only very small amounts are taken up by plants and fish. We do not know exactly how long 1,2-dichloroethane remains in water, but we do know that it remains longer in lakes than in rivers.

In soil, 1,2-dichloroethane either evaporates into the air or travels down through soil and enters underground water. Small organisms living in soil and groundwater may transform it into other less harmful compounds, although this happens slowly. If a large amount of 1,2-dichloroethane enters soil from an accident, hazardous waste site, or landfill, it may travel a long way underground and contaminate drinking water wells.

More information on what happens to 1,2-dichloroethane in the environment can be found in Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO 1,2-DICHLOROETHANE?

Humans are exposed to 1,2-dichloroethane mainly by breathing air or drinking water that contains 1,2-dichloroethane. Human exposure usually happens where the chemical has been improperly disposed of, or spilled onto the ground. However, low levels of 1,2-dichloroethane have also been found in the air near industries where it is made or used in manufacturing. Humans can be exposed to low levels of 1,2-dichloroethane through the skin or air by contact with old products made with 1,2-dichloroethane, such as cleaning agents, pesticides, and adhesives used to glue wallpaper and carpets. Such exposure is probably not enough to cause harmful health effects.

1,2-Dichloroethane has been found in U.S. drinking water at levels ranging from 0.05 to 64 parts of 1,2-dichloroethane per billion (ppb) parts of water. An average amount of 175 ppb has been found in 12% of the surface water and groundwater samples taken at 2,783 hazardous wastes sites. 1,2-Dichloroethane has also been found in the air near urban areas at levels of 0.10–1.50 ppb and near hazardous waste sites at levels of 0.01–0.003 ppb. Small amounts of 1,2-dichloroethane have also been found in foods.

Humans may also be exposed to 1,2-dichloroethane through its use as a gasoline additive to reduce lead content, but these small levels are not expected to affect human health. This is probably not an important way that people are exposed to 1,2-dichloroethane in the United States, since leaded gasolines are rarely used today.

Additional information on levels in the environment and potential for human exposure are presented in Chapter 6.

1.4 HOW CAN 1,2-DICHLOROETHANE ENTER AND LEAVE MY BODY?

1,2-Dichloroethane can enter the body when people breathe air or drink water that contains 1,2-dichloroethane. Studies in animals also show that 1,2-dichloroethane can enter the body through the skin. Humans are most likely to be exposed at work and outside the workplace by drinking water that contains 1,2-dichloroethane, or by breathing 1,2-dichloroethane that has escaped from contaminated water or soil into the air.

Experiments in animals show that 1,2-dichloroethane that is breathed in or swallowed goes to many organs of the body, but usually leaves in the breath within 1 or 2 days. The breakdown products of 1,2-dichloroethane in the body leave quickly in the urine. Soil near hazardous waste sites probably does not have high amounts of 1,2-dichloroethane because it evaporates quickly into the air. This suggests that exposure near a hazardous waste site would most likely occur by breathing contaminated air rather than by touching contaminated soil.

Further information on how 1,2-dichloroethane can enter and leave the body is presented in Chapter 3.

1.5 HOW CAN 1,2-DICHLOROETHANE 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.

People who were accidentally exposed to large amounts of 1,2-dichloroethane in the air or who swallowed 1,2-dichloroethane by accident or on purpose often developed nervous system disorders and liver and kidney disease. Lung effects were also seen after a large amount of 1,2-dichloroethane was inhaled. People often died from heart failure. We do not know what levels of 1,2-dichloroethane caused these effects, but they are probably high. Studies in laboratory animals also found that breathing or swallowing large amounts of 1,2-dichloroethane produced nervous system disorders, kidney disease, or lung effects. Reduced ability to fight infection was also seen in laboratory animals who breathed or swallowed 1,2-dichloroethane, but we do not know if this also occurs in humans. Longer-term exposure to lower doses also caused kidney disease in animals.

So far, exposure to 1,2-dichloroethane has not been associated with cancer in humans. One study showed a relationship between increased cancer and exposure to pollutants in groundwater, including 1,2-dichloroethane, but the people were probably exposed to many other chemicals at the same time. Cancer was found in laboratory animals who were fed large doses of 1,2-dichloroethane. When 1,2-dichloroethane was put on the skin of laboratory animals, they developed lung tumors. We are not sure whether breathing 1,2-dichloroethane causes cancer in animals. Because of the cancer findings in animals, the possibility of cancer in humans cannot be ruled out. The Department of Health and Human Services (DHHS) has determined that 1,2-dichloroethane may reasonably be expected to cause cancer. The International Agency for Research on Cancer (IARC) has determined that 1,2-dichloroethane can possibly cause cancer in humans. EPA has determined that 1,2-dichloroethane is a probable human carcinogen.

Additional information regarding the health effects of 1,2-dichloroethane can be found in Chapter 3.

1.6 HOW CAN 1,2-DICHLOROETHANE AFFECT CHILDREN?

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

Children can be exposed to 1,2-dichloroethane by breathing contaminated air, and possibly by drinking contaminated water. In the past, 1,2-dichloroethane had been used in certain household items, such as cleaning products and adhesives, but is no longer used in these products. There is a possibility that using of one of these older household products containing 1,2-dichloroethane to clean floors or glue carpets could result in exposure, since children often crawl on floors and play on carpets. Such exposures would probably last a few days or less, since 1,2-dichloroethane evaporates very quickly. Children are not likely to be exposed to 1,2-dichloroethane from parents' clothing or other items removed from the workplace. Because 1,2-dichloroethane has been detected in human milk, it is possible that young children could be exposed to 1,2-dichloroethane from breast-feeding mothers who had been exposed to sources of 1,2-dichloroethane.

There have been no studies of health effects in children exposed to 1,2-dichloroethane, and we have no reliable information on whether 1,2-dichloroethane causes birth defects in children. One study broadly suggests that heart problems could occur in the human fetus from mothers being exposed to 1,2-dichloroethane along with some other chemicals, but the information is not reliable enough for us to be sure whether 1,2-dichloroethane is responsible for the defects. Studies of pregnant laboratory animals indicate that it probably does not produce birth defects or affect reproduction. We do know, however, that when the pregnant animal is exposed to 1,2-dichloroethane, the fetus is probably also exposed.

It is likely that children exposed to 1,2-dichloroethane after birth would show the same health effects that are expected to occur in adults, especially liver and kidney disease. There is no information to determine whether children differ from adults in their sensitivity to the health effects of 1,2-dichloroethane.

More information regarding children's health and 1,2-dichloroethane can be found in Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 1,2-DICHLOROETHANE?

If your doctor finds that you have been exposed to significant amounts of 1,2-dichloroethane, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

In the past, 1,2-dichloroethane was used in small amounts in household products such as cleaning agents, pesticides, and wallpaper and carpet glue. It is possible that you may have old containers of such products in your home. Risk of exposure from this source could be eliminated if these older products were immediately discarded. Otherwise, household chemicals 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 that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number next to the phone. Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to 1,2-dichloroethane by inhaling products containing it. Talk with your children about the dangers of sniffing chemicals. The exposure of your family to 1,2-dichloroethane can be reduced by throwing away any household products that contain it. You may wish to contact your county health department for appropriate disposal methods.

1,2-Dichloroethane has been found in drinking water in the United States. Most of the time, 1,2-dichloroethane has been found in small amounts that do not pose a major health risk. You may want to contact your water supplier or local health department to get information about the levels of 1,2-dichloroethane in the drinking water.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,2-DICHLOROETHANE?

1,2-Dichloroethane has been found in the breath, blood, breast milk, and urine of exposed people. Because breath samples are easily collected, testing breathed-out or exhaled air is now a possible way to find out whether someone has recently been exposed to 1,2-dichloroethane. However, tests that measure small amounts in human breath, tissues, and fluids may not be available at your doctor's office because they require special equipment. Your physician can refer you to a facility where these tests are done. Although these tests can show that you have been exposed to 1,2-dichloroethane, it is not possible to tell if you will experience any harmful health effects. Because 1,2-dichloroethane leaves the body fairly quickly, these methods are best for finding exposures that occurred within the last several days. Exposure to 1,2-dichloroethane at hazardous waste sites will probably include exposure to other organic compounds at the same time. Therefore, levels of 1,2-dichloroethane measured in the body by these methods may not show exposure to 1,2-dichloroethane only. Medical tests available at a doctor's office include lung-, liver-, and kidney-function tests, but these tests look for damage that has already occurred from general chemical exposure and do not determine the cause of damage. Damage could also be the result of lifestyle (e.g., drinking alcohol, smoking) or general exposure to environmental agents. Other methods to measure the effects of exposure to 1,2-dichloroethane (such as abnormal enzyme levels) do not measure the effects of exposure to 1,2-dichloroethane only, but measure effects of other chemicals as well.

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 1,2-dichloroethane include the following:

The federal government has developed regulatory standards and guidelines to protect people from the possible health effects of 1,2-dichloroethane in air. OSHA has set a limit of 50 parts of 1,2-dichloroethane per million parts of air (ppm, 1 ppm is 1,000 times more than 1 ppb) in the workplace for an 8-hour day, 40-hour week. NIOSH recommends that a person not be exposed daily in the workplace to more than 1 ppm 1,2-dichloroethane for a 10-hour day, 40-hour week. NIOSH calls 1,2-dichloroethane a possible occupational carcinogen. EPA also calls the compound a probable human cancer-causing agent, based on experiments in animals.

The federal government has also set regulatory standards and guidelines to protect people from the possible health effects of 1,2-dichloroethane in drinking water. EPA has set a limit in water of 0.005 milligrams of 1,2-dichloroethane per liter (5 ppb).

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737) or (404) 639-6357
Fax: (404) 639-6359

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,2-DICHLOROETHANE IN THE UNITED STATES

1,2-Dichloroethane, also called ethylene dichloride, is a volatile, clear, manufactured liquid that is not found naturally in the environment. It has a pleasant smell and a sweet taste and burns with a smoky flame. 1,2-Dichloroethane is readily soluble in water and several organic solvents such as alcohol, chloroform, and ether. 1,2-Dichloroethane is one of the most widely produced chemicals in the world. Its predominant use is in the manufacture of vinyl chloride. 1,2-Dichloroethane was formerly used in varnish and finish removers, soaps and scouring compounds, organic synthesis for extraction and cleaning purposes, metal degreasers, ore flotation, and paints, coatings, and adhesives.

1,2-Dichloroethane is a widespread contaminant released to the environment during its production and use, with the vast majority of the fugitive emissions going into the air. Vapor-phase 1,2-dichloroethane is photochemically degraded in the atmosphere with an estimated reaction half-life of about 73 days. If released to soil, 1,2-dichloroethane is not expected to adsorb strongly and may leach into groundwater. Volatilization is expected to be an important environmental fate process for 1,2-dichloroethane in soil and bodies of water. Biodegradation is expected to occur slowly in both water and soil surfaces. Hydrolysis and photolysis are not expected to be important fate processes, and the potential for bioconcentration in aquatic organisms appears to be low.

The general population is exposed to 1,2-dichloroethane primarily from inhalation of ambient air, particularly near point sources. Other potential routes of exposure for the general population include ingestion of 1,2-dichloroethane in contaminated drinking water or food items and dermal absorption. In addition, inhalation exposure may occur from 1,2-dichloroethane that has volatilized from water during activities such as cooking, bathing, showering, and dishwashing, if 1,2-dichloroethane is in the water supply. Occupational exposure to 1,2-dichloroethane occurs through inhalation and dermal contact with the compound at workplaces where it is produced or used. Children are expected to be exposed to 1,2-dichloroethane by the same routes as adults. 1,2-Dichloroethane has been detected in human milk, indicating that infants could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of child exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available.

Median daily atmospheric concentrations of 1,2-dichloroethane are typically in the 0.01–0.1 ppb range for urban, suburban, rural, and remote sites, and slightly higher near point sources such as factories, treatment plants, and hazardous waste sites. The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day, a level well below ATSDR's intermediate oral MRL of 0.2 mg/kg/day for 1,2-dichloroethane. Since the levels of 1,2-dichloroethane in food products of Japan are similar to those in the United States, the daily intake value may also be similar.

Populations residing near hazardous waste disposal sites or municipal landfills may be subject to higher than average levels of 1,2-dichloroethane in ambient air and drinking water since 1,2-dichloroethane is volatile and is mobile in soil and may leach into drinking water supplies. 1,2-Dichloroethane is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA), and has been found in at least 570 of the 1,585 current or former National Priorities List (NPL) sites. However, the total number of NPL sites evaluated for 1,2-dichloroethane is not known. As more sites are evaluated, the sites at which 1,2-dichloroethane is found may increase.

2.2 SUMMARY OF HEALTH EFFECTS

Short-, intermediate-, and long-term health effects can result from inhalation or ingestion of, or dermal contact to, 1,2-dichloroethane. Main targets of mammalian toxicity include the liver, kidneys, and neurological, cardiovascular, and immune systems. A limited amount of information is available regarding effects in humans, most coming from case reports of people who died following acute exposure to high levels by inhalation or ingestion. Symptoms and signs in these people included central nervous system depression, nausea and vomiting, corneal opacity, bronchitis, respiratory distress, lung congestion, myocardial lesions, hemorrhagic gastritis and colitis, increased blood clotting time, hepatocellular damage, renal necrosis, and histopathological changes in brain tissue. Death was most often attributed to cardiac arrhythmia. Inhalation and oral studies in animals have found similar effects, as well as immunological, genotoxic, and carcinogenic effects not reported in humans. Animal data further indicate that 1,2-dichloroethane is unlikely to cause reproductive or developmental toxicity at doses below those that are maternally toxic.

Route-related differences in some toxic and carcinogenic responses have been observed between gavage and drinking water or inhalation exposure in animal studies of 1,2-dichloroethane. The differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing. As discussed in Chapter 3 (Section 3.5, Mechanisms of Action), effects of 1,2-dichloroethane in various

tissues appear to be largely mediated by reactive intermediates formed by conjugation with glutathione. The reaction of 1,2-dichloroethane and glutathione is unusual in that it results in activation rather than detoxification (i.e., the typical consequence of conjugation of xenobiotics with glutathione). Toxicity may occur when the biotransformation processes are saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated. Therefore, even though certain health effects might be expected in humans ingesting sufficient doses of 1,2-dichloroethane, it is uncertain whether the effects would occur following typical drinking water and inhalation exposures.

Hepatic Effects. Liver effects have been observed in cases of humans who died following acute inhalation or ingestion of 1,2-dichloroethane. Hepatotoxicity was indicated by an increase in levels of serum markers of liver dysfunction, an enlarged liver, and extensive centrilobular necrosis in a man who was exposed to concentrated 1,2-dichloroethane vapors for 30 minutes and subsequently died. Necrosis and cirrhosis were reported in people following acute high-level oral exposure to $570 mg/kg/day. Evidence from animal studies supports the conclusion that the liver is a target organ for 1,2-dichloroethane. Hepatic effects in exposed animals were not limited to any specific route or duration of exposure and included increased levels of serum markers of liver dysfunction, increased liver weight, and fatty degeneration. For inhalation exposure, the lowest concentrations producing hepatic effects were 400 ppm for acute-duration exposure and 100 ppm for intermediate-duration exposure. As discussed in Section 2.3, liver histopathology is the basis of the chronic-duration minimal risk level (MRL) for inhalation oral exposure. For oral exposure, the lowest dose producing hepatic effects was 18 mg/kg/day for intermediate-duration exposure.

Renal Effects. 1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects observed in individuals who died following acute high-level exposure were diffuse necrosis, tubular necrosis, and kidney failure. Renal effects seen in experimental animals include increased kidney weight, cloudy swelling of the tubular epithelium, tubular degeneration and regeneration, karyomegaly, dilatation, protein casts, and mineralization. The effects in animals were not limited to any specific route or duration of exposure and support the conclusion that the kidney is a target organ for 1,2-dichloroethane. For inhalation exposure, the lowest concentration reported to produce renal effects was 400 ppm for durations of 8–12 days and 8 months. For oral exposure, the lowest dose producing renal effects was 58 mg/kg/day for 13 weeks. Increased kidney weight, considered to be an early-stage adverse effect because it leads to histopathological changes at higher doses, was used to derive the intermediate-duration MRL for oral exposure to 1,2-dichloroethane as discussed in Section 2.3.

Immunological and Lymphoreticular Effects. Immunological effects have not been reported in humans exposed to 1,2-dichloroethane. In mice, however, this chemical had immunosuppressive effects following both acute inhalation exposure and acute oral exposure. A single 3-hour inhalation exposure to 5–11 ppm increased susceptibility of mice to bacterial infection, although no changes in bactericidal activity or other immune function end points were found in rats after a single 5-hour exposure to 200 ppm or 12 5-hour exposures to 100 ppm. Effects observed in mice following gavage administration of 4.9 or 49 mg/kg/day for 14 days included reduced humoral immunity (immunoglobulin response to sheep red blood cells) and cell-mediated immunity (delayed-type hypersensitivity response to sheep erythrocytes). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice. Because of the apparent interspecies differences in immunotoxicity; however, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute exposure by inhalation or ingestion.

Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane. Immune function also has not been evaluated after chronic oral exposure, although mice given up to 189 mg/kg/day of 1,2-dichloroethane in drinking water for 90 days had no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens. Leucocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats, and intermediate and chronic oral exposures did not produce histological changes in immune system tissues in rats and mice. Although immunological effects might be expected in humans ingesting sufficient doses of undiluted 1,2-dichloroethane, it is uncertain whether the effects would occur in people exposed via drinking water from wells located near hazardous waste sites.

Neurological Effects. Neurological symptoms and signs in people acutely exposed to high levels of 1,2-dichloroethane by inhalation or ingestion included headache, irritability, drowsiness, tremors, partial paralysis, and coma. Autopsies of people who died revealed effects in the brain including hyperemia, hemorrhage, myelin degeneration, diffuse changes in the cerebellum, shrunken appearance and pyknotic nuclei in the Purkinje cell layer of the cerebellum, and parenchymous changes in the brain and spinal cord.

The results of animal inhalation studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis were observed after high-level acute vapor exposures. In

addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks. In contrast, no clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks, and no brain lesions were seen in rats intermittently exposed to 50 ppm for 2 years. The effects seen in the gavage study at a level lower than the NOAEL in the drinking water study might be attributable to the method of dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Acute exposure levels high enough to produce neurological effects would not be expected to occur at hazardous waste sites or in the workplace, but might result from accidental occupational exposure or accidental or intentional ingestion.

Cardiovascular Effects. Cardiac arrhythmia was given as the cause of death of a man briefly exposed to 1,2-dichloroethane as a concentrated vapor. Autopsy revealed diffuse degenerative changes in the myocardium (fragmentation, interstitial edema, loss of nuclei from myocardial fibers). In addition, cardiovascular insufficiency and hemorrhage were major factors contributing to death in people following acute high-level oral exposure to $570 mg/kg/day. In laboratory animals, myocardial inflammation was reported following acute inhalation of lethal concentrations, and fatty infiltration of the myocardium was observed in guinea pigs that died following exposure to 200 ppm for 25 weeks and in monkeys that survived the same exposure regimen. These findings in animals were based upon a very limited number of observations and in some cases did not include comparison to controls. More complete animal studies did not report cardiovascular histopathologic effects following high-level intermediate-duration oral exposure or low-level chronic-duration inhalation exposure. Overall, the data suggest that the heart could be a target of 1,2-dichloroethane following acute high-level exposure and possibly longer-term inhalation exposure as well. Levels that might produce cardiovascular effects are not likely to be found at hazardous waste sites or a well-regulated workplace.

Developmental Effects. The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes that found increased odds ratios for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects). Primary routes of exposure in these epidemiologic studies may have been both oral and inhalation, including inhalation of 1,2-dichloroethane volatilized from household water. It has been previously shown that taking a 10-minute shower is equivalent to drinking 1–3 liters of the same water contaminated with some volatile organic compounds. In these studies, the study populations were

also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive and do not establish a cause-and-effect relationship.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryolethality at maternally toxic doses have been reported. (There are reports of increased embryo and pup mortality following intermediate-duration inhalation of lower [not maternally toxic] concentrations of 1,2-dichloroethane, but the reliability of the results is uncertain due to the lack of statistical analysis and inadequate description of methods.) The possibility of induction of cardiac malformations in human offspring by 1,2-dichloroethane, as suggested by the epidemiologic data, was not confirmed in available animal studies because the teratology protocols did not include detailed examinations of dissected hearts. Studies of dichloroethylene and trichloroethylene, which are metabolized to some of the same reactive intermediates as 1,2-dichloroethane, have also shown evidence of heart malformations in humans as well as animal cardiac teratogenicity. Overall, the available information does not indicate that 1,2-dichloroethane is a developmental toxicant in animals at doses below those that cause other toxic effects.

Reproductive Effects. A single study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a reduction in gestation duration, but co-exposure to other chemicals occurred in most cases, and the adequacy of the study design could not be evaluated because of reporting deficiencies. Results of animal studies indicate that 1,2-dichloroethane is unlikely to cause reproductive impairment at doses that are not maternally toxic. Some inhalation studies found that exposure of dams to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryolethality in rats, although the study methods were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study. One- and two-generation reproduction studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats, but exposure to higher oral doses caused increases in nonsurviving implants and resorptions in rats that also experienced maternal toxicity. Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results, but reproductive function was not evaluated in these studies. Although 1,2-dichloroethane appears to have induced embryotoxic effects in some animal studies, the

overall indication of the data is that this chemical is unlikely to impair reproduction at doses that do not also cause other toxic manifestations.

Cancer. Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity in humans, due to complicating co-exposures to various other chemicals. In animals, no tumors were produced in rats and mice exposed to 1,2-dichloroethane via inhalation. The inhalation data are limited by use of a single, subthreshold exposure level in one study, and exceedance of the maximum tolerated dose in rats, less-than-lifetime study duration, and poor survival in mice in the other study.

1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, causing statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice. Other animal bioassays provide supportive or suggestive evidence for the carcinogenicity of 1,2-dichloroethane. One study showed compound-related lung papillomas following lifetime dermal exposure of female mice. Two additional studies found that pulmonary adenomas were induced in mice by intraperitoneal injection.

The positive and suggestive carcinogenicity results from animal bioassays, along with data indicating that 1,2-dichloroethane and some metabolites are mutagenic and capable of forming DNA adducts (see Chapter 3, Section 3.3), provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well. The Department of Health and Human Services (DHHS) has determined that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen. The International Agency Research on Cancer (IARC) has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans), and the EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen).

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

An acute-duration inhalation MRL has not been derived for 1,2-dichloroethane. The lowest effect level for acute inhalation exposure is 5.4 ppm for significantly increased mortality in mice from streptococcal (*Streptococcus zooepidemicus*) bacterial challenge following a single 3-hour exposure to 1,2-dichloroethane. Significantly increased mortality from streptococcal challenge in addition to decreased bactericidal activity after challenge with *Klebsiella pneumoniae* were seen in mice at 10.8 ppm. The no-observed-adverse-effect-level (NOAEL) for susceptibility to streptococcal challenge in mice was 2.3 ppm after a single 3-hour exposure or five 3-hour exposures on consecutive days. In the same study, rats did not show decreased bactericidal activity from *K. pneumoniae* challenge following single exposures of up to 200 ppm, or multiple 5-hour exposures of up to 100 ppm of 1,2-dichloroethane. Sherwood et al. indicated that the clear interspecies difference in immunotoxic susceptibility suggests against extrapolating from animals to humans. The MRL Workgroup concluded that the massive streptococcal challenge to mice, consisting of whole-body, 30-minute exposures to aerosols of bacteria for an estimated challenge exposure of $2x10^4$ inhaled viable streptococci, is unlikely to be relevant to normal human immunological challenge and that, therefore, the increased mortality in mice observed in the Sherwood et al. study is not a suitable basis for an acute inhalation MRL. Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane, although immunosuppressive effects have been reported in mice that were orally exposed to 1,2-dichloroethane for 14 days.

- An MRL of 0.6 ppm has been derived for chronic-duration inhalation exposure (>365 days) to 1,2-dichloroethane. This chronic MRL is also expected to be protective for intermediate-duration inhalation exposure (15–364 days).

The MRL was derived by dividing a NOAEL of 50 ppm for liver histopathology in rats exposed for 7 hours/day, 5 days/week for 2 years by an uncertainty factor of 90 (3 for interspecies extrapolation after dosimetric adjustment; 10 for human variability; and 3 as a modifying factor for database deficiencies). Although other concentrations of 1,2-dichloroethane were not tested, confidence in the NOAEL is high due to the group size (50 of each sex) and scope of the study. Additionally, the liver is a documented target of 1,2-dichloroethane toxicity in several acute- and intermediate-duration inhalation studies, as well as in a number of studies of orally exposed animals. Limitations in the acute and intermediate inhalation studies preclude considering them as the basis for MRL derivation, but the weight of evidence indicates

that NOAELs for hepatotoxicity in the intermediate-duration studies are higher than the chronic liver NOAEL. Consequently, the chronic-duration inhalation MRL of 0.6 ppm is also expected to be protective of toxic effects after intermediate-duration inhalation exposures to 1,2-dichloroethane.

Oral MRLs

An MRL has not been derived for acute-duration oral exposure (#14 days) to 1,2-dichloroethane. The lowest effect level that can be identified for acute oral toxicity is a lowest-observed-adverse-effect level (LOAEL) of 4.9 mg/kg/day for immunosuppression from a mouse study. Doses lower than 4.9 mg/kg/day were not tested, precluding identification of a NOAEL. Male mice that were treated with 4.9 or 49 mg/kg/day by gavage for 14 days showed a significant dose-related reduction in humoral immune response (IgM response to sheep erythrocytes). The number of antibody-forming cells (AFCs) was dose-related and statistically significantly reduced at both dose levels; when adjusted to AFC/10^6 cells, there was an apparent negative trend with dose, but a significant reduction occurred only in the high-dose group. The cell-mediated immune response (delayed-type hypersensitivity response to sheep erythrocytes) was significantly reduced in both dose groups, but not in a dose-related manner. There was also a depression in leukocytes in the high dose group. However, because administration of 1,2-dichloroethane in the drinking water at doses as high as 189 mg/kg/day for 90 days failed to induce immunosuppressive effects in mice, it was determined that it may not be appropriate to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism).

- An MRL of 0.2 mg/kg/day was derived for intermediate-duration oral exposure (15–364 days) to 1,2-dichloroethane.

This MRL was derived by dividing a LOAEL of 58 mg/kg/day for increased absolute and relative kidney weights in rats that were exposed to 1,2-dichloroethane in drinking water for 13 weeks by an uncertainty factor of 300 (3 for use of minimal LOAEL; 10 for interspecies extrapolation; and 10 for human variability). Doses lower than 58 mg/kg/day were not tested, precluding identification of a NOAEL. The increases in kidney weight were dose-related and were considered to be an early-stage adverse effect in a known target organ, because histopathological changes were manifested in the kidney at higher doses in the rats as well as in similarly exposed mice in the same study. Tissue examinations showed dose-related, increased incidences of minimal-to-moderate renal regeneration in rats at $102 mg/kg/day and mice at $249 mg/kg/day. These changes are indicative of previous tubular injury with subsequent repair. More

severe kidney effects including karyomegaly, dilatation, protein casts, and mineralization occurred in male mice exposed to 4,210 mg/kg/day. Observations of increased relative kidney weight in rats that were treated with $75 or 90 mg/kg/day by gavage for 90 days are supportive of the 58 mg/kg/day LOAEL.

An MRL has not been derived for chronic oral exposure ($365 days) to 1,2-dichloroethane, because an appropriate study was not identified. The only chronic oral study tested rats and mice that were treated by gavage 5 days/week for up to 78 weeks. This study had several limitations such as dosage adjustments, possible contamination by other chemicals tested in the same laboratory, poor survival, and small numbers of control animals. Additionally, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism).

3. HEALTH EFFECTS

3.1 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 on the toxicology of 1,2-dichloroethane. 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.

3.2 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-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which

major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) 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 1,2-dichloroethane are indicated in Tables 3-1 and 3-2 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,2-dichloroethane. 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.

3.2.1 Inhalation Exposure

Adverse health effects in humans associated with acute and occupational inhalation exposure to 1,2-dichloroethane vapor were described in a number of studies. A case study reported by Nouchi et al. (1984) detailed the clinical effects, blood chemistry, and autopsy findings of a 51-year-old man who died after being exposed to 1,2-dichloroethane vapor for 30 minutes while removing 1,2-dichloroethane residue from the hold of an oil tanker. Exposure is likely to have occurred both by the inhalation and dermal routes. No estimate of the exposure concentration was available, although exposure conditions were described as a "thick vapor of dichloroethane." This study, considered a reliable description of the manifestations of 1,2-dichloroethane-induced toxic effects in humans, is the source for much of the discussion of human data in this section. The available information suggests that massive, acute inhalation exposure to 1,2-dichloroethane can induce neurotoxic, nephrotoxic, and hepatotoxic effects in humans, as well as respiratory distress, cardiac arrhythmia, nausea, and vomiting. The possibility that existing medical conditions contributed to the observed symptoms and autopsy findings could not be evaluated because the individual's medical and behavioral histories were not reported. No information was located regarding immunological, reproductive, or developmental effects in humans following inhalation exposure to 1,2-dichloroethane.

Although considerable information is available on the effects of 1,2-dichloroethane following inhalation exposure in laboratory animals, many of the short-term studies used only a limited number of animals and are, therefore, of only limited utility. Targets of 1,2-dichloroethane inhalation toxicity in animals include the immune system, central nervous system, liver, and kidney. Limited evidence suggests that the heart may also be a target organ. 1,2-Dichloroethane has also produced genotoxic effects in animals exposed by inhalation (see Section 3.3).

Table 3-1 and Figure 3-1 describe the health effects observed in experimental animals associated with exposure level and exposure duration. Effects of 1,2-dichloroethane in humans are not included in the LSE table and figure because exposure levels were not reported and the effects investigated were not subtle.

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	5 d 7hr/d				1500 (29/29 died)	Heppel et al. 1945
2	Rat (Wistar)	1d 7hr				1500 (4/20 died)	Heppel et al. 1945
3	Rat (NS)	14 d 5 d/wk 7 hr/d				1000 (20/26 died)	Heppel et al. 1946
4	Rat (Sprague-Dawley)	9 d Gd 6-15 7 hr/d				300 (10/16 died)	Rao et al. 1980; Schlacter et al. 1979
5	Rat	9 d Gd6-15 7hr/d				300 (2/3 died)	Schlacter et al. 1979
6	Rat (Wistar)	1 d 0.1 to 8 hr				1000 (LC_{50})	Spencer et al. 1951
7	Rat (Wistar)	2-3 d 7 hr/d				400 (24/40 died)	Spencer et al. 1951
8	Mouse (NS)	1 d 7hr				1500 (20/20 died)	Heppel et al. 1945
9	Gn Pig (NS)	1 d 7 hr				1500 (6/12 died)	Heppel et al. 1945
10	Gn Pig (NS)	4 d 7hr/d				1500 (9/9 died)	Heppel et al. 1945

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
11	Gn Pig (NS)	4 d 5d/wk 7 hr/d				1000 (16/16 died)	Heppel et al. 1946
12	Gn Pig (NS)	14-32 d 5d/wk 7hr/d				400 (8/8 died)	Spencer et al. 1951
13	Dog (NS)	6 d 7hr/d				1500 (2/3 died)	Heppel et al. 1945
14	Rabbit (NS)	5 d 7 hr/d				1500 (4/5 died)	Heppel et al. 1945
15	Rabbit (NS)	1 d 7hr				3000 (12/16 died)	Heppel et al. 1945
16	Rabbit (New Zealand)	12 d Gd 6-18 7 hr/day				100 (4/21 died)	Rao et al. 1980; Schlacter et al. 1979
	Systemic						
17	Monkey (Rhesus)	8-12 d 5d/wk 7hr/d	Hemato	100	400 (increased clotting time)		Spencer et al. 1951
			Hepatic	100	400 (fatty degeneration)		
			Renal	100	400 (tubular degeneration)		
18	Rat (Sprague-Dawley)	14 d Gd 6-20 6 hr/d	Bd Wt	254 F	329 F (24% reduced maternal body weight gain)		Payan et al. 1995
19	Rat	10 d Gd6-15 7hr/d	Bd Wt	100		300 (12% maternal body weight loss)	Schlacter et al. 1979

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
20	Gn Pig (NS)	1-14 d 5d/wk 7hr/d	Hepatic		400 M (slight parenchymal degradation)		Spencer et al. 1951
			Renal		400 M (increased kidney weight, swelling of tubular epithelium)		
	Immunological/Lymphoreticular						
21	Rat (Sprague-Dawley)	12 d 5d/wk 5hr/d		100			Sherwood et al. 1987
22	Rat (Sprague-Dawley)	1 d 5hr		200			Sherwood et al. 1987
23	Mouse (CD-1)	5 d 3hr/d		2.3			Sherwood et al. 1987
	Developmental						
24	Rat (Sprague-Dawley)	14 d Gd 6-20 6 hr/d		329 F			Payan et al. 1995
25	Rat (Sprague-Dawley)	9 d Gd6-15 7hr/d		100		300 (embryolethality at maternally toxic exposure level)	Rao et al. 1980; Schlacter et al. 1979
26	Rabbit (New Zealand)	12 d Gd 6-18 7 hr/d		300			Rao et al. 1980; Schlacter et al. 1979

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
	Death							
27	Monkey (NS)	9 wk 7 hr/d 5d/w				1000	(2/2 died)	Heppel et al. 1946
28	Rat (NS)	14 wk 5d/wk 7hr/d				400	(9/16 died)	Heppel et al. 1946
29	Gn Pig (NS)	25 wk 5 d/wk 7 hr/d				200	(5/14 died)	Heppel et al. 1946
30	Gn Pig (NS)	14 wk 5 d/wk 7 hr/d				400	(7/12 died)	Heppel et al. 1946
31	Dog (NS)	9 wk 5 d/wk 7hr/d				1000	(2/6 died)	Heppel et al. 1946
32	Rabbit (NS)	20 wk 5 d/wk 7hr/d				400	(5/5 died)	Heppel et al. 1946
33	Rabbit (NS)	13 wk 5 d/wk 7 hr/d				1000	(5/6 died)	Heppel et al. 1946
34	Cat (NS)	11wk 5 d/wk 7 hr/d				1000	(2/6 died)	Heppel et al. 1946

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
35	Monkey (NS)	25 wk 5 d/wk 7 hr/d	Resp	200			Heppel et al. 1946
			Cardio		200 (fatty degeneration)		
			Hepatic		200 (fatty degeneration)		
			Renal	200			
			Endocr		200 (calcification of the adrenal medulla)		
36	Rat (NS)	15 wk 5 d/wk 7 hr/d	Resp	100			Heppel et al. 1946
			Cardio	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
37	Rat (Wistar)	198-212d 5 d/wk 7 hr/d	Resp	200			Spencer et al. 1951
			Cardio	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Endocr	200			
			Bd Wt	200			
38	Mouse (NS)	4 wk 5 d/wk 7 hr/d	Resp	100			Heppel et al. 1946
			Cardio	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
39	Gn Pig (NS)	246 d 5 d/wk 7 hr/d	Resp	200			Spencer et al. 1951
			Cardio	200			
			Hemato	200			
			Hepatic		100 (increased liver weight, fatty degeneration)		
			Renal	200			
			Endocr	200			
			Bd Wt	200			
40	Dog (NS)	8 mo 5 d/wk 7 hr/d	Resp	400			Heppel et al. 1946
			Cardio	400			
			Hemato	400			
			Hepatic		400 (fatty degeneration)		
			Renal		400 (fatty changes)		
			Endocr	400			
41	Rabbit (NS)	25 wk 5 d/wk 7 hr/d	Resp	200			Heppel et al. 1946
			Cardio	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Endocr	200			

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
42	Rabbit (albino)	232-248 d 5 d/wk 7 hr/d	Resp	400			Spencer et al. 1951
			Cardio	400			
			Hemato	400			
			Hepatic	400			
			Renal	400			
			Endocr	400			
			Bd Wt	400			
	Immunological/Lymphoreticular						
43	Rat (Wistar)	198-212d 5 d/wk 7 hr/d		200			Spencer et al. 1951
44	Gn Pig (NS)	246 d 5 d/wk 7 hr/d		200			Spencer et al. 1951
45	Rabbit (albino)	232-248 d 5 d/wk 7 hr/d		400			Spencer et al. 1951
	Neurological						
46	Dog (NS)	8 mo 5 d/wk 7 hr/d		400			Heppel et al. 1946
	Reproductive						
47	Rat (Sprague-Dawley)	1 gen 7 d/wk 6 hr/d		150			Rao et al. 1980

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
48	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d	Resp	50			Cheever et al. 1990
			Cardio	50			
			Gastro	50			
			Hemato	50			
			Musc/skel	50			
			Hepatic	50[b]			
			Renal	50			
			Dermal	50			
			Ocular	50			
			Endocr	50			
			Bd Wt	50			
	Immunological/Lymphoreticular						
49	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990
	Neurological						
50	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
51	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive a chronic inhalation minimal risk level (MRL) of 0.6 ppm; exposure level divided by an uncertainty factor of 90 (3 for interspecies extrapolation, 10 for human variability, and 3 as a modifying factor for database deficiencies).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; gen = generation; Hemato = hematological; hr = hour; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk=week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Acute (≤14 days)

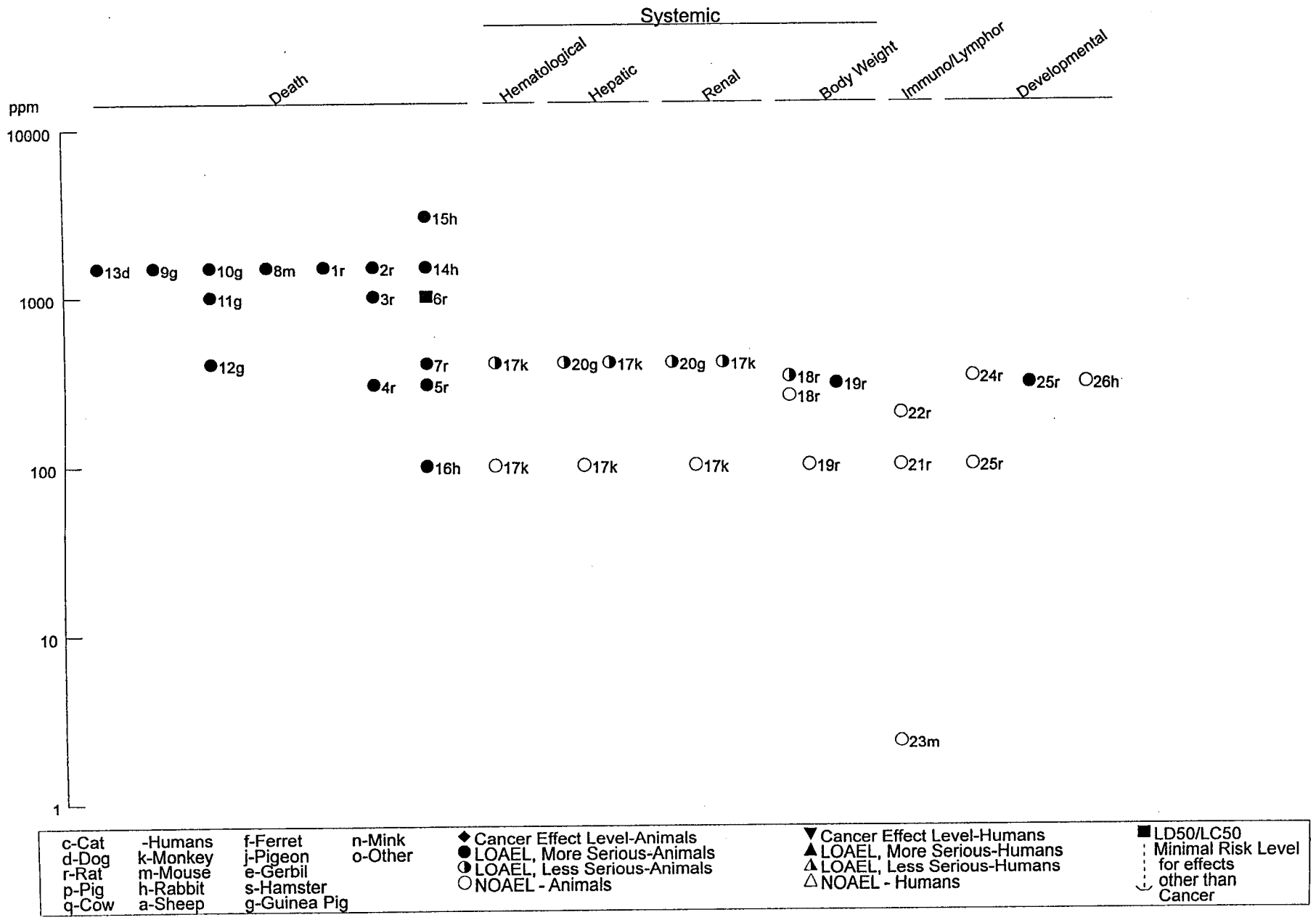


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Intermediate (15-364 days)

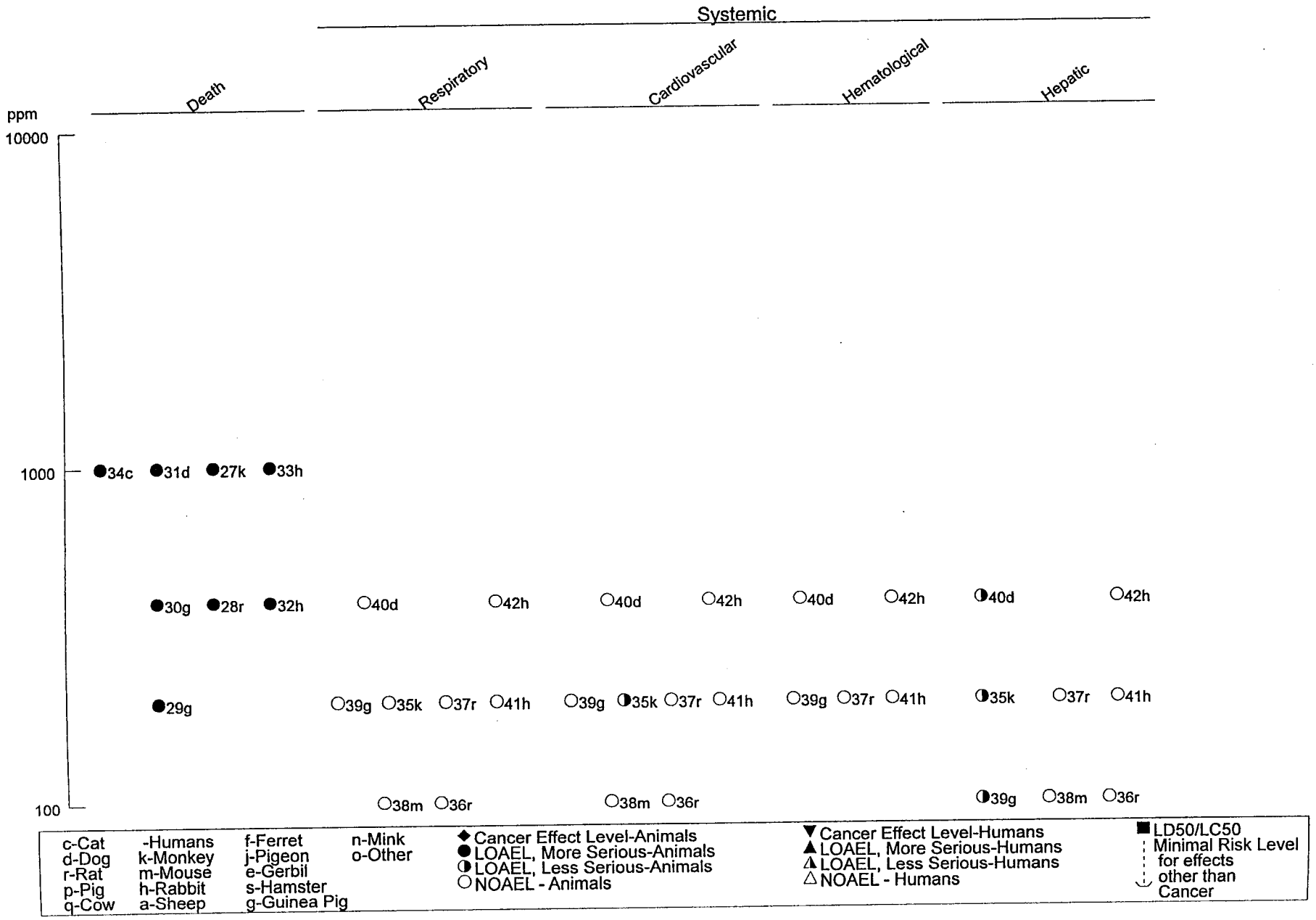


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Intermediate (15-364 days)

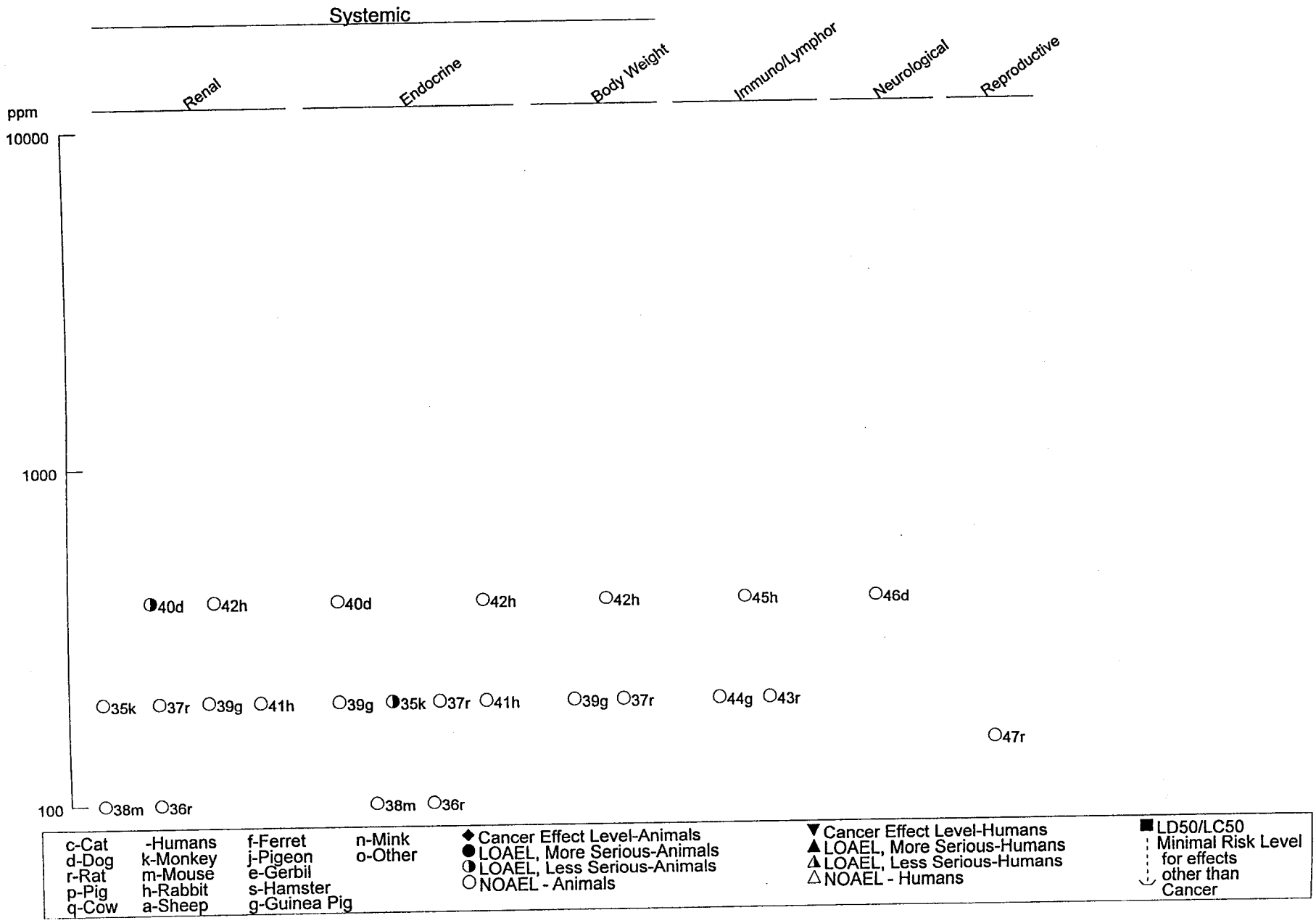
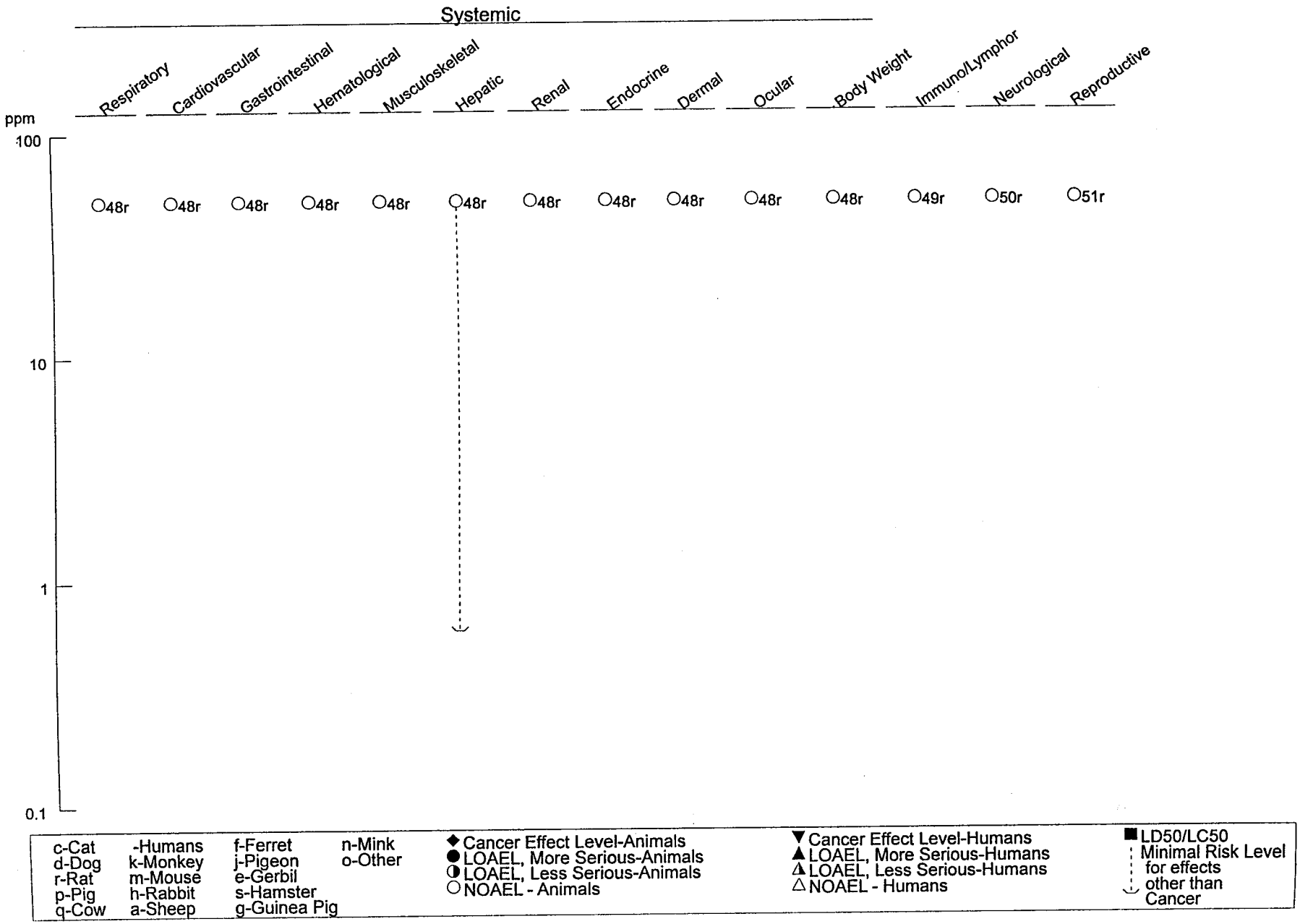


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Chronic (≥365 days)



3.2.1.1 Death

Exposure to concentrated 1,2-dichloroethane vapor can be lethal to humans. A 51-year-old man who inhaled concentrated vapor for only 30 minutes died 5 days later from cardiac arrhythmia (Nouchi et al. 1984). No attempt was made to estimate the actual exposure concentration, although it was described as a "thick vapor of dichloroethane." An autopsy revealed congestion of the lungs, degenerative changes in the myocardium, liver necrosis, renal tubular necrosis, and shrunken nerve cells in the brain.

In animals, acute inhalation exposure to 1,2-dichloroethane in sufficient concentrations also causes death. Heppel et al. (1945, 1946) and Spencer et al. (1951) examined the toxic effects of inhaled 1,2-dichloroethane in a number of species. Acute intermittent exposure (#14 days) resulted in death in rabbits at 100 ppm, in rats and guinea pigs at 400 ppm, and in mice, and dogs at 1,500 ppm. These were the lowest exposure concentrations that produced death in animals. Gross observations at necropsy revealed liver and kidney effects ranging from increased organ weight to necrosis, pulmonary congestion, and fatty infiltration and degeneration of the myocardium (Heppel et al. 1945, 1946; Spencer et al. 1951). An LC_{50} of 1,000 ppm was determined for an 8-hour exposure in rats; shorter exposure durations resulted in higher LC_{50} values (Spencer et al. 1951). Necropsy of these rats revealed histopathological changes in the liver and kidney. High mortality (10/16 died) was seen in rat dams exposed to 300 ppm for 7 hours/day on 9 consecutive days during gestation (Rao et al. 1980; Schlacter et al. 1979).

Intermediate-duration intermittent exposures (6–25 weeks) caused deaths in guinea pigs, rats, and mice exposed to 200 ppm, rats and rabbits exposed to 400 ppm, and dogs, cats, and monkeys exposed to 1,000 ppm (Heppel et al. 1946). Necropsy of these animals showed liver, kidney, heart, and lung effects similar to those observed following acute exposure. In a chronic inhalation study, there was no exposure-related effect on survival in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

The LC_{50} value and LOAEL values from each reliable study for death in each species and duration category are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The systemic effects of 1,2-dichloroethane in humans and animals after inhalation exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for all systemic end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Short-term exposure to concentrated 1,2-dichloroethane in air may produce adverse respiratory effects in humans. In the case study reported by Nouchi et al. (1984), respiratory distress was reported 20 hours after the initial exposure; autopsy revealed that the lungs were severely congested and edematous. Chronic bronchitis and a dry pharynx were reported in a packing plant employee following 5 months of repeated exposures to unreported air concentrations of 1,2-dichloroethane (McNally and Fostvedt 1941), but the authors regarded the symptoms as transitory.

In animals, acute exposure to high concentrations of 1,2-dichloroethane was also associated with pulmonary congestion. A single 7-hour exposure to 3,000 ppm of 1,2-dichloroethane produced death with accompanying pulmonary congestion in mice, rats, rabbits, and guinea pigs (Heppel et al. 1945). Lower concentrations of 1,2-dichloroethane did not produce lung lesions.

No pulmonary lesions were found by histological examination in rats and mice exposed to 100 ppm intermittently for 4–15 weeks, rabbits and monkeys exposed to 200 ppm intermittently for 25 weeks, or dogs exposed to 400 ppm intermittently for 8 months (Heppel et al. 1946). A limited number of rabbits, monkeys, and dogs were exposed, and not all of these animals were histologically examined. Similarly, there were no histopathological changes in the lung following intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs, or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). Chronic intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years caused no histological alterations in respiratory tract of rats (Cheever et al. 1990).

Cardiovascular Effects. Autopsy findings in a 51-year-old man included diffuse degenerative changes of the myocardium such as fragmentation, loss of nuclei of myocardial fibers, and interstitial edema (Nouchi et al. 1984); death was attributed to cardiac arrhythmia. However, since Nouchi et al. (1984) did not report on the medical and behavioral history of the individual, data were insufficient to conclude that these cardiac effects were due exclusively to 1,2-dichloroethane. Blood pressure was within the normal range in two packing plant employees subsequent to repeated occupational exposures

to unreported air concentrations of 1,2-dichloroethane over 2- or 5-month periods (McNally and Fostvedt 1941).

Cardiac lesions have also been reported in animals exposed to 1,2-dichloroethane. Acute lethal concentrations produced myocarditis in rats, dogs, and monkeys (Heppel et al. 1946). Guinea pigs that died following intermittent exposure to $200 ppm for 25 weeks had fatty infiltration and degeneration of the heart (Heppel et al. 1946). Among animals that survived intermediate-duration exposure to 1,2-dichloroethane, cardiac changes were observed only in monkeys. Fat droplets were found in the myocardium of 2 monkeys intermittently exposed to 200 ppm for 25 weeks; no control animals were used (Heppel et al. 1946). No cardiovascular lesions were seen upon gross or microscopic examination in rats and mice intermittently exposed to 100 ppm for 4–15 weeks, in rabbits intermittently exposed to 200 ppm for 25 weeks, or in dogs intermittently exposed to 400 ppm for 8 months (Heppel et al. 1946). However, only two to six rabbits and three dogs per exposure level were tested, and histopathology was conducted on only a few animals. Similarly, there were no histopathological changes in the heart following intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs, or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). In a chronic study, intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years failed to produce cardiovascular lesions in rats (Cheever et al. 1990).

Gastrointestinal Effects. A 51-year-old man who inhaled a thick vapor of 1,2-dichloroethane for 30 minutes vomited periodically immediately following exposure (Nouchi et al. 1984). He died 5 days later. Nausea and vomiting were reported shortly following a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Two packing plant employees who were repeatedly exposed to unreported air concentrations of 1,2-dichloroethane on the job for 2 to 5 months experienced periods of epigastric pain, nausea, and vomiting (McNally and Fostvedt 1941).

In animal studies, gastrointestinal effects, including emesis and passing of red watery stools, preceded death in dogs intermittently exposed to 1,500 ppm of 1,2-dichloroethane for 6 days (Heppel et al. 1945). Congestion of the gastrointestinal tract was noted in these animals at necropsy. Gastrointestinal lesions were not found in rats exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

Hematological Effects. Transient leukocytosis was reported during 5 days subsequent to a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). McNally and Fostvedt (1941)

indicated that hematological parameters (hemoglobin concentration, erythrocyte count, leukocyte count, and differential counts) in packing plant workers were not adversely affected subsequent to repeated occupational exposures to unreported (but potentially occasionally high) air concentrations of 1,2-dichloroethane over 2- or 5-month periods.

Only one study provided any indication of hematological effects in animals. Increased plasma prothrombin clotting time was reported in 2 monkeys exposed to 400 ppm of 1,2-dichloroethane intermittently for 8–12 days (Spencer et al. 1951). This study was limited because only two monkeys were examined and one moribund monkey was killed after eight exposures. Intermediate-duration studies of 1,2-dichloroethane found no hematological changes in rats, guinea pigs, rabbits, or dogs following intermittent exposures to 200–400 ppm for . 32–35 weeks (Heppel et al. 1946; Spencer et al. 1951). Chronic exposure to 50 ppm for 2 years did not produce indications of blood cell changes in rats as detectable by histological examination of the spleen and bone marrow (Cheever et al. 1990); blood parameters were not monitored, limiting the usefulness of the study for assessing hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to 1,2-dichloroethane.

Histological examination of skeletal muscle and skin showed no effects in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

Hepatic Effects. The liver may be a target of 1,2-dichloroethane toxicity following inhalation exposure in humans. Nouchi et al. (1984) found an enlarged liver, high serum levels of lactate and ammonia, and increased serum levels of aspartate amino transferase (AST; also known as glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; also known as glutamic pyruvic transaminase [SGPT]), 2 enzymes routinely used as indicators of liver damage, in a man exposed to concentrated 1,2-dichloroethane vapors for 30 minutes. The man died 5 days after exposure, and postmortem histopathological examination of the liver revealed extensive centrilobular necrosis and the presence of very few vacuolated cells, although it is not known to what degree this condition was pre-existing. Mixed workplace exposure to 1,2-dichloroethane and vinyl chloride (exposure levels ranging up to 5.3 and 23.5 ppm, respectively, by area sampling, and up to 334 and 6.2 ppm, respectively, by personal sampling) was associated with a combined exposure-related increase in the prevalence of abnormal levels of ALT in a group of 251 male workers in a vinyl chloride manufacturing facility (Cheng et al. 1999); the contribution of 1,2-dichloroethane to the observed effect is uncertain.

There are also reports of hepatic effects in animals following acute-duration inhalation exposure to 1,2-dichloroethane. Serum levels of enzymes used as indicators of hepatic damage (e.g., AST, ALT, sorbitol dehydrogenase [SDH]) were significantly elevated in rats exposed to $850 ppm for 4 hours (Brondeau et al. 1983). No effect was seen at 618 ppm. No histopathology was performed in this study to verify the occurrence of damage to the liver, but other studies have reported liver lesions in animals acutely exposed to lower concentrations. Monkeys intermittently exposed to 400 ppm for 8–12 days had marked fatty degeneration of the liver (Spencer et al. 1951). Monkeys exposed to 100 ppm did not show this effect. Slight parenchymatous degradation of the liver was found in guinea pigs exposed to 400 ppm for #14 days (Spencer et al. 1951). This study was limited by the use of a small number of animals.

Longer-term exposure to 1,2-dichloroethane vapor produced hepatic effects in guinea pigs, dogs, and monkeys. Guinea pigs intermittently exposed to 100 ppm of 1,2-dichloroethane for 246 days exhibited increased liver weight and hepatic fatty infiltration (Spencer et al. 1951). Monkeys exposed to 200 ppm for 25 weeks and dogs exposed to 400 ppm for 8 months also exhibited fatty degeneration of the liver (Heppel et al. 1946). However, no hepatic effects were observed upon gross and microscopic examination in mice, rats, or rabbits intermittently exposed to concentrations of 100–400 ppm for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). There were a number of deficiencies in the studies of Heppel et al. (1946) and Spencer et al. (1951); many of the tests used a limited number of animals, and no control monkeys were examined by Heppel et al. (1946).

In the only chronic inhalation study of 1,2-dichloroethane, groups of 50 male and 50 female rats were intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). No histological changes were found in the liver, bile duct, or any other tissues, indicating that the exposure concentration is a NOAEL. Based on the NOAEL of 50 ppm for liver effects, and considering the other evidence for hepatotoxicity of 1,2-dichloroethane following longer-term vapor exposures, a chronic inhalation MRL of 0.6 ppm was calculated as described in the footnote to Table 3-1 and in Appendix A.

Renal Effects. 1,2-Dichloroethane is acutely nephrotoxic in humans following inhalation exposure. In the case study reported by Nouchi et al. (1984), a man who inhaled 1,2-dichloroethane fumes for 30 minutes had hepatic dysfunction and eventually exhibited kidney failure, as part of general organ failure, followed by cardiac arrest and death. Microscopic examination revealed acute tubular necrosis.

Acute-duration inhalation exposure to 1,2-dichloroethane also produced renal effects in animals. Cloudy swelling of the renal tubular epithelium and increased kidney weight were reported in guinea pigs, and

degeneration of the tubular epithelium was reported in monkeys following intermittent exposure to 400 ppm for 8–12 days (Spencer et al. 1951). No renal effects were noted in monkeys exposed to 100 ppm for 8–12 days. These were the only species examined for renal effects following acute exposure, and only a small number of animals was examined in each case.

Kidney lesions have also been reported following longer-term exposure of animals to 1,2-dichloroethane. Dogs intermittently exposed to 400 ppm for 8 months exhibited fatty changes in the kidney (Heppel et al. 1946). In guinea pigs, degeneration of the kidney was observed, but only at lethal concentrations (Heppel et al. 1946). Renal effects were not detected in rats, mice, guinea pigs, or rabbits intermittently exposed to 100–400 ppm of 1,2-dichloroethane for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). In all of these studies, a limited number of animals were exposed, and only a few of those were examined for histopathology. In a chronic study, no histopathological changes developed in the kidneys of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to 1,2-dichloroethane.

Endocrine function has not been evaluated in inhalation toxicity studies in animals. Histological examinations of endocrine system tissues were performed in several studies with essentially negative results, but lack of histopathology does not necessarily indicate that there were no functional endocrinologic changes. Acute intermittent exposure to 1,2-dichloroethane caused congestion of the adrenal cortex in guinea pigs exposed to 1,500 ppm for 4 days (Heppel et al. 1945, 1946), but this exposure was lethal in most animals. An intermediate-duration study noted calcification of the adrenal medulla in 1 of 2 monkeys intermittently exposed to 200 ppm for 25 weeks (Heppel et al. 1946), but the evidence for this effect is inconclusive because only 2 monkeys were studied, no control animals were examined, and adrenal effects have not been reported in other long-term inhalation studies by Heppel et al. (1946) or other investigators. Histopathological examinations failed to detect changes in endocrine tissues following intermittent exposures to 100 ppm for 4 or 15 weeks in rats and mice (Heppel et al. 1946), 200 ppm for .25–35 weeks in rats, guinea pigs, and rabbits (Heppel et al. 1946; Spencer et al. 1951), 200 or 400 ppm for .32–35 weeks in rabbits (Heppel et al. 1946; Spencer et al. 1951), or 400 ppm for 8 months in dogs (Heppel et al. 1946). The histological examinations in these studies were limited to the adrenal gland and/or pancreas.

The only chronic inhalation study of 1,2-dichloroethane found that intermittent exposure to 50 ppm for 2 years induced a slight increase in the incidence of unspecified basophilic focal changes in the pancreas in female rats, but no histological alterations in the adrenal, thyroid, parathyroid, or pituitary glands (Cheever et al. 1990). The toxicological significance of the pancreatic changes is unclear because the incidence was not reported, the effect was induced in only one sex (females), additional exposure levels were not tested, and the study was designed to evaluate carcinogenicity.

The highest NOAEL values and all LOAEL values from each reliable study for endocrine effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to 1,2-dichloroethane.

Histological examinations showed no changes in the skin of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to 1,2-dichloroethane.

Ocular effects reported in animals acutely exposed to 1,2-dichloroethane by inhalation were corneal clouding and lacrimation (Heppel et al. 1945, 1946). These effects probably resulted from direct ocular contact with 1,2-dichloroethane vapor and are discussed in more detail in Section 3.2.3. In a chronic study, rats that were exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years had no histological changes in the eyes (Cheever et al. 1990).

Body Weight Effects. No studies were located regarding effects on body weight in humans after acute inhalation exposure to 1,2-dichloroethane. A weight loss of 10 pounds was reported in a packing plant employee who was repeatedly exposed to unreported, but potentially high, air concentrations of 1,2-dichloroethane for 9 weeks, although the period over which the weight was lost relative to the exposure period was not reported (McNally and Fostvedt 1941).

Adverse changes in body weight (decreased gain or weight loss) occurred in maternal rats that were intermittently exposed to 300 or 329 ppm of 1,2-dichloroethane during gestation, although these effects were not observed at 100 or 254 ppm (Payan et al. 1995; Rao et al. 1987; Schlacter et al. 1979). No

changes in body weight gain were caused by intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs (Spencer et al. 1951), 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951), or 50 ppm for 2 years in rats (Cheever et al. 1990).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1,2-dichloroethane.

Acute intermittent exposure to 1,2-dichloroethane caused chronic splenitis in rats exposed to 1,000 ppm for 14 days (Heppel et al. 1946), but this exposure was lethal in most of the animals tested.

There is evidence that acute exposure to 1,2-dichloroethane affects the ability to fight infection arising from inhaled microbial pathogens in animals. Female mice (4–5 weeks old) exposed to 5.4–10.8 ppm of 1,2-dichloroethane for 3 hours exhibited increased susceptibility to *Streptococcus zooepidemicus* (i.e., increased mortality following infection), suggesting reduced pulmonary defenses in the exposed mice (Sherwood et al. 1987); male mice were not evaluated. No effect was observed at 2.3 ppm. Additionally, female mice that were similarly exposed to 10.8 ppm had reduced bactericidal activity in the lungs 3 hours after exposure to *Klebsiella pneumoniae*. Male rats exposed to #100 ppm for 5 hours/day for 12 days, or to a single 5-hour exposure to #200 ppm, did not exhibit reduced bactericidal activity after *K. pneumoniae* challenge (female rats were not evaluated); mortality following *S. zooepidemicus* challenge was not evaluated in rats. In addition, no effects on lymphocyte function (as indicated by blastogenesis to T- and B-cell mitogens) were seen in rats exposed to #100 ppm 5 hours/day for 12 days. Results reported in Sherwood et al. (1987) suggest that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females. The relevance of the immunological effects in mice to human immunotoxicity is uncertain, since the massive bacterial challenges given to mice in the study are unlikely to be representative of normal immunological challenges in humans. In addition, Sherwood et al. (1987) concluded that the interspecies differences in immunotoxicity observed in the study suggest against extrapolating from animals to humans.

Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane, although histopathological examinations failed to detect lesions in immune system tissues following intermittent exposure to 200 ppm for 212–246 days in rats and guinea pigs (Spencer et

al. 1951), to 400 ppm for 232–248 days in rabbits (Spencer et al. 1951), or to 50 ppm for 2 years in rats (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Inhalation of high concentrations of 1,2-dichloroethane can affect the nervous system of humans. It has been reported that 1,2-dichloroethane is an anesthetic narcotic in humans, and that it is as potent an anesthetic as gasoline, benzene, carbon tetrachloride, and chloroform when inhaled for periods of an hour or more (Garrison and Leadingham 1954). A 51-year-old sailor exposed to a concentrated vapor of 1,2-dichloroethane for 30 minutes suffered central nervous system effects, such as irritability and periodic vomiting, immediately following exposure (Nouchi et al. 1984). Twenty hours later, he was drowsy and became delirious and tremulous; he lapsed into a coma 4 hours later, with a generalized continuous clonic jerk. His electroencephalogram showed slow wave abnormality. He died 5 days after exposure. Upon autopsy, the Purkinje cell layer of his cerebellum showed a shrunken appearance with pyknotic nuclei. Weakness, dizziness, and trembling were reported shortly following a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Two packing plant employees who were repeatedly exposed to unreported air concentrations of 1,2-dichloroethane on the job for 2–5 months reported drowsiness during work hours or sleeplessness, and upon physical examination, they exhibited nervousness, “marked” nystagmus, tremor of the tongue, or sluggish patellar reflex (McNally and Fostvedt 1941).

Acute-duration exposure to concentrated 1,2-dichloroethane also produces neurological effects in animals. Rats experienced central nervous system depression after exposure to $12,000 ppm for 30 minutes (Spencer et al. 1951); the authors did not conclusively attribute apparent neurological effects of inactivity, stupor, and “slowness of response to handling” observed at #3,000 ppm to central nervous system depression. Exposure to 20,000 ppm for 15 minutes resulted in central nervous system depression sufficient to cause death; no histopathology was conducted on the brain or peripheral nerves. Uncertain gait, narcosis, prostration, or unconsciousness were seen in rats, guinea pigs, and rabbits exposed once to 3,000 ppm for 7 hours, but were not reported at 1,500 ppm; 7-hour exposures to 1,500 ppm on 5 consecutive days induced transitory tremors, convulsions, or coma in rats and dogs (Heppel et al. 1945).

Longer-term exposure to lower concentrations of 1,2-dichloroethane did not appear to produce neurological effects, although sensitive indicators of subtle neurological effects were not examined. Negative results were obtained by physical examination (without histopathology) of dogs intermittently exposed to 400 ppm for 8 months (Heppel et al. 1946) and by histopathological examination of the brain from rats intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). The highest NOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Studies regarding reproductive effects in humans after inhalation exposure to 1,2-dichloroethane are limited to a single account of increased rates of premature births in female workers and in wives of male workers who were exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). Concentrations of 1,2-dichloroethane ranged from 0.4 to 384 ppm at two locations. Female subjects were exposed throughout pregnancy, and male workers were exposed for at least 1 year before their wives became pregnant. These results should be treated with caution because the study evaluated a small number of subjects (44 male and 54 female exposed workers), the authors indicated that co-exposure to other chemicals occurred in most cases, and the study was generally deficient in reporting the study design including accounting for possible confounding environmental and behavioral factors.

Some studies in rodents (Vozovaya 1974, 1977; Zhao et al. 1989) found that inhalation exposure to 1,2-dichloroethane either prior to mating and continuing into gestation or throughout gestation caused pre-implantation loss and embryolethality, although the reliability of these studies is unclear because of deficiencies in reporting study design and results. Pre-implantation loss was reportedly increased (31.0% compared to 10.2% in controls, $p<0.05$) in unspecified rodents that were exposed to 51.9 ppm “during the entire pregnancy period”; one account of the study indicated that a 2-week pre-mating exposure also occurred (Zhao et al. 1997), although this could not be corroborated from the original study (Zhao et al. 1989). Intermittent exposure of rats to 4.7±7 ppm for 4 months prior to the mating period, followed by inhalation exposure during pregnancy, produced a statistically significant ($p<0.01$) increase in embryo mortality (Vozovaya 1977). Fertility was decreased, and stillbirths and perinatal mortality were increased in the first generation of a two-generation reproduction study in rats that were intermittently exposed to 14 ppm of 1,2-dichloroethane over a period of 6 months (Vozovaya 1974). In contrast to the studies summarized above, a well-designed study by Rao et al. (1980) showed no adverse effects on the fertility, gestation, or survival in pups of male and female rats intermittently exposed to #150 ppm for 60 days pre-

mating, then throughout mating, gestation, and lactation (excluding gestation day 21 through postpartum day 4). No gross or histopathological lesions were observed in reproductive organs of rats exposed to 50 ppm intermittently for 2 years (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,2-dichloroethane.

The overall evidence from inhalation studies in rats and rabbits indicates that 1,2-dichloroethane is not a developmental toxicant. 1,2-Dichloroethane was not fetotoxic or teratogenic in the offspring of rats that were intermittently exposed to 100 ppm on days 6–15 of gestation (Rao et al. 1980; Schlacter et al. 1979). Exposure to 300 ppm produced high maternal mortality with fetolethality, and one rat had a total resorption of the litter. Another study similarly found that exposure to 1,2-dichloroethane during gestation days 6–20 was not fetotoxic or teratogenic to rats at concentrations as high as those producing maternal toxicity (329 ppm) (Payan et al. 1995). There were no exposure-related changes in numbers of implantations, resorptions, and live fetuses, fetal sex ratio or body weights, or external, visceral, or skeletal development, although maternal body weight gain was 24% reduced at 329 ppm; no maternal effects occurred at lower concentrations (150–254 ppm). Developmental toxicity was reported in one study in rats, but the reliability of the data is unclear (Vozovaya 1977). Exposure to 4.7±7 ppm of 1,2-dichloroethane for 4 months before mating followed by exposure during pregnancy was embryotoxic and caused hematomas in the head and neck region and anterior extremities of the fetuses. The reliability of the Vozovaya (1977) data cannot be assessed due to lack of statistical analysis and uncertainties in the reported results. Zhao (1984) reported no developmental changes in F1 and F2 generations of mice after the parental dams were exposed by inhalation for 4 hours per day to up to 62.5 ppm on gestation days 6–15, or to 250 ppm on gestation days 9 and 10. The F1 generation was not postnatally exposed to 1,2-dichloroethane. No changes were observed in the following parameters: fetal survival, length, or weight; external, skeletal, or visceral appearance; pup survival; onset of pup physical changes and reflex acquisition; or pup weight gain. In spite of reporting deficiencies leading to critical uncertainties in the adequacy of the study design, the results are suggestive that 1,2-dichloroethane is not developmentally toxic in mice under reported study conditions.

Rabbits that were intermittently exposed to 100 or 300 ppm of 1,2-dichloroethane on days 6–18 of gestation experienced some maternal deaths, but there were no chemical-related fetotoxic or teratogenic effects as indicated by pregnancy and resorption incidences, litter size, fetal body measurements, and soft-tissue and skeletal examinations (Rao et al. 1980).

The highest NOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

Specific evidence associating inhalation exposure to 1,2-dichloroethane with the occurrence of cancer in humans was not found in the literature reviewed. Several epidemiological studies have been conducted on workers in the chemical industry to investigate the high incidence of brain tumors observed among workers employed in petrochemical plants (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), the incidence of stomach cancer and leukemia at a plant that used 1,2-dichloroethane in the production of ethylene oxide (Hogstedt et al. 1979), and the increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers in a cohort of workers in chlorohydrin production plants where 1,2-dichloroethane was a production byproduct (Benson and Teta 1993). Increased risk of primary breast cancer (odds ratio [OR]=2.2; 95% confidence interval [CI]=1.4–3.6; no latency) was observed in Danish men who were occupationally exposed to unreported levels of gasoline and combustion products containing 1,2-dichloroethane, compared to workers who were not exposed (according to job type and trade code) (Hansen 2000). The OR increased to 2.5 (95% CI=1.3–4.5) among workers with a latency of >10 years (Hansen 2000). Male residents in areas near a municipal solid waste site in Montreal, Quebec, which emitted airborne 1,2-dichloroethane (among a number of other volatile substances) showed increased risk of stomach cancers (relative risk [RR]=1.3; 95% CI=1.0–1.5), liver and intrahepatic bile duct cancers (RR=1.3; 95% CI=0.9–1.8), and cancers of the trachea, bronchus, and lung (RR=1.1; 95% CI=1.0–1.2) (Goldberg et al. 1995). Female residents showed increased risk of stomach cancer (RR=1.2; 95% CI=0.9–1.5) and cervix uteri cancer (RR=1.2; 95% CI=1.0–1.5). None of these epidemiology studies dealt with 1,2-dichloroethane exposure exclusively, and the concurrent exposure to other chemicals or solvents confounded the results. None of these studies could specifically link chemical exposure with the excess cancer incidence.

The carcinogenicity of inhaled 1,2-dichloroethane has been evaluated in chronic experiments in both rats and mice. Maltoni et al. (1980) exposed Sprague-Dawley rats and Swiss mice to 1,2-dichloroethane at

concentrations of #250 ppm 7 hours/day, 5 days/week, for 78 weeks; no treatment-related increase in the incidence of tumors was observed in treated rats or mice. However, this study is limited for a number of reasons. Chemical administration and study duration were less than lifetime. Furthermore, the maximum tolerated dose was exceeded at the highest dose tested (250 ppm), and survival in mice was poor. Therefore, only a small number of surviving animals were at risk for late-developing tumors. The plausible explanations for the negative results obtained in this study may include the differences in the metabolic pathways and the amount of toxic metabolites reaching the target tissues (see Section 3.5.1). A chronic study in which rats were exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years also failed to find carcinogenic effects (Cheever et al. 1990). However, this study was limited by the use of a single dose level that may have been considerably lower than the maximum tolerated dose (MTD) (the relatively low exposure concentration of 50 ppm was chosen because it was the U.S. occupational standard at the time the experiment was initiated). An abstract reported that inhalation exposure to 1,2-dichloroethane at unreported levels for 6 hours/day, 5 days/week, for 2 years induced mammary gland fibroadenomas and subcutis fibromas in both sexes of F344 rats, mammary gland adenocarcinomas/ adenomas in female rats, peritoneal mesotheliomas in male rats, hepatic hemangiosarcomas in male BDF1 mice, and bronchio-alveolar carcinomas/adenomas, mammary gland adenocarcinomas, and uterine endometrial stromal polyps in female mice (Matsushima et al. 1998). The full study report was not located and, thus, adequacy of the study design and conduct could not be evaluated.

3.2.2 Oral Exposure

Information concerning the toxic effects of ingested 1,2-dichloroethane in humans was derived primarily from case reports of individuals who accidentally or intentionally ingested 1,2-dichloroethane. Only crude estimates of ingested dose were available, limiting the value of the data. The available information indicates that 1,2-dichloroethane can cause death from cardiac arrhythmia after a sufficient single oral dose (Garrison and Leadingham 1954; Hueper and Smith 1935; Martin et al. 1969; Schönborn et al. 1970). Other symptoms reported include bronchitis, hemorrhagic gastritis and colitis, hepatocellular damage, renal tubular necrosis and calcification, central nervous system depression, and histological changes in brain tissue (Hueper and Smith 1935; Lochhead and Close 1951; Przezdziak and Bakula 1975; Yodaiken and Babcock 1973). No studies were located regarding immunological, reproductive, or developmental effects in humans following oral exposure to 1,2-dichloroethane.

The toxicity of ingested 1,2-dichloroethane has been well studied in animals. Targets of 1,2-dichloro-ethane toxicity in orally exposed animals included the immune system, central nervous system, liver, and

kidney. 1,2-Dichloroethane also produced genotoxic effects (see Section 3.3) and carcinogenic effects in animals exposed by this route.

Table 3-2 and Figure 3-2 describe the health effects observed in laboratory animals associated with oral exposure levels at varying time and exposure durations.

3.2.2.1 Death

Ingestion of large amounts of 1,2-dichloroethane may be lethal to humans. Hueper and Smith (1935) reported a case in which a 63-year-old man accidentally swallowed approximately 2 ounces (60 mL) of 1,2-dichloroethane and died 22 hours later of circulatory failure. A 50-year-old man mistakenly ingested approximately 30 mL of 1,2-dichloroethane and died after 10 hours (Lochhead and Close 1951). A 14-year-old boy died 5 days after ingesting 15 mL of 1,2-dichloroethane (Yodaiken and Babcock 1973). A 30-year-old man ingested approximately 40 mL of 1,2-dichloroethane and died 28 hours later (Garrison and Leadingham 1954). Another man who drank 50 mL of 1,2-dichloroethane died 22 hours later of circulatory failure (Hueper and Smith 1935). Schönborn et al. (1970) reported a case of an 18-year-old man who became drowsy and cyanotic, and exhibited bradycardia after drinking approximately 50 mL of Marament (a pharmaceutical formulation), which was equivalent to 50 g of 1,2-dichloroethane (714 mg/kg, assuming 70 kg body weight); he died 17 hours later in a state of circulatory shock. A hospital patient accidentally ingested a "small" quantity of 1,2-dichloroethane and died 18 hours later after intensive supportive measures were taken; the immediate cause of death was not reported (Hubbs and Prusmack 1955). In two other cases of 1,2-dichloroethane poisoning, the patients drank 15–20 mL Marament; they suffered gastrointestinal disorders and were discharged from the hospital in a few days (Schönborn et al. 1970). These patients received prophylactic heparinization 3–4 days before the appearance of blood coagulation disorders. Only crude estimates of ingested dose were available, limiting the value of the data.

Death has also occurred in animals following oral exposure to 1,2-dichloroethane. An acute oral LD_{50} value of 680 mg/kg has been reported for rats (McCollister et al. 1956); treatment was by gavage, but the dosage levels tested and the time of death after administration were not reported. Daily gavage doses of 300 mg/kg for 10–14 days caused 80–100% mortality in rats (Daniel et al. 1994; van Esch et al. 1977). Munson et al. (1982) used log probability analysis to determine LD_{50} values of 489 and 413 mg/kg for male and female mice, respectively; the mice died over a 48-hour period following gavage.

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	once				714 (death)	Schonborn et al. 1970
2	Rat (Sprague-Dawley)	10 d 1x/d (GO)				300 M (death in 8/10 F and 10/10 M)	Daniel et al. 1994
3	Rat (albino)	1 d (G)				680 (LD_{50})	McCollister et al. 1956
4	Rat (F344/N)	3 d 1x/d (GO)				480 M (10/10 died)	NTP 1991a
5	Rat (Wistar)	14 d 5d/wk 1x/d (GO)				300 (6/6 died)	van Esch et al. 1977
6	Mouse (CD-1)	1 d (G)				413[b] F (LD_{50})	Munson et al. 1982
						489 M (LD_{50})	
	Systemic						
7	Human	once	Resp			570 (congestion and edema)	Martin et al. 1969
			Cardio			570 (cardiac arrest)	
			Gastro			570 (gastrointestinal hemorrhage)	
			Hemato			570 (incoagulable blood)	
			Hepatic			570 (severe atrophy of liver)	

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Human	once	Cardio			714 (decreased coagulation factors, circulatory shock, bradycardia)	Schonborn et al. 1970
			Gastro			714 (necrosis and hemorrhagic enteritis)	
			Hemato			714 (decreased coagulation factors)	
			Hepatic			714 (necrosis)	
			Renal			714 (bleeding; hyperemia)	
9	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Resp	100		300 (gross pathologic changes in lungs of rats that died)	Daniel et al. 1994
			Cardio	100			
			Gastro	30	100 (minimal inflammatory changes in forestomach)		
			Hemato	100			
			Musc/skel	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Dermal	100			
			Bd Wt	100			
10	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)	Bd Wt	158 F	198 F (30% decreased maternal body weight gain)		Payan et al. 1995

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
11	Rat (Wistar)	14 d 5d/wk 1x/d (GO)	Resp	100			van Esch et al. 1977
			Hemato	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Bd Wt	100			
12	Mouse (CD-1)	14 d 1x/d (G)	Resp	49			Munson et al. 1982
			Hemato	4.9	49	(decreased leukocytes)	
			Hepatic	49			
			Renal	49			
	Immunological/Lymphoreticular						
13	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994
	Neurological						
14	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994
15	Rat (Sprague-Dawley)	once (G)		170			Kanada et al. 1994
	Reproductive						
16	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
17	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)		158		198 F (increased resorptions and nonsurviving implants, decreased maternal body weight gain)	Payan et al. 1995
	Developmental						
18	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)		158		198 F (increased resorptions and nonsurviving implants, decreased maternal body weight gain)	Payan et al. 1995
19	Mouse (CD-1)	7 d Gd 7-14 ad lib (W)		510			Kavlock et al. 1979

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
20	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)				240 (10/10 died)	NTP 1991a
21	Mouse (B6C3F1)	6 wk 5d/wk 1x/d (GO)				398[b] M (5/5 died) 631 F (5/5 died)	NCI 1978
22	Mouse (B6C3F1)	13 wk (W)				4926 (9/10 died)	NTP 1991a
	Systemic						
23	Rat (NS)	5-7 wk 2x/d (F)	Hepatic	66	176 (increased liver total fat and triglycerides)		Alumot et al. 1976

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
24	Rat (Sprague-Dawley)	90 d 1x/d (GO)	Resp	150			Daniel et al. 1994
			Cardio	150			
			Gastro	150			
			Hemato	150			
			Musc/skel	150			
			Hepatic	150			
			Renal	150			
			Endocr	150			
			Dermal	150			
			Ocular	150			
			Bd Wt	75	150 (17% reduced body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
25	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)	Resp	492			NTP 1991a
			Cardio	492			
			Gastro	492			
			Hemato	492			
			Musc/skel	492			
			Hepatic	492			
			Renal		58[c] (increased absolute and relative kidney weights with renal tubular regeneration at higher doses)		
			Endocr	492			
			Dermal	492			
			Ocular	492			
			Bd Wt	147	259 (10% decreased body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)	Resp	480			NTP 1991a
			Cardio	480			
			Gastro	120	240 (forestomach hyperplasia and inflammation)		
			Hemato	240			
			Musc/skel	480			
			Hepatic	480			
			Renal	480			
			Endocr	480			
			Dermal	480			
			Ocular	480			
			Bd Wt	480			
27	Rat (Wistar)	90 d 5d/wk 1x/d (GO)	Resp	90			van Esch et al. 1977
			Cardio	90			
			Gastro	90			
			Hemato	90			
			Musc/skel	90			
			Hepatic	90			
			Renal	90			
			Endocr	90			
			Bd Wt	30	90 M (22% decreased body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
28	Mouse (CD-1)	90 d ad lib (W)	Resp	189					Munson et al. 1982
			Hemato	189					
			Hepatic	189					
			Renal	189					
29	Mouse (B6C3F1)	13 wk (W)	Resp	4207					NTP 1991a
			Cardio	4207					
			Gastro	4207					
			Hemato	4207					
			Musc/skel	4207					
			Hepatic	4207					
			Renal		249	(tubular regeneration)	4207	(karyomegaly, mineralization, tubular dilation, protein casts)	
			Endocr	4207					
			Dermal	4207					
			Ocular	4207					
			Bd Wt	2710	4207	(10% decreased body weight gain)			
	Immunological/Lymphoreticular								
30	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150					Daniel et al. 1994
31	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		120	240	(thymic necrosis in rats that were moribund or died)			NTP 1991a

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
32	Rat	13 wk (W)		492				NTP 1991a
33	Mouse (CD-1)	90 d ad lib (W)		189				Munson et al. 1982
34	Mouse (B6C3F1)	13 wk (W)		4207				NTP 1991a
	Neurological							
35	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150				Daniel et al. 1994
36	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		120		240	(tremors and necrosis in cerebellum in rats that died)	NTP 1991a
37	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)		492				NTP 1991a
38	Rat (Wistar)	90 d 5d/wk 1x/d (GO)		90				van Esch et al. 1977

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Mouse (B6C3F1)	13 wk (W)		4207			NTP 1991a
	Reproductive						
40	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150			Daniel et al. 1994
41	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		480			NTP 1991a
42	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)		492			NTP 1991a
43	Rat (Wistar)	90 d 5d/wk 1x/d (GO)		90			van Esch et al. 1977
44	Mouse (ICR Swiss)	49 wk 2 gen ad lib (W)		50			Lane et al. 1982
45	Mouse (ICR Swiss)	24 wk F/1B gen ad lib (W)		50			Lane et al. 1982

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Mouse (B6C3F1)	13 wk (W)		4207			NTP 1991a
	Developmental						
47	Mouse (ICR Swiss)	18 d ad lib (W)		50			Lane et al. 1982
	Cancer						
48	Mouse Eu-pim-1 transgenic	40 wk 7d/wk 1x/d (GO)				141 F (CEL-malignant lymphoma in 33% of predisposed strain of mice)	Storer et al. 1995

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
49	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)				95 (42/50 (84%) died)	NCI 1978
50	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)				299 (36/50 (72%) died)	NCI 1978
	Systemic						
51	Rat (NS)	2 yr 2x/d (F)	Hepatic	42.5			Alumot et al. 1976
			Renal	42.5			
52	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)	Resp	95			NCI 1978
			Cardio	95			
			Gastro		47 F (forestomach acanthosis and hyperkeratosis)		
			Hepatic	95			
			Renal	95			
			Endocr	95			
			Bd Wt	95			

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
53	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)	Resp	299 F			NCI 1978
			Cardio	299 F			
			Gastro	299 F			
			Hepatic	299 F			
			Renal	299 F			
			Endocr	299 F			
			Bd Wt	149 F	299 F (30% reduced body weight gain in mice that had tumors and high mortality)		
	Immunological/Lymphoreticular						
54	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95			NCI 1978
55	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		299 F			NCI 1978
	Neurological						
56	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95			NCI 1978

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
57	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		299 F				NCI 1978
	Reproductive							
58	Rat (NS)	2 yr 2x/d (F)		42.5				Alumot et al. 1976
59	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95				NCI 1978
60	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		195 M 299 F				NCI 1978
	Cancer							
61	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)					47 (CEL-hemangiosarcoma of the spleen, liver, adrenal gland, pancreas, and other organs)	NCI 1978

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
62	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)				149 F	(CEL-pulmonary adenoma, mammary gland adenocarcinomas, and combined endometrial polyps and sarcomas)	NCI 1978

[a]The number corresponds to entries in Figure 3-2.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive an intermediate oral minimal risk level (MRL) of 0.2 mg/kg-day; dose divided by an uncertainty factor of 300 (10 for interspecies extrapolation, 3 for use of minimal LOAEL, and 10 for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = feed; Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; gen = generation; (GO) = gavage in oil; Hemato = hematological; kg = kilogram; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Acute (≤14 days)

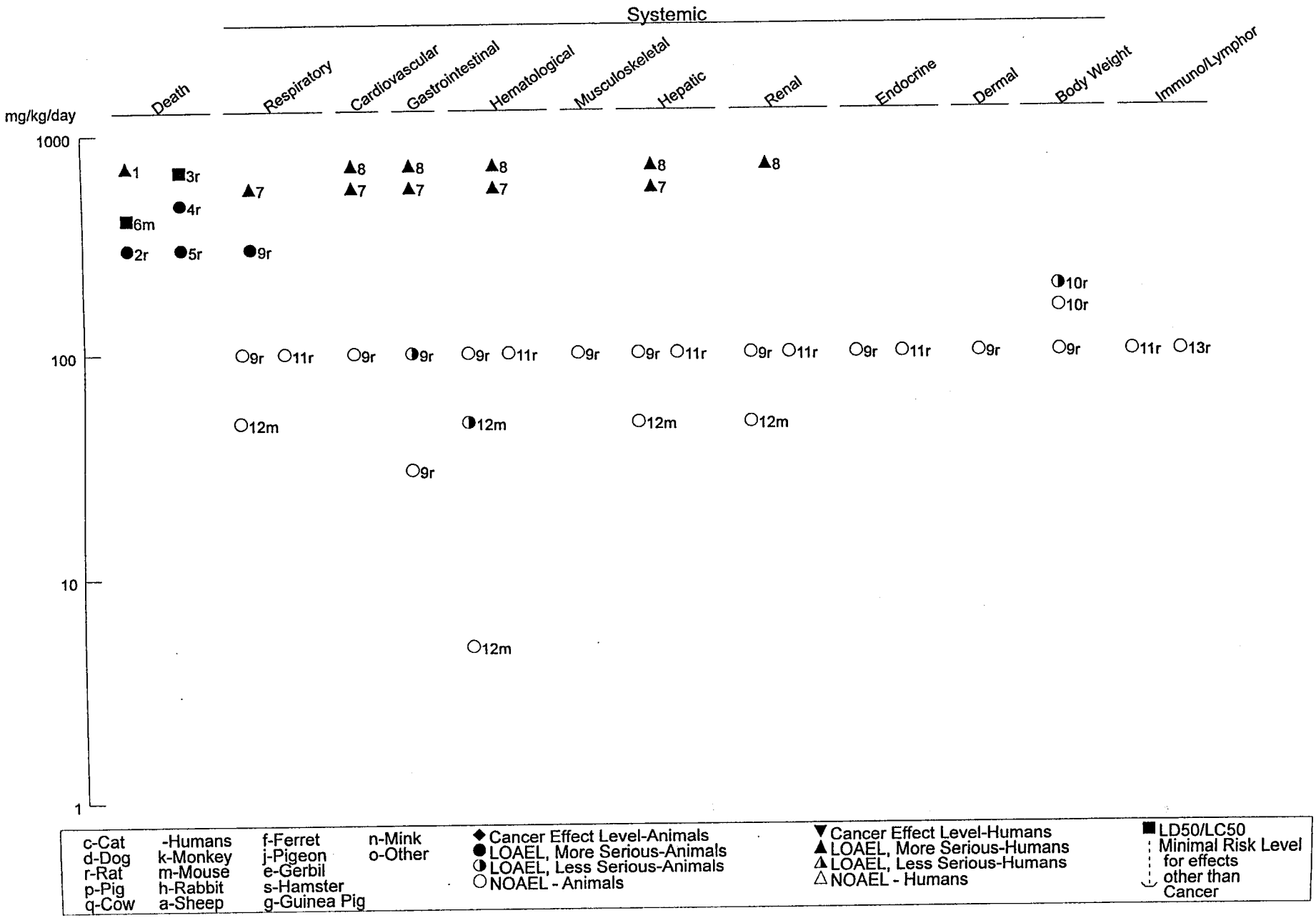


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Acute (≤14 days)

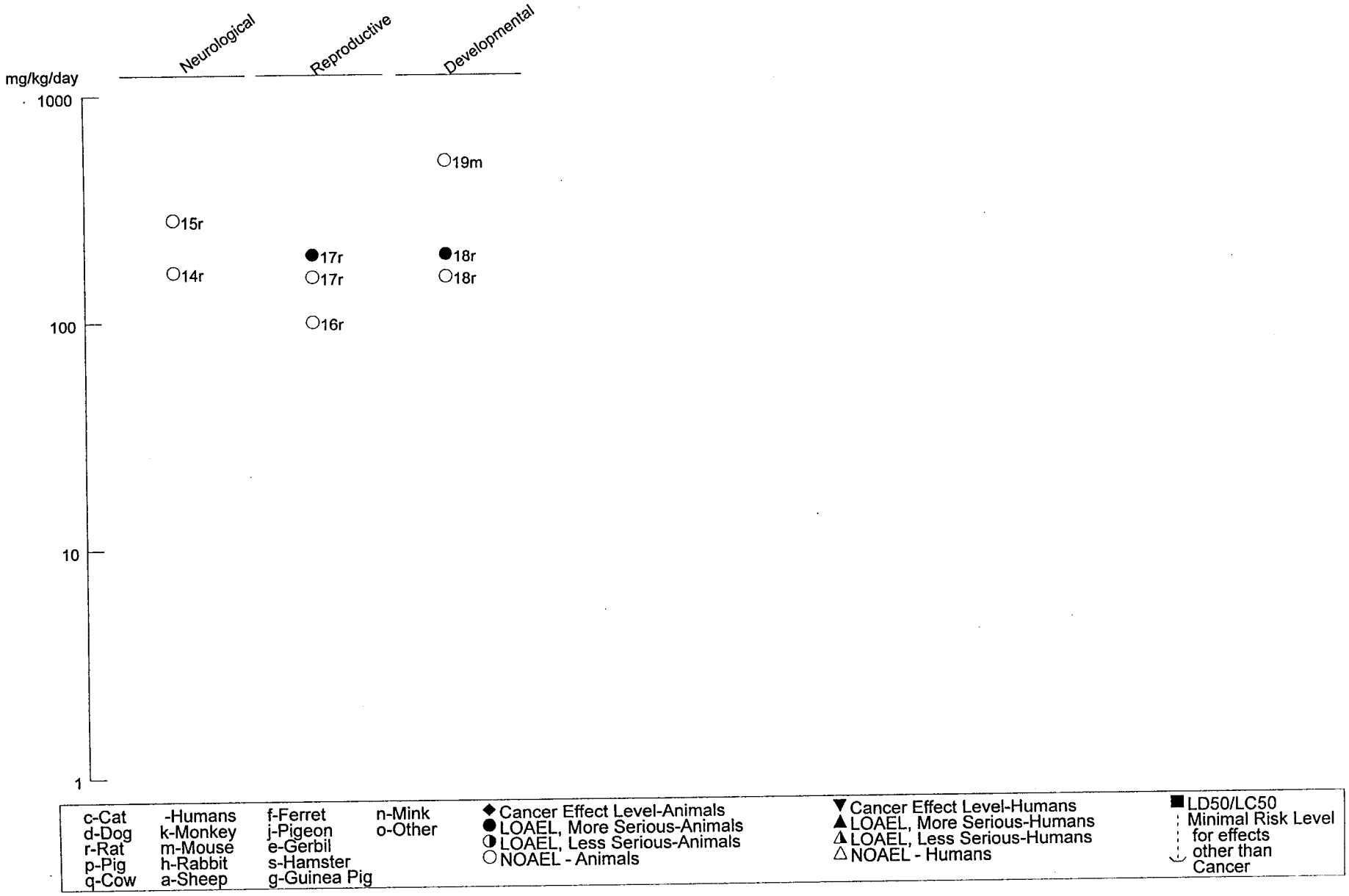


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Intermediate (15-364 days)

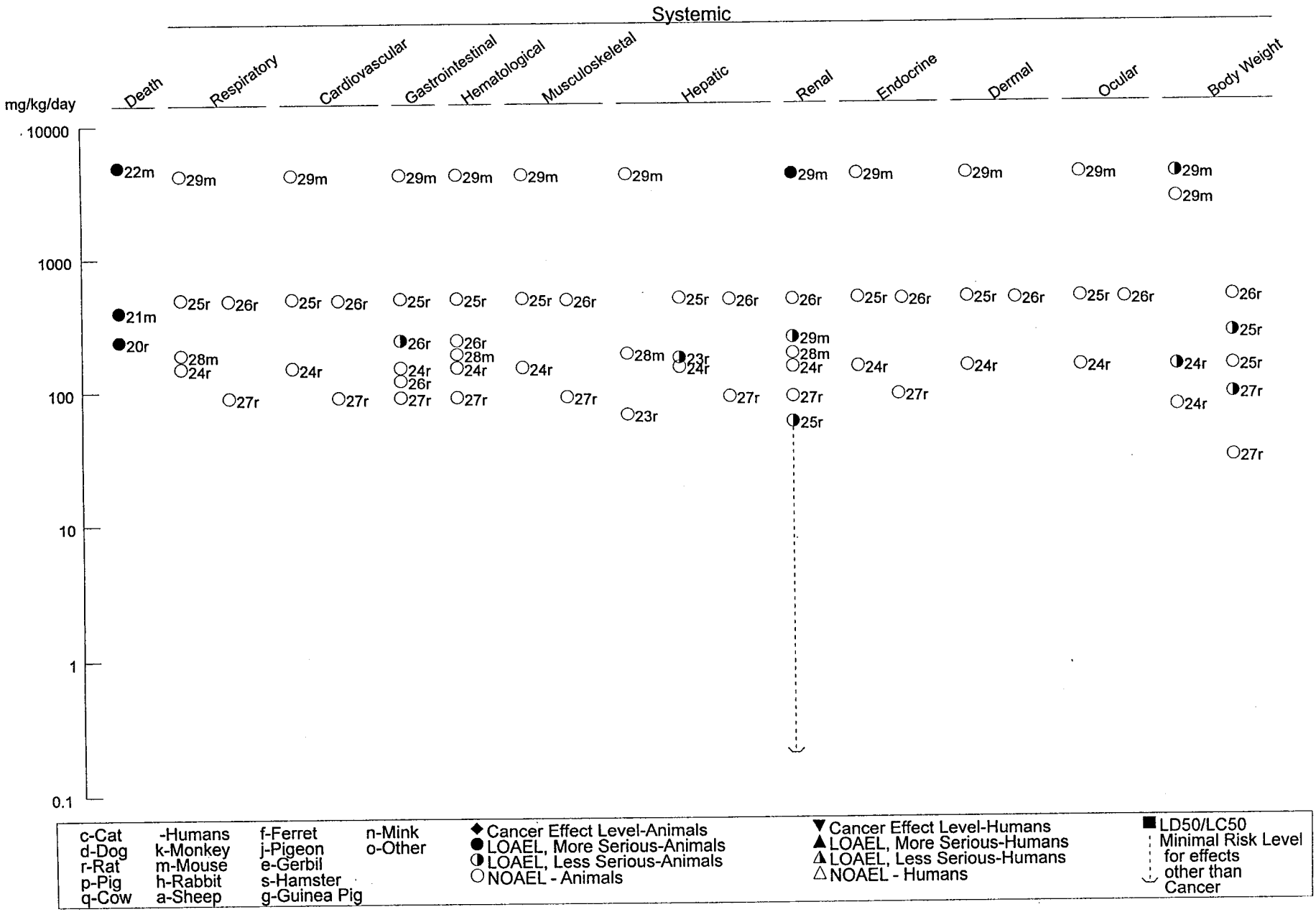
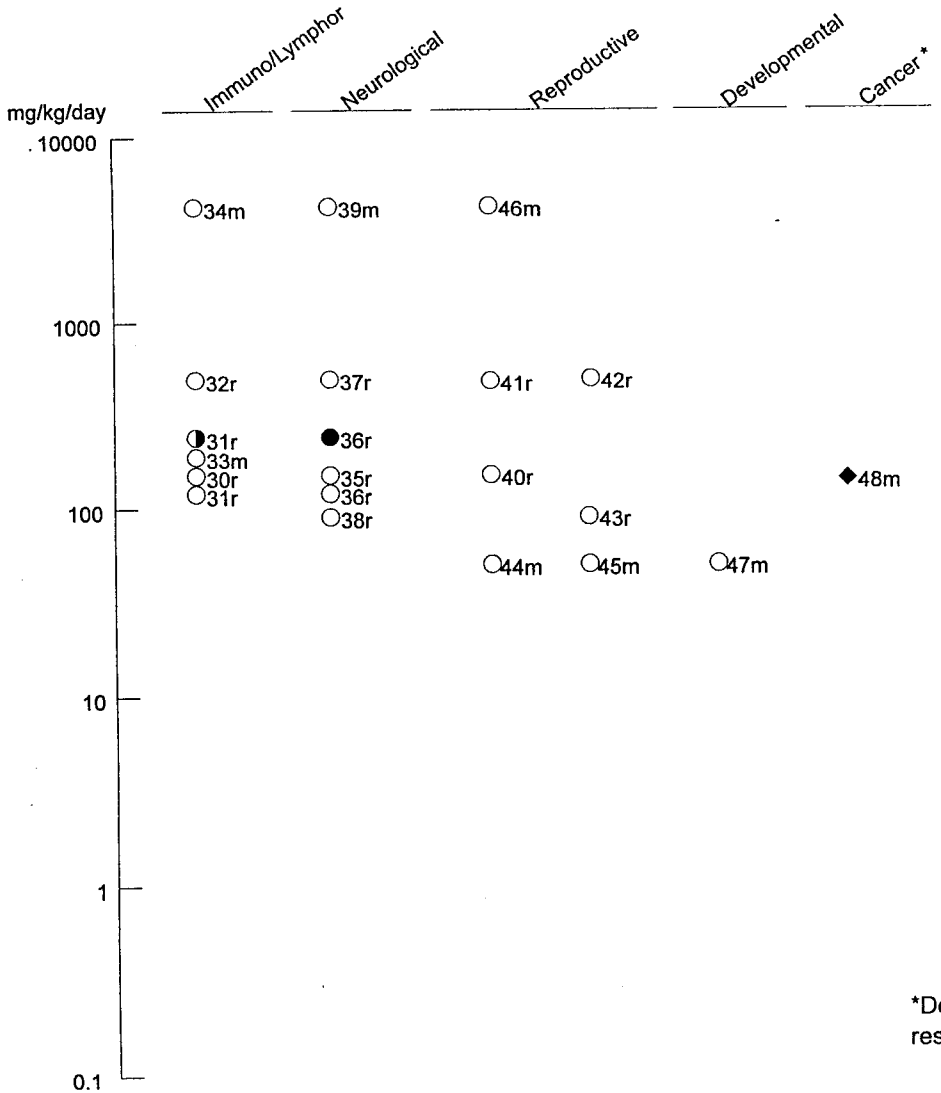


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

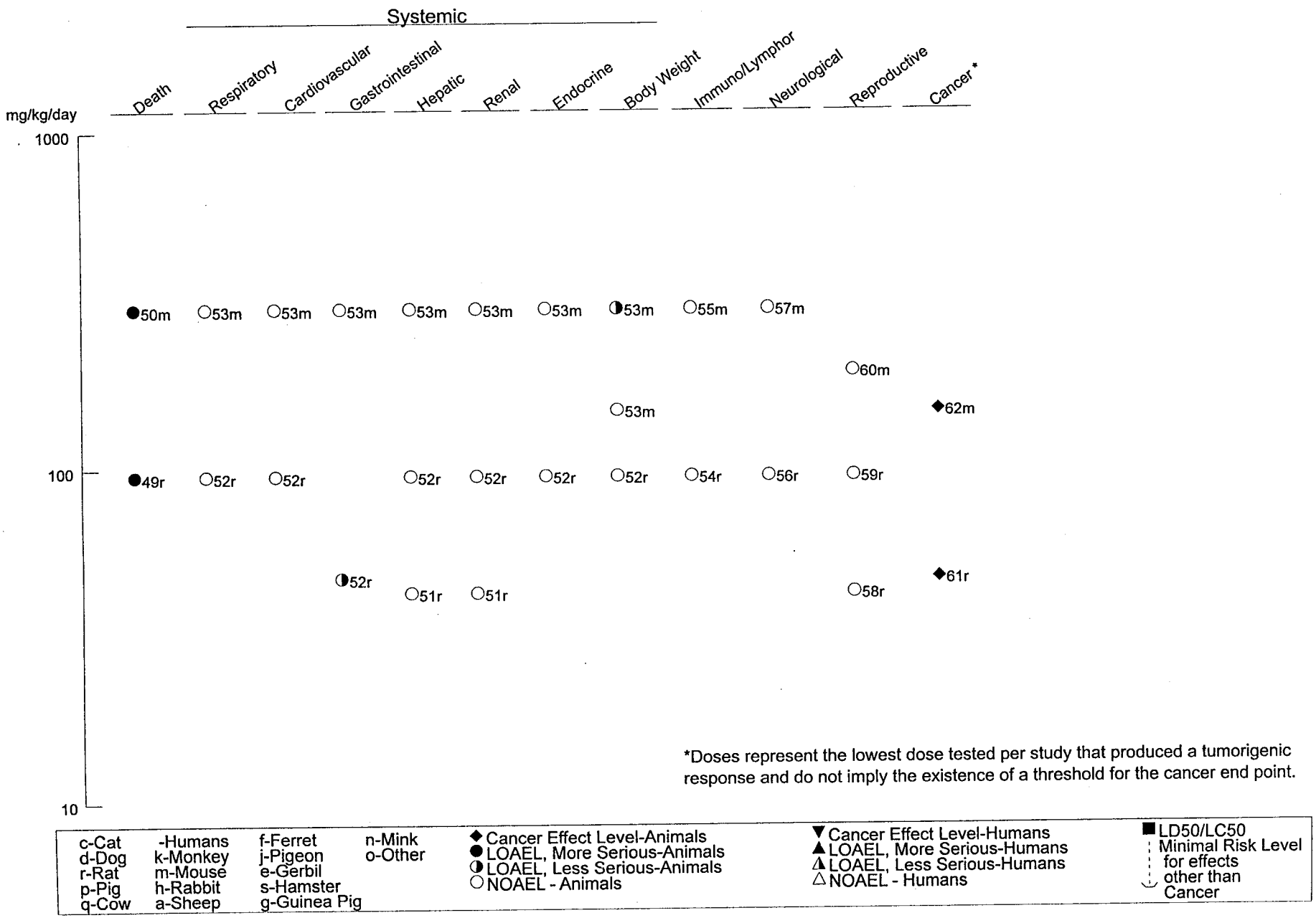
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

Intermediate-duration studies in animals indicate that the lethality of 1,2-dichloroethane is much higher by gavage than by ingestion in drinking water. Complete mortality occurred at 398 mg/kg/day in male mice and at 631 mg/kg/day in female mice exposed to 1,2-dichloroethane by gavage for 6 weeks (NCI 1978). Similarly, in rats exposed by gavage for 6 or 13 weeks, doses $240 mg/kg/day caused deaths in all animals (NTP 1991a). However, much higher dose levels were required to produce death following drinking water exposure. No deaths occurred among rats exposed to doses #727 mg/kg/day in the drinking water for 13 weeks (NTP 1991a). Mice that were exposed to 1,2-dichloroethane in drinking water for 13 weeks experienced mortality only at the high dose of 4,930 mg/kg/day (NTP 1991a). The mortality in the NTP (1991a) drinking water studies began to increase during the first 2 weeks of exposure and approached or reached 100% after 13 weeks (NTP 1991a). In the 13-week gavage study, 240 and 480 mg/kg/day produced 100% mortality in male rats within 13 weeks and 3 days, respectively (NTP 1991a).

Chronic exposure to 1,2-dichloroethane by gavage caused reduced survival in rats and mice. Treatment with 95 mg/kg/day for 78 weeks caused 84% mortality in rats (NCI 1978). The mortality was seen as early as week 2 and became substantial after 15 weeks. The data suggest that the dose levels tested might be lethal to rats under both acute and chronic conditions. In mice, 72% mortality occurred in females exposed to 299 mg/kg/day by gavage for 78 weeks; mortality became evident after . 10 weeks (NCI 1978).

The LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The systemic effects of 1,2-dichloroethane in humans and animals after oral exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. The respiratory effects exhibited by individuals who died following acute oral exposure to 1,2-dichloroethane include congestion, pulmonary edema (at 570 mg/kg/day), dyspnea, and bronchitis (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Yodaiken and Babcock 1973). The pulmonary edema reported in the case report by Yodaiken and Babcock (1973) may have been chemical pneumonitis due to aspiration of 1,2-dichloroethane.

The literature reviewed provided no evidence that 1,2-dichloroethane induces adverse effects on the respiratory system following acute, intermediate, or chronic oral exposure in animals. Gross and histological examinations showed no effects in the respiratory tract following gavage exposure in rats treated with #100 mg/kg/day for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), rats treated with #480 mg/kg/day for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or rats and mice treated with #95 and #299 mg/kg/day, respectively, for #78 weeks (NCI 1978). Similarly, no histopathological changes in the respiratory tract were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of #492 and #4,210 mg/kg/day, respectively, for #90 days (NTP 1991a). The histological examinations performed by NTP (1991a) were more complete than in the other studies because they included the nasal cavity and turbinates in addition to the lungs and bronchi. Other studies in mice found no changes in lung weight or gross appearance following exposure to #49 mg/kg/day by gavage for 14 days or #189 mg/kg/day in drinking water for #90 days (Munson et al. 1982), but these results are limited by lack of histological examinations.

Cardiovascular Effects. Clinical investigation of patients who died following acute ingestion of 1,2-dichloroethane determined that cardiovascular insufficiency and hemorrhage were major factors contributing to death (Garrison and Leadingham 1954; Hueper and Smith 1935; Martin et al. 1969; Schönborn et al. 1970). Numerous surficial petechial hemorrhages of the heart were observed at autopsy in a man who died from ingesting a “small” quantity of 1,2-dichloroethane (Hubbs and Prusmack 1955).

Cardiovascular histopathological effects were not found in animals orally exposed to 1,2-dichloroethane, even at lethal doses. Histological examinations showed no cardiovascular effects following gavage exposure in rats treated with #100 mg/kg/day for 10 days (Daniel et al. 1994), rats treated with #480 mg/kg/day for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or rats and mice treated with #95 and #299 mg/kg/day, respectively, for #78 weeks (NCI 1978). Similarly, no histopathological changes in the heart were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of #492 and #4,210 mg/kg/day, respectively, for #90 days (NTP 1991a).

Gastrointestinal Effects. Gastrointestinal symptoms have been observed in humans prior to death following oral exposure to 570 or 714 mg/kg/day of 1,2-dichloroethane. These symptoms included nausea, vomiting, and diarrhea (Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970; Yodaiken and Babcock 1973). Hemorrhagic colitis, hemorrhagic gastritis, and focal hemorrhages of the gastrointestinal tract have also been reported upon autopsy (Garrison and

Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970).

Gastrointestinal lesions have also been found in animals given bolus doses of 1,2-dichloroethane. Forestomach lesions developed in rats given gavage doses of 100 mg/kg/day for 10 days (minimal mucosal and submucosal inflammation), $240 mg/kg/day for #13 weeks (mild hyperplasia and inflammation), or $47 mg/kg/day for #78 weeks (acanthosis and hyperkeratosis) (Daniel et al. 1994; NCI 1978; NTP 1991a). Similar lesions were not found in rats exposed to corresponding doses (#492 mg/kg/day) in the drinking water for 13 weeks or mice exposed to much higher doses (#4,210 mg/kg/day) in the drinking water for 13 weeks (NTP 1991a). No increase in histopathologies in the stomach or intestines was observed in rats after intermittent gavage doses of up to 90 mg/kg/day over a 90-day period (van Esch et al. 1977). The incidences of non-neoplastic lesions of the stomach, large intestine, and colon were also not increased in mice intermittently administered up to 299 mg/kg/day by gavage for 78 weeks (NCI 1978). The gastrointestinal lesions observed in humans and animals ingesting bolus doses are probably produced by direct contact with concentrated 1,2-dichloroethane; the concentration in drinking water (8,000 mg/L) tested by NTP (1991a), although close to the solubility limit for this chemical (9,000 mg/L), was apparently too low to have this effect.

Hematological Effects. Adverse hematological effects, such as increased prothrombin time and reduction in blood clotting factors, were observed in 18- and 57-year-old men who had ingested approximately 40 mL ($570 mg/kg) of 1,2-dichloroethane (Martin et al. 1969; Schönborn et al. 1970) and in a 14-year-old boy who had ingested approximately 15 mL (360 mg/kg, using an approximate body weight of 51.3 kg [EPA 1988d]) of 1,2-dichloroethane (Yodaiken and Babcock 1973). These are only crude estimates of the ingested doses. The alterations in coagulation parameters described above may have been associated to some degree with liver dysfunction. The liver plays an important role in blood clotting homeostasis, and hepatic disorders may result in abnormalities in coagulation tests. The liver is the site of production of most of the plasma coagulant factors such as fibrinogen, prothrombin, and factors V, VII, IX, and X.

Similar effects have not been reported in animals following oral exposure. However, a 30% decrease in leukocytes was reported in mice given daily gavage doses of 49 mg/kg of 1,2-dichloroethane for 2 weeks (Munson et al. 1982). This effect may have had some relation to immunosuppressive effects reported in the same study. Mice that ingested #189 mg/kg/day in the drinking water for 90 days did not exhibit any differences from control animals with regard to hemoglobin, hematocrit, red or white blood cell counts, or

platelets (Munson et al. 1982). Similarly, there were no hematological changes in mice exposed to #4,210 mg/kg/day in the drinking water for up to 13 weeks (NTP 1991a). In order to explain the apparent contradiction in their results, Munson et al. (1982) suggested that more 1,2-dichloroethane may enter systemic circulation when the animals are given a concentrated solution in bolus form, than when they are allowed to drink water containing lower concentrations of 1,2-dichloroethane. They also suggested that, during the longer exposure time, 1,2-dichloroethane might induce its own metabolism and therefore be removed from the blood and other organs more rapidly. In rats, hematological parameters were unaffected by exposure to #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or #492 mg/kg/day in drinking water for 90 days (NTP 1991a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,2-dichloroethane.

There is no indication that ingested 1,2-dichloroethane produces musculoskeletal effects in animals. Histological changes in muscle and bone were not observed in rats administered #100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or in rats and mice exposed at #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a).

Hepatic Effects. 1,2-Dichloroethane has been implicated as a hepatotoxin in humans after acute oral poisoning (Przezdziak and Bakula 1975). Ingestion of $570 mg/kg/day of 1,2-dichloroethane resulted in severe hepatocellular damage and liver atrophy (Martin et al. 1969) and necrosis (Schönborn et al. 1970), although the degree to which these conditions were pre-existing is unknown. No gross changes were reported in the liver of a man who died from ingesting a “small” quantity of 1,2-dichloroethane, but hepatocellular fatty vacuolation and inflammation, “engorged” hepatic vasculature, and mild lymphocytic infiltration of portal spaces were observed microscopically (Hubbs and Prusmack 1955).

Studies in orally exposed animals have not found serious liver effects like those reported in humans. Hepatic biochemical changes consisting of a 15% increase in fat accumulation and increases in total triglycerides (indicative of liver damage), were observed in rats fed 80 mg/kg/day of 1,2-dichloroethane in the diet for 5–7 weeks (Alumot et al. 1976). Histological examinations were not performed, although liver weight was unchanged. The NOAEL for liver changes in this study was 30 mg/kg/day. Increased liver weight with no hepatic histological alterations occurred in intermediate-duration studies conducted

by NTP (1991a) in rats and mice. Following a 13-week gavage exposure in rats, both liver weight and liver-to-body-weight ratio were elevated in a dose-related fashion. The increase over controls was significant at 18–150 mg/kg/day in females and 120 mg/kg/day in males (liver weight was not measured in higher-dose animals because of mortality). Following a 13-week drinking water exposure, liver weight increases were noted at 60 mg/kg/day in rats (liver-to-body-weight ratio was significantly elevated at 60–518 mg/kg/day in Sprague-Dawley males without corresponding decreases in body weight), and at 249 mg/kg/day in mice (liver-to-body-weight ratio was significantly elevated in a dose-related manner at 249–4,210 mg/kg/day in males without corresponding decreases in body weight). Similarly, relative liver weights were increased with no accompanying histopathological changes in rats administered #150 mg/kg/day by gavage for #90 days (Daniel et al. 1994; van Esch et al. 1977). In the absence of histopathological or biochemical changes in the liver, the changes in liver weight are not considered to be adverse effects. Based on these findings, the liver does not appear to be a sensitive target organ for 1,2-dichloroethane toxicity in animals.

Other animal studies of 1,2-dichloroethane did not find hepatic effects. No changes in liver weight were observed in mice exposed to #49 mg/kg/day by gavage for 14 days or #189 mg/kg/day in drinking water for 90 days (Munson et al. 1982); histology was not evaluated. Rats administered single gavage doses (80 mg/kg) of 1,2-dichloroethane showed no effect on liver triglyceride, SDH, and ALT levels (Aragno et al. 1992; Danni et al. 1992). Chronic exposure of rats to 25 mg/kg/day in food for 2 years did not result in abnormalities in liver function, as measured by transaminases and cholesterol values (Alumot et al. 1976). In this chronic feeding study, the animals were not evaluated grossly or microscopically for liver lesions. There also were reported losses of 1,2-dichloroethane due to volatilization from the food; consequently, actual exposures would probably have been less than nominal exposures. No histological changes were observed in the liver of rats and mice that were administered #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978).

Renal Effects. Acute renal damage resulting from ingestion of 1,2-dichloroethane has been observed in humans. Bleeding and hyperemia of the kidney were observed in an 18-year-old man who ingested a single dose of 714 mg/kg (Schönborn et al. 1970), and in a male hospital patient who died after accidentally ingesting a “small” quantity of 1,2-dichloroethane (Hubbs and Prusmack 1955). Observations upon microscopic examination included swelling, vacuolation, and degeneration of the renal tubule epithelial cells and sloughing of the glomerular capsular epithelium, and nearly complete loss of the bladder epithelium (Hubbs and Prusmack 1955). In one case study, renal damage that resulted from acute oral poisoning of a 25-year-old man was not considered severe or permanent, and the patient fully

recovered (Przezdziak and Bakula 1975). The amount of 1,2-dichloroethane ingested was not reported. However, individuals who died following ingestion of 15–30 mL of 1,2-dichloroethane had severe kidney damage, primarily in the form of diffuse renal necrosis (Hueper and Smith 1935; Lochhead and Close 1951; Yodaiken and Babcock 1973). These are only crude estimates of ingested dose.

Renal effects reported in animals were limited to increases in kidney weight and minimal-to-moderate histopathological changes after longer-term exposures. Relative kidney weight was increased without altered histology in rats that were treated with 75–90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977). An NTP (1991a) 13-week gavage study in rats found significant dose-related increases in kidney weight and kidney-to-body-weight ratio at 30–120 mg/kg/day in males and 75–150 mg/kg/day in females (kidney weight was not measured in higher-dose animals because of mortality). Exposure to 1,2-dichloroethane in the drinking water for 13 weeks caused significant dose-related increases in kidney weight and kidney-to-body-weight ratio in rats at $58 mg/kg/day and mice at $244 mg/kg/day (NTP 1991a). The increase in kidney weight is considered to be an early-stage adverse effect in a known target tissue because renal histopathological changes occurred at higher doses. Histopathological examination of the animals in the drinking water study showed dose-related increased incidences of minimal-to-moderate renal regeneration in female rats at $102 mg/kg/day and male mice at $249 mg/kg/day. These changes are indicative of previous tubular injury with subsequent repair. More severe renal effects including karyomegaly, dilation, protein casts, and mineralization occurred in male mice exposed at 4,210 mg/kg/day. Based on these results, NTP (1991a) concluded that the kidney was a target organ for 1,2-dichloroethane in mice. Using a LOAEL of 58 mg/kg/day based on kidney effects, an intermediate oral MRL of 0.2 mg/kg/day was calculated as described in the footnote in Table 3-2 and in Appendix A.

Other studies in animals failed to find evidence of kidney damage produced by 1,2-dichloroethane. Acute (10–14 days) gavage administration of up to 100 mg/kg/day did not result in treatment-related changes in kidney weight or in the incidence of gross or histopathological changes in the kidney in rats (Daniel et al. 1994; van Esch et al. 1977). There were no changes in kidney weight in mice after administration of 49 mg/kg/day by gavage for 14 days or exposure to 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982), and kidney function, as measured by changes in serum levels of urea and uric acid, was normal in rats exposed to 25 mg/kg/day in food for 2 years (Alumot et al. 1976). Histological examination of the kidney was not performed in either of these studies. No histological changes were observed in the kidneys of rats and mice that were administered #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). The discrepancy between the negative results of this bioassay and

the finding of kidney effects in the NTP (1991a) 13-week study may be related to animal strain. NTP (1991a) found compound-related renal changes in F344/N rats, whereas Osborne-Mendel rats were tested by NCI (1978); tests of Osborne-Mendel and Sprague-Dawley rats by NTP (1991a) were also negative.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,2-dichloroethane.

Endocrine function has not been evaluated in oral toxicity studies in animals. Histological examinations of endocrine system tissues were performed in several studies with essentially negative results, but lack of histopathology does not necessarily indicate that there were no functional endocrinologic changes. Histopathological examinations failed to detect changes in endocrine tissues in rats administered #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). The examinations in the NCI (1978) and NTP (1991a) studies were the most extensive and included tissues from the adrenal, pancreas, pituitary, thyroid, and parathyroid glands.

The highest NOAEL values and all LOAEL values from each reliable study for endocrine effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,2-dichloroethane.

Histological examinations showed no changes in the skin of rats administered #100 mg/kg/day by gavage for 14 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a).

The highest NOAEL values and all LOAEL values from each reliable study for dermal effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to 1,2-dichloroethane.

Ophthalmoscopic examinations showed no effects in rats that were treated with #150 mg/kg/day of 1,2-dichloroethane by gavage in a 90-day study; the exams were performed prior to treatment and during the last week of the study (Daniel et al. 1994). Other 90-day studies similarly found no gross ocular changes in the eyes of rats treated with #480 mg/kg/day by gavage, or in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water (NTP 1991a).

The highest NOAEL values and all LOAEL values from each reliable study for ocular effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Body Weight Effects. No studies were located regarding effects on body weight in humans after oral exposure to 1,2-dichloroethane.

Acute-duration animal studies found no effects on body weight in rats administered #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), although gavage treatment with 198 mg/kg/day (but not #158 mg/kg/day) for 14 days during pregnancy caused a 30% reduction in maternal body weight gain (Payan et al. 1995). Reduced growth (10–30% decreases in body weight gain) has been observed in animals following intermediate- and chronic-duration oral exposures, including rats administered $90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), rats and mice exposed to $259 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (NTP 1991a), and mice administered 299 mg/kg/day by gavage for #78 weeks (NCI 1978). No effect on body weight was seen in rats administered up to 95 mg/kg/day by gavage for 78 weeks (NCI 1978).

The highest NOAEL values and all LOAEL values from each reliable study for body weight effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.3 Immunological and Lymphoreticular Effects

Limited information was located regarding immunological effects in humans after oral exposure to 1,2-dichloroethane. Gross findings at autopsy of a male patient who ingested a “small” quantity of 1,2-dichloroethane included a dark appearance of the spleen; hemorrhaging and congestion of the red pulp were observed microscopically (Hubbs and Prusmack 1955).

Evidence from animal studies suggests that the immune system is a target of 1,2-dichloroethane toxicity after oral exposure. In 5-week-old mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day, there

was a significant dose-related reduction in humoral immunity (measured by immunoglobulin M [IgM] response to sheep erythrocytes), and a significant, but not dose-related, reduction in cell-mediated immunity (measured by delayed-type hypersensitivity response to sheep erythrocytes) (Munson et al. 1982). In mice given 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number.

Mice given drinking water containing up to 189 mg/kg/day of 1,2-dichloroethane for 90 days displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982). The authors suggested that the conflicting results in mice treated by gavage and those exposed to 1,2-dichloroethane in drinking water may reflect differences in compound administration and exposure duration, as discussed earlier (see the discussion of hematological effects in Section 3.2.2.2). No increase in the incidences of gross or histopathological changes were observed in the spleen, lymph nodes, or thymus in rats administered up to 100 mg/kg/day by gavage for 10 days (Daniel et al. 1994).

Immune system function tests were not included in intermediate- and chronic-duration studies conducted by NTP (1991a). However, immune system tissues were examined for histopathological lesions in some of these studies. Thymic necrosis was observed in rats given $240 mg/kg/day of 1,2-dichloroethane by gavage #13 weeks (NTP 1991a). Because this lesion was found only in moribund animals, the study authors concluded that it was a result of generalized stress rather than a target organ effect. 1,2-Dichloroethane did not produce lesions in immune system tissues in rats and mice exposed to #492 mg/kg/day and #4,210 mg/kg/day, respectively, in drinking water for 13 weeks (NTP 1991a), in rats exposed by gavage to 150 mg/kg/day for 90 days (Daniel et al. 1994), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological effects, such as central nervous system depression, have been reported in humans following acute oral intoxication with 1,2-dichloroethane (Hubbs and Prusmack 1955; Lochhead and Close 1951; Yodaiken and Babcock 1973). Morphological alterations in the nervous system were observed in patients who died of acute oral poisoning by 1,2-dichloroethane. These alterations included vascular disorders,

diffuse changes in cerebellar cells, parenchymatous changes in brain and spinal cord, myelin degeneration, and hyperemia, swelling, edema, and hemorrhage of the brain (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951). The morphological changes observed in the cerebellum may affect the coordination of muscular movements.

Neurological effects have also been observed in animals exposed to 1,2-dichloroethane by ingestion. Clinical signs in rats exposed to $240 mg/kg/day by gavage for #13 weeks included tremors, salivation, emaciation, abnormal posture, ruffled fur, and dyspnea (NTP 1991a). Upon microscopic examination, mild necrotic lesions were observed in the cerebellum of rats dosed with 240 or 300 mg/kg/day. These lesions were not found in rats dosed with 480 mg/kg/day, but these rats all died after only 3 days of treatment and may not have had time to develop the lesion. Intermittent gavage exposure to 90 mg/kg/day in female rats over a 90-day period induced a slight increase in relative brain weight (+8%) in female rats, but no clinical signs or histological changes in the brain or spinal cord were observed, and no neurological effects of any kind were seen in males at 90 mg/kg/day or in either sex at lower exposure levels (van Esch et al. 1977). Similarly, gavage administration of 75 and 150 mg/kg/day induced a significant increase in brain weight (+8 and +22%, respectively) in male rats without increases in the incidences of neurological clinical signs or lesions of the brain or sciatic nerve; no neurological effects of any kind were reported in females at $75 mg/kg/day or in either sex at lower exposure levels (Daniel et al. 1994). In the Daniel et al. (1994) study, the increase in relative brain weight may have been due to an observed dose-related decrease in body weight in the male rats, and may not necessarily be due to an actual change in brain weight; absolute organ weights were not reported. Exposure to 1,2-dichloroethane in the drinking water for 13 weeks did not produce increased brain weights, abnormal clinical signs, or lesions in nervous system tissues in rats (#492 mg/kg/day) or mice (#4,210 mg/kg/day) (NTP 1991a). (See the discussion of hematological effects in Section 3.2.2.2 regarding why effects that occur following bolus exposure might not occur following drinking water exposure). A 10-day gavage exposure to up to 100 mg/kg/day did not induce an increase in brain weight or an increase in the incidences of gross or microscopic lesions in nervous system tissues of rats (Daniel et al. 1994), and a single gavage exposure to 170 mg/kg in rats did not significantly alter neurotransmitter levels in various parts of the brain (Kanada et al. 1994).

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 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,2-dichloroethane.

Studies in animals suggest that reproductive effects of 1,2-dichloroethane may be induced at oral doses that are maternally toxic. One-and two-generation reproduction studies showed no dose-dependent effects on fertility, gestation, viability, or lactation indices in mice exposed to doses of 5–50 mg/kg/day in drinking water for 24–49 weeks (Lane et al. 1982). Similarly, there were no effects on fertility indices (e.g., percentage pregnant, percent bearing litters, and litter size) in five pregnancies throughout a 2-year study during which rats ingested dietary doses of 21.3 or 42.5 mg/kg/day (Alumot et al. 1976). In a study using higher doses of 1,2-dichloroethane, rats that were treated with $198 mg/kg/day for 14 days during gestation showed 30% reduced body weight gain and dose-related increased percentages of nonsurviving implants per litter (resorptions plus dead fetuses) and resorption sites per litter (Payan et al. 1995). These effects did not occur at #158 mg/kg/day, and no changes in mean number of implantation sites or live fetuses per litter were observed.

Histological examinations showed no changes in male or female reproductive tissues in rats administered #100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #13 weeks (NTP 1991a), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). Reproductive performance was not evaluated in these studies.

The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans exposed solely to 1,2-dichloroethane by ingestion. A cross-sectional epidemiologic study investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995). The study population consisted of all live births and fetal deaths that occurred during 1985–1988 to residents

of 75 towns in a four-county area where some municipal water supplies were contaminated. A total of 80,938 live births and 594 fetal deaths, excluding plural births, fetal deaths due to therapeutic abortions, and chromosomal anomalies, were studied. The comparison group comprised 52,334 (all) live births from the study population that had no birth defects and were not low birth weight, small for gestational age, or pre-term. A number of associations between various chemicals and birth outcomes were found, including a positive association between 1,2-dichloroethane and major cardiac defects for exposure levels >1 ppb compared to #1 ppb (OR=2.11). The odds ratio increased to 2.81 when exposure was recategorized as detected versus not detected. Croen et al. (1997) reported an increased crude odds ratio (OR=2.8; 95% CI 1.0–7.2; 14 exposed cases) for neural tube defects in offspring of residents within the census tract of NPL sites contaminated with 1,2-dichloroethane. The OR for residence within 1 mile of the NPL site was elevated, but was not significant (OR=1.7; 95% CI 0.8–3.6; 18 exposed cases). Although an association between 1,2-dichloroethane in drinking water and major birth defects was found in these epidemiological studies, concurrent mixed chemical exposures indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution. Primary routes of exposure in these epidemiological studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water).

Developmental toxicity studies in animals have not shown 1,2-dichloroethane to be fetotoxic or teratogenic following oral exposure, although indications of embryolethality at maternally toxic doses have been reported. Drinking water studies in mice found no increased incidences of fetal visceral and skeletal abnormalities following exposure to 50 mg/kg/day on gestation days 0–18 (Lane et al. 1982) or #510 mg/kg/day on gestation days 7–14 (Kavlock et al. 1979). Rats that were treated with $198 mg/kg/day by gavage on gestation days 6–20 showed 30% reduced body weight gain and some embryolethal effects (increased nonsurviving implants and resorption sites per litter), but no fetotoxicity or teratogenicity as indicated by fetal sex ratio, fetal body weight, and incidences of visceral and skeletal variations and malformations (Payan et al. 1995). The highest NOAEL values from each reliable study for developmental effects in mice after acute and intermediate exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Little information is available concerning the development of cancer in humans following ingestion of 1,2-dichloroethane. Isacson et al. (1985) used indices of drinking water contamination to examine the relationship between cancer incidence and exposure to environmental pollutants in groundwater and

surface water samples. A statistically significant association was observed between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon ($p=0.009$) and rectal ($p=0.02$) cancer in men aged 55 years or older. However, it is highly likely that the study population was concomitantly exposed to other chemicals.

1,2-Dichloroethane was found to be carcinogenic in rats and mice that were exposed by gavage for up to 78 weeks (NCI 1978). Statistically significant increases in multiple tumor types (malignant and benign) were noted in treated animals of both species. An increased incidence of fibromas of the subcutaneous tissue and hemangiosarcomas of the spleen, liver, pancreas, and adrenal gland (as well as other organs and tissues) occurred in male rats of both exposure groups (47 and 95 mg/kg/day). In the high-dose group (95 mg/kg/day), male rats had increased squamous cell carcinomas of the forestomach, and female rats had increased frequencies of adenocarcinomas and fibroadenomas of the mammary gland. In mice, the incidence of hepatocellular carcinomas and pulmonary adenomas increased in males given 195 mg/kg/day. In female mice from both the 149- and 299-mg/kg/day exposure groups, there were increased incidences of pulmonary adenomas, adenocarcinomas of the mammary gland, and endometrial polyps and sarcomas. In conclusion, 1,2-dichloroethane administered by gavage produced tumors in rats and mice in tissues distant from the site of administration. The NCI (1978) study has a number of limitations including dosage adjustments throughout the course of the bioassay (because of the toxicity of 1,2-dichloroethane), testing of other volatile organic chemicals in the same room, small numbers of concurrent controls, poor survival of treated animals, imprecise reporting of 1,2-dichloroethane purity, and use of a corn oil vehicle, which can alter the disposition of lipophilic compounds and the incidence of some spontaneous tumors. Despite these study limitations, it is prudent to consider the possibility of tumor induction when the chemical is administered via other routes and absorbed into systemic circulation as well.

In another study, 1,2-dichloroethane was administered to $B6C3F_1$ mice in their drinking water using a two-stage (initiation/promotion) treatment protocol; no increase in tumorigenicity was found (Klaunig et al. 1986). In this study, mice were initiated with diethylnitrosamine (DENA) for 4 weeks and subsequently treated with 159 or 475 mg/kg/day 1,2-dichloroethane for 52 weeks. 1,2-Dichloroethane did not increase the incidence of lung or liver tumors either alone or as a tumor promoter following DENA initiation. However, severe study limitations (including short duration, high liver-tumor incidence in untreated controls [20%] and in DENA-initiated [100%] mice after 52 weeks, lack of positive controls, and failure to specify the compound purity) invalidate any conclusions about the lack of carcinogenicity of 1,2-dichloroethane. A shorter-term initiation/promotion study in rats, based on the use of enzyme-

altered liver foci as a marker for preneoplastic changes, also failed to confirm the carcinogenic potential of 1,2-dichloroethane (Milman et al. 1988), but was limited by use of a single dose level (100 mg/kg), short exposure duration (single dose in initiation study and 7 weeks in promotion study), and monitoring of an end point not firmly established as proof of carcinogenicity.

In another two-stage oral cancer assay (Pott et al. 1998), a 16-week co-administration of 1,2-dichloroethane and arsenic (in drinking water) with vinyl chloride and trichloroethylene (administered by gavage) (all of which are chemicals commonly found at hazardous waste sites) produced dose-related inhibition of the promotion of preneoplastic hepatic lesions and bronchoalveolar hyperplasia and pulmonary adenomas in male Fisher 344 rats, after a 4-week initiation with a series of three broad-spectrum initiators. The drinking water concentrations of 1,2-dichloroethane ranged from 3 ppm (approximately 0.47 mg/kg/day) in the low exposure group (with relatively low levels of the other test substances) to 300 ppm (approximately 47 mg/kg/day) in the high exposure group (with relatively high levels of the other test substances). The study has limited usefulness for understanding lifetime risk of cancer from 1,2-dichloroethane exposure because of co-exposure with other known carcinogens, the use of a short promotion exposure period (16 weeks), small numbers of test animals (15 per exposure group), and evaluation of effects to only one sex (males).

CEL values from the chronic NCI (1978) study in rats and mice are recorded in Table 3-2 and plotted in Figure 3-2.

EPA has derived a slope (potency) factor (q_1*) of 0.091 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to 1,2-dichloroethane based on the study by NCI (1978) in rats (IRIS 2001). This slope factor corresponds to a drinking water unit risk of $2.6x10^{-6}$ $(\mu g/L)^{-1}$ and an inhalation unit risk of $2.6x10^{-5}$ $(\mu g/m^3)^{-1}$. Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} are $1x10^{-3}$, $1x10^{-4}$, $1x10^{-5}$, and $1x10^{-7}$ mg/kg/day, respectively. These risk levels correspond to one excess cancer death in 10,000, 100,000, 1 million, and 10 million persons, respectively, and are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane. The range of doses associated with excess lifetime cancer risks of 10^{-4} to 10^{-7} is plotted in Figure 3-2. The estimated excess cancer risks are upper-bound risks (i.e., the true risks are not likely to exceed the upper-bound risk estimate and may be lower).

3.2.3 Dermal Exposure

No studies were located regarding effects after dermal exposure to 1,2-dichloroethane in humans. In animals, ocular effects were produced by direct contact between the eye and 1,2-dichloroethane vapor in the air. Skin lesions and benign pulmonary tumors were reported in animals exposed to liquid 1,2-dichloroethane dermally.

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 1,2-dichloroethane.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to 1,2-dichloroethane. Dermal and ocular effects in animals dermally exposed to 1,2-dichloroethane are discussed below.

Dermal Effects. No studies were located regarding effects on the skin in humans after dermal exposure to 1,2-dichloroethane.

A single animal study was located that investigated dermal effects following direct application of 1,2-dichloroethane to the skin as a liquid. In guinea pigs, dermal exposure to unspecified amounts for 4 hours applied to the skin under a cover slip resulted in skin changes, including karyopyknosis (shrinkage of cell nuclei), perinuclear edema, spongiosis, and junctional separation (Kronevi et al. 1981); however, only one dose was tested and no control data were presented.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to 1,2-dichloroethane.

Studies in animals reported direct-contact effects following exposure to 1,2-dichloroethane as a vapor in the air. Dogs exposed to 1,2-dichloroethane as a vapor in the air developed corneal opacity. This corneal clouding was observed in 3 dogs that died following intermittent exposure to 1,500 ppm for 6 days

(Heppel et al. 1945). Corneal opacity was not reported in other similarly exposed species studied by Heppel et al. (1945, 1946). However, lacrimation was reported in guinea pigs exposed to 1,500 ppm of 1,2-dichloroethane vapor in air intermittently for 4 days (Heppel et al. 1945).

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,2-dichloroethane:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to 1,2-dichloroethane.

The carcinogenicity of 1,2-dichloroethane following dermal exposure has been evaluated in mice (Van Duuren et al. 1979). In this study, a statistically significant increase ($p<0.0005$) in pulmonary papillomas was observed in mice treated with 126 mg of 1,2-dichloroethane 3 times/week for 428–576 days. These results, which indicate a significant increase in benign tumors remote from the site of application, provide suggestive or supportive evidence that 1,2-dichloroethane is carcinogenic and that it can penetrate through the skin into the circulatory system.

3.3 GENOTOXIC EFFECTS

No studies were located regarding genotoxic effects in humans after inhalation exposure to 1,2-dichloroethane. Inhalation of 1,2-dichloroethane has produced genotoxic effects in animals. Exposure to 1,000 ppm for 4 hours produced irreversible deoxyribonucleic acid (DNA) damage in mice as evidenced by single-stranded breaks in hepatocytes. This genetic damage was seen at a concentration that produced mortality in 80–100% of treated mice within 24 hours (Storer et al. 1984). A brief account of a mouse dominant lethal assay reported reduced impregnation rate, increased preimplantation loss, and increased ratio of total embryonic loss to number of corpora lutea compared to controls in female mice mated to males that had been exposed by inhalation to 200 ppm 1,2-dichloroethane for 4 hours/day for 2 weeks (Zhao et al. 1989). No effects were observed after exposure to 6.3 ppm for 2 weeks, nor at any

concentration after exposure durations of 1, 3, or 4 weeks. The reliability of the results is uncertain because of reporting deficiencies in the study design. In a study investigating the relationship between inhalation exposure to 1,2-dichloroethane and covalent binding to liver and lung DNA, female Fischer-344 rats were exposed either to 80 ppm of 1,2-dichloroethane for 4 hours ("constant-low" exposure) or 4,400 ppm for a few minutes ("peak" exposure) (Baertsch et al. 1991). The DNA covalent binding index was elevated, compared to controls, after both exposure scenarios. However, in both the liver and the lung, the effect was much greater (approximately 35 times greater) after peak exposure, suggesting that acute exposure to highly concentrated 1,2-dichloroethane may pose a greater genotoxic hazard than protracted low-level exposure. The results of this study support the hypothesis that toxicity of 1,2-dichloroethane is associated with saturation of mixed function oxidation (MFO) enzymes (see Section 3.4, Mechanisms of Action). Also consistent with this hypothesis is the fact that oral doses were more potent than comparable inhalation doses, and that a route-of-administration effect has been reported for 1,2-dichloroethane carcinogenicity.

No studies were located regarding genotoxicity in humans after oral exposure to 1,2-dichloroethane, although oral exposure has produced genotoxic effects in animals. A single oral dose of 100 mg/kg of 1,2-dichloroethane produced irreversible DNA damage in mice, as revealed by single-stranded breaks in hepatocytes (Storer et al. 1984). Hepatocytic DNA damage was also induced in female rats receiving two oral gavage doses of 1,2-dichloroethane (in corn oil) at 134 mg/kg each, but not in rats receiving two doses of 13.4 mg/kg (Kitchin and Brown 1994). A single oral dose of 150 mg/kg produced high levels of DNA binding in the liver of rats (Cheever et al. 1990). The level of binding produced was similar in rats that had previously been exposed via inhalation to 50 ppm of 1,2-dichloroethane vapor for 2 years, and in rats that had served as controls in the 2-year study.

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 1,2-dichloroethane.

The results of *in vivo* genotoxicity studies by all routes of exposure are summarized in Table 3-3. As indicated in the table, the ability of 1,2-dichloroethane to bind DNA in rodents *in vivo* has been well established in the liver as well as in other organs such as the kidney and lung. DNA binding has been observed not only after inhalation and oral exposures, but also in rats (Banerjee 1988; Prodi et al. 1986) and mice (Banerjee 1988; Hellman and Brandt 1986; Prodi et al. 1986) administered a single intraperitoneal injection of 1,2-dichloroethane at dose levels as low as 6.35 µmol/kg (0.00635 mg/kg) (Prodi et al. 1986). Actual structural damage to DNA, in the form of single-stranded breaks and

Table 3-3. Genotoxicity of 1,2-Dichloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian assays:			
Mouse/spot test	Gene mutation	(+)	Gocke et al. 1983
Mouse bone marrow	Sister chromatid exchange	+	Giri and Hee 1988
Mouse	Micronuclei	–	Jenssen and Ramal 1980; King et al. 1979
Mouse	Micronuclei	–	Sasaki et al. 1994
Mouse, Eμ-PIM-1	Micronuclei	–	Armstrong and Galloway 1993
Mouse liver, kidney, lung, and stomach	DNA binding	+	Prodi et al. 1986
Mouse forestomach and kidney	DNA binding	+	Hellman and Brandt 1986
Mouse liver	DNA binding	+	Banerjee 1988
Rat liver, kidney, lung, and stomach	DNA binding	+	Prodi et al. 1986
Rat liver and kidney	DNA binding	+	Inskeep et al. 1986
Rat liver and lung	DNA binding	+	Baertsch et al. 1991
Rat liver	DNA binding	+	Banerjee 1988
Rat liver	DNA binding	+	Cheever et al. 1990
Mouse liver	DNA damage	+	Storer and Conolly 1983, 1985; Storer et al. 1984
Mouse liver	DNA damage	+	Taningher et al. 1991
Mouse liver, kidney, bladder, lung, brain, bone marrow	DNA damage	+	Sasaki et al. 1998
Insect assays:			
Drosophila melanogaster//somatic mutation	Gene mutation	+	Nylander et al. 1978
D. melanogaster/somatic mutation	Gene mutation	+	Romert et al. 1990
D. melanogaster/somatic mutation	Gene mutation	+	Kramers et al. 1991
D. melanogaster/somatic mutation	Gene mutation	+	Ballering et al. 1994
D. melanogaster/somatic mutation	Gene mutation	+	Vogal and Nivard 1993
D. melanogaster/sex-linked recessive	Gene mutation	+	King et al. 1979
D. melanogaster/sex-linked recessive	Gene mutation	+	Kramers et al. 1991
D. melanogaster/recessive lethal	Gene mutation	+	Ballering et al. 1993
D. melanogaster	Chromosomal recombination	(+)	Rodriguez-Arnaiz 1998
D. melanogaster/chromosome loss	Chromosomal aberration	+	Ballering et al. 1993
D. melanogaster	DNA binding	+	Fossett et al. 1995

Table 3-3. Genotoxicity of 1,2-Dichloroethane *In Vivo (continued)*

Species (test system)	End point	Results	Reference
Host-mediated assays:			
Escherichia coli K12/343/113 mouse host-mediated assay	Gene mutation	–	King et al. 1979

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acidtable 3-3

unwinding of the DNA molecule, has also been demonstrated in mice after single intraperitoneal injections of 45–360 mg/kg (Sasaki et al. 1998; Storer and Conolly 1983, 1985; Storer et al. 1984; Taningher et al. 1991). In one study, DNA binding was associated with decreased rates of DNA synthesis and transcription (Banerjee 1988). However, the results of this study are questionable. Genotoxicity assays for clastogenic effects obtained mixed results, with a positive effect on sister chromatid exchange (believed to be caused by strand breakage) in mouse bone marrow cells of mice administered a single intraperitoneal injection of up to 16 mg/kg, but no effect on micronucleus formation in mice after 14 weeks of daily gavage administrations of up to 300 mg/kg/day or in mice after a single intraperitoneal injection of between 45–400 mg/kg (Jenssen and Ramel 1980; King et al. 1979; Sasaki et al. 1994). The only *in vivo* assay for mutagenicity in mammalian cells produced only a marginal response after a single intraperitoneal injection of an unreported dose. However, there is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in *Drosophila melanogaster in vivo*.

The results of *in vitro* genotoxicity studies are presented in Table 3-4. The evidence from these studies overwhelmingly indicates that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects *in vitro*. Results were positive in assays for point mutations in human cells, animal cells, and bacteria, unscheduled DNA synthesis (i.e., DNA repair activity) in human and animal cells, DNA binding in animal cells, and mitotic segregation aberrations leading to aneuploidy in fungi. The results in bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione *S*-transferases (DeMarini and Brooks 1992). The presence of an exogenous mammalian metabolic system was not required, but increased mutagenic activity was observed in tests with a metabolic activation system supplemented with glutathione. Mutagenicity was increased in TA100 strain *Salmonella typhimurium* expressing the alpha class of human glutathione *S*-transferase via regulatable tac promoter expression, but not in bacteria expressing the pi class of human glutathione *S*-transferase (Simula et al. 1993). *S*-(Chloroethyl)-cysteine, an analog of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, was a potent inducer of unscheduled DNA synthesis and micronucleus formation in mammalian cells *in vitro* (Vamvakas et al. 1988, 1989). *S*-(2-Chloroethyl)-glutathione itself was found to be a potent mutagen in *S. typhimurium*. Although it produced only intermediate levels of alkylation, the results indicate that the guanyl adduct that is formed appears to be unusually mutagenic (Humphreys et al. 1990). 1,2-Dichloroethane was found to be nonmutagenic in somatic cells and mature spermatozoa in *D. melanogaster*, further suggesting the lack of genotoxicity through a direct mechanism (Ballering et al. 1993).

Table 3-4. Genotoxicity of 1,2-Dichloroethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	+	+	Milman et al. 1988
S. typhimurium	Gene mutation	+	+	Barber et al. 1981
S. typhimurium	Gene mutation	+	+	Kanada and Uyeta 1978
S. typhimurium	Gene mutation	+	+	Nestmann et al. 1980
S. typhimurium	Gene mutation	+	+	Rannug et al. 1978
S. typhimurium	Gene mutation	+	+	Van Bladeren et al. 1981
S. typhimurium	Gene mutation	+	No data	Rannug and Beije 1979
S. typhimurium	Gene mutation	+	–	Cheh et al. 1980
S. typhimurium	Gene mutation	+	–	Moriya et al. 1983
S. typhimurium	Gene mutation	–	–	King et al. 1979
S. *typhimurium*	Gene mutation	No data	+	Thier et al. 1993
S. *typhimurium*	Gene mutation	No data	+	Simula et al. 1993
S. typhimurium/spot test	Gene mutation	No data	(+)	Brem et al. 1974
S. typhimurium/spot test	Gene mutation	No data	–	Buijs et al. 1984
S. typhimurium/Ara test (standard)	Gene mutation	+	–	Roldan-Arjona et al. 1991
S. typhimurium/Ara test (liquid)	Gene mutation	(+)	(+)	Roldan-Arjona et al. 1991
Escherichia coli K12/343/113	Gene mutation	–	–	King et al. 1979
E. coli WP2	Gene mutation	No data	(+)	Hemminki et al. 1980
E. coli WP2	Gene mutation	–	–	Moriya et al. 1983
E. coli Pol A	DNA damage	No data	(+)	Brem et al. 1974
Bacillus subtilis/rec-assay	DNA damage	No data	–	Kanada and Uyeta 1978

Table 3-4. Genotoxicity of 1,2-Dichloroethane *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Eukaryotic organisms:				
Fungi:				
Aspergillus nidulans	Gene mutation	No data	–	Crebelli and Carere 1988
A. nidulans	Mitotic segregation aberrations	No data	+	Crebelli et al. 1984
A. nidulans	Aneuploidy induction	No data	+	Crebelli et al. 1988
Animal cells:				
Hamster CHO/HGPRT	Gene mutation	+	(+)	Tan and Hsie 1981
Hamster Chinese SP5	Intrachromosomal	–	No data	Zhang and Jenssen 1994
Rat hepatocytes	recombination	No data	+	Williams et al. 1989
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Milman et al. 1988
Mouse liver DNA	Unscheduled DNA synthesis	+	No data	Banerjee 1988
Calf thymus DNA	DNA binding	+	No data	Prodi et al. 1986
Salmon sperm DNA	DNA binding	+	–	Banerjee and Van Duuren 1979; Banerjee et al. 1980
	DNA binding			
Mouse BALB/c-3T3	Cell transformation	No data	–	Milmann et al. 1988
Human cells:				
Human lymphoblasts AHH-1	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts AHH-1	Micronuclei	No data	+	Doherty et al. 1996
Human lymphoblasts MCL-5	Micronuclei	No data	+	Doherty et al. 1996
Human lymphoblasts h2E1	Micronuclei	No data	+	Doherty et al. 1996
Human embryo epithelial-like EUE cells	Gene mutation	No data	+	Ferreri et al. 1983
Human peripheral lymphocytes	Unscheduled DNA synthesis	+	–	Perocco and Prodi 1981
Human peripheral lymphocytes	Micronuclei	–	+	Tafazoli et al. 1998
Human peripheral lymphocytes	DNA damage	–	+	Tafazoli et al. 1998

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

3.4 TOXICOKINETICS

1,2-Dichloroethane is well absorbed through the lungs following inhalation exposure, the gastrointestinal tract following oral exposure, and the skin following dermal exposure in humans. In animal studies, equilibrium blood concentrations of 1,2-dichloroethane were obtained 2–3 hours after inhalation exposure, 15–60 minutes after oral exposure, and 1–2 hours after aqueous dermal exposure. Absorption probably occurs by passive diffusion for all three routes of exposure. Upon absorption, 1,2-dichloroethane is widely distributed within the body. Experiments in animals exposed orally or by inhalation showed that the highest concentrations of 1,2-dichloroethane (7–17 times that of the blood) were found in adipose tissue. The liver and lung contained lower equilibrium levels of 1,2-dichloroethane than the blood.

1,2-Dichloroethane is readily metabolized in the body. The primary metabolic pathways for this chemical are MFO and glutathione conjugation. Oxidation products include chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid. MFO metabolism of 1,2-dichloroethane appears to be saturable at oral gavage doses $25 mg/kg and inhalation concentrations of $150 ppm (. 500 mg/kg), both of which correspond to blood levels of 5–10 µg/mL. Glutathione conjugation becomes relatively more important at larger doses, and increased metabolism by this pathway may be responsible for the toxic effects noted at these high doses.

Excretion of 1,2-dichloroethane and metabolites is rapid; in animal studies, excretion was essentially complete 48 hours after acute exposure. Following inhalation exposure to labeled 1,2-dichloroethane, excretion of 1,2-dichloroethane was primarily in the form of metabolites (thiodiglycolic acid and thiodiglycolic acid sulfoxide) in the urine (84%), and as carbon dioxide (CO_2) in the exhaled air (7%). Following oral exposure to labeled 1,2-dichloroethane, the amount of radioactivity excreted by these routes was reduced, and a large percentage of the dose (29%) was excreted as unchanged 1,2-dichloroethane in the exhaled air. The increased exhalation of unchanged 1,2-dichloroethane may reflect the saturation of biotransformation enzymes.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

1,2-Dichloroethane is readily absorbed through the lungs following inhalation exposure in both humans and experimental animals. This is expected, based on 1,2-dichloroethane's high vapor pressure and high serum/air partition coefficient. Thus, absorption occurs most likely via passive diffusion across alveolar membranes. Nursing women exposed to 15.6 ppm of 1,2-dichloroethane in the workplace air (with concurrent dermal exposure) accumulated the chemical in breast milk (Urusova 1953). The concentration of the chemical in milk gradually increased, reaching the maximum level 1 hour after work ended, although the validity of the results could not be assessed because of a lack of sufficient detail in reported methods and because the sample size was not provided. EPA (1980a) also found 1,2-dichloroethane in the milk of lactating women. These results indicate that 1,2-dichloroethane is absorbed through the lungs by humans and accumulates (because of its high lipid-water partition coefficient) in the breast milk of nursing women. Concurrent levels of 1,2-dichloroethane in blood were not measured (EPA 1980a; Urusova 1953).

Nouchi et al. (1984) reported a fatal case of 1,2-dichloroethane poisoning in a man exposed to 1,2-dichloroethane vapors for approximately 30 minutes in an enclosed space (concentration in air not specified), providing further evidence that this chemical is readily absorbed through the lungs by humans. However, adverse effects were seen at 20 hours postexposure, prompting the authors to suggest that the formation of reactive metabolites is a necessary first step in the expression of 1,2-dichloroethane-induced toxicity. An alternative explanation is that the 1,2-dichloroethane is, in part, slowly released from adipose tissue or other compartments after an initial rapid release (see Section 3.4.3)

The rapid absorption of 1,2-dichloroethane following inhalation exposure has also been demonstrated in experimental animals. Reitz et al. (1980, 1982) found that peak blood levels were constant 1–2 hours after the onset of a 6-hour inhalation exposure to 150 ppm of 1,2-dichloroethane in rats. The plateau concentration in blood was approximately 8 μg/mL and was reached within 2 hours. Similar results were obtained by Spreafico et al. (1980) at inhalation exposures of 50 ppm of 1,2-dichloroethane. However, at 250 ppm of 1,2-dichloroethane, equilibrium was not achieved until 3 hours from the start of exposure. It is likely that as the concentration of inspired 1,2-dichloroethane increases, the time required to reach an equilibrium concentration of 1,2-dichloroethane in the blood also increases. In rats that had been exposed to 1,2-dichloroethane vapor (50 ppm) intermittently for 2 years, blood levels of 1,2-dichloroethane

15 minutes after the end of a 7-hour exposure to 50 ppm were 0.26–0.28 µg/mL (Cheever et al. 1990). Blood levels were not increased, but rather only slightly reduced after an additional 2 hours, which suggests that equilibrium had been reached during the exposure period.

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to 1,2-dichloroethane. However, it can be inferred from case studies, which described toxic effects (including death) subsequent to accidental (Hueper and Smith 1935) or intentional (Lochhead and Close 1951; Yodaiken and Babcock 1973) ingestion of 1,2-dichloroethane by humans, that 1,2-dichloroethane is rapidly absorbed into the systemic circulation following exposure by the oral route. 1,2-Dichloroethane is lipophilic and is expected, therefore, to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract.

Studies in experimental animals indicate that the oral absorption of 1,2-dichloroethane is rapid, complete, and essentially linear (Reitz et al. 1980, 1982; Spreafico et al. 1980). Reitz et al. (1982) reported that peak blood levels of 1,2-dichloroethane were reached within 15 minutes after oral administration of 150 mg/kg by gavage in corn oil to male Osborne-Mendel rats, attesting to the rapid nature of oral absorption. These investigators reported complete recovery of orally administered radioactivity (from [^{14}C]-1,2-dichloroethane) in exhaled air, urine, and carcass, thereby demonstrating that absorption of 1,2-dichloroethane from the gastrointestinal tract of rats is virtually complete (Reitz et al. 1980). The percentage of recovered radioactivity found in the feces following inhalation or oral exposure to [^{14}C]-1,2-dichloroethane was 1.7–2.1%; 7.0–7.7% of the recovered dose was found in the expired air following exposure by either route (Reitz et al. 1980). This implies that at least 90% of the inhaled or orally administered 1,2-dichloroethane was absorbed.

Data reported by Spreafico et al. (1980) supported the observation that absorption of 1,2-dichloroethane is rapid and complete. In Sprague-Dawley rats, peak blood levels were achieved within 30–60 minutes of oral administration at doses of 25, 50, and 150 mg/kg in corn oil. One-half of the low dose was absorbed within 3.3 minutes, and one-half of the high dose was absorbed within 6.4 minutes (Spreafico et al. 1980). Peak blood levels achieved were proportional to the dose administered, thus providing evidence that 1,2-dichloroethane is absorbed by passive transport across the gastrointestinal tract. Furthermore, comparison of blood levels attained after intravenous (i.e., reflective of 100% absorption) and oral

administration of 1,2-dichloroethane in rats indicates that oral absorption is 100%, if first-pass effects through the liver and lung are taken into consideration (Spreafico et al. 1980).

The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) found that 1,2-dichloroethane is absorbed more readily by the gastrointestinal tract when administered in water than in corn oil. Peak blood concentrations of 1,2-dichloroethane were about four times higher following oral administration in water than when given in corn oil. This may relate to higher solubility vehicles regarding the absorption of xenobiotics. Furthermore, the time taken to reach peak levels was approximately three times longer when administered in corn oil, compared to water. This may have important implications with regard to human exposure to 1,2-dichloroethane. Since animal data and the available information in humans indicate that oral absorption of 1,2-dichloroethane in aqueous solutions is rapid and complete, ingestion of water contaminated with high levels of 1,2-dichloroethane is of particular concern and could result in adverse health effects in humans. However, no unequivocal information was available concerning health effects in humans after long-term exposure to low levels of 1,2-dichloroethane in drinking water.

3.4.1.3 Dermal Exposure

Urusova (1953) reported a gradual increase in the concentration of 1,2-dichloroethane in the breast milk of nursing women following both dermal and inhalation exposure to 1,2-dichloroethane at the workplace. Maximum levels were reached within 1 hour (2.8 mg/100 mL of milk) after skin contact and decreased over time. Eighteen hours later, the concentration of 1,2-dichloroethane in milk ranged between 0.195 and 0.63 mg/100 mL of milk. The findings of Urusova (1953) indicate that percutaneous absorption via contact with contaminated water or the chemical itself may be a significant route of exposure to 1,2-dichloroethane in humans. No details of analytical methodology were reported, and the sample size was not provided, and thus, the validity of these results cannot be assessed.

Studies in animals have shown that 1,2-dichloroethane is well absorbed through the skin following dermal exposure. Male rats exposed to 2 mL of 1,2-dichloroethane under cover on a shaved area of the back had blood 1,2-dichloroethane levels of 25 µg/mL after 30 minutes (Morgan et al. 1991). After 24 hours, blood levels were 135 µg/mL and a total of 1.08 mL had been absorbed. The continued build-up of blood levels throughout the 24-hour exposure period shows that the rate of absorption exceeded that of distribution and elimination throughout this entire period. When the experiment was repeated using solutions of 1,2-dichloroethane in water, blood levels peaked after 1–2 hours (at concentrations of

0.35–1.4 µg/mL, depending on degree of saturation of the applied solution) and then declined to control levels within 24 hours. Analysis of the aqueous solutions remaining in the exposure chamber after 24 hours showed that they contained <1% of the initial 1,2-dichloroethane concentration. This result suggests that 1,2-dichloroethane in water was rapidly and completely absorbed from solution, thus allowing elimination processes to reduce blood concentration to control levels within the 24-hour exposure period. 1,2-Dichloroethane was among the best absorbed of the 14 volatile organic compounds tested in this experiment.

Supporting data for the time course of absorption following neat exposure were obtained by Jakobson et al. (1982), who studied the dermal absorption of 1,2-dichloroethane in anesthetized guinea pigs. Blood concentrations rose rapidly during the first half-hour after application, followed by steadily increasing blood levels throughout the 12-hour exposure period. Tsuruta (1975) estimated the rate of percutaneous absorption of 1,2-dichloroethane. After a 15-minute exposure, the absorption rate through the abdominal skin of mice was 480 nmol/minute/cm^2. In contrast to the results of Morgan et al. (1991), comparisons of this absorption rate with those of other chlorinated hydrocarbons tested in the same study did not support the conclusion that 1,2-dichloroethane is among the more rapidly absorbed of these chemicals.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

1,2-Dichloroethane was detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg % [per 100 mL]) of nursing mothers 1 hour after leaving factory premises containing 15.6 ppm 1,2-dichloroethane in the air (Urusova 1953). This observation suggests a rapid distribution of 1,2-dichloroethane in humans following inhalation exposure.

The distribution of 1,2-dichloroethane in rats following a 6-hour inhalation exposure to 50 or 250 ppm occurred readily throughout body tissues; levels achieved in tissues were dose-dependent (Spreafico et al. 1980). The investigators measured 1,2-dichloroethane in blood, liver, lung, and fat, and found that blood and tissue levels reached equilibrium by 2 hours after exposure to 50 ppm and 3 hours after exposure to 250 ppm. Concentrations of 1,2-dichloroethane in liver and lung were lower than those in blood. The highest concentration of 1,2-dichloroethane was found in fat (8–9 times that seen in blood). 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female

rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977), but the reliability of the data is unclear. The geometric mean concentration of 1,2-dichloroethane in maternal blood and in fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level (Withey and Karpinski 1985), indicating transplacental distribution of 1,2-dichloroethane. The slope and intercept of the relation between fetal concentration of 1,2-dichloroethane (µg/g) and exposure level were 0.035 and -3.95, respectively, and for concentration in maternal blood (µg/g), they were 0.092 and -10.4, respectively. However, details of the methods used to detect 1,2-dichloroethane and quantify its concentration in tissues were not provided in Withey and Karpinski (1985), so the validity of the results cannot be confirmed.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 1,2-dichloroethane. However, the wide variety of effects noted in humans following oral exposure suggest a wide distribution.

1,2-Dichloroethane was distributed readily throughout the body following oral administration of single doses to rats (Spreafico et al. 1980). As was seen following inhalation exposure, peak tissue levels were dose-dependent. Spreafico et al. (1980) reported that 1,2-dichloroethane absorbed through the gastrointestinal tract reached peak concentrations in the liver within 10 minutes. Again, equilibrium levels in liver and lung (achieved by 2 hours postexposure) were lower than in blood, while levels in fat were 7–17 times greater than in blood. This difference in tissue levels decreased with increasing dose. Thus, there is little difference between oral and inhalation exposure with regard to tissue distribution in animals, and specific target organ toxicity cannot be explained by differential distribution of 1,2-dichloroethane.

Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single bolus dose of approximately 160 mg/kg on gestation day 12. At 1 hour after exposure, 50% of the orally administered dose was in gastrointestinal tract tissues, falling to 0.2% of the administered dose by 48 hours after exposure, while less than 1% was accounted for in the feces. Aside from the absorptive tissues, the liver and kidney accounted for most of the distributed radioactivity throughout the 48-hour postexposure observation period, although adipose tissue and brain and spinal cord tissues, possible sites of accumulation, were not included in the evaluation. The highest tissue concentrations were found in the liver, ovary, and kidney. Transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus at 1 hour postexposure, with the highest amount in the

conceptus (0.057% of administered dose) occurring at approximately 4 hours postexposure. At 48 hours postexposure, most of the residual radioactivity was located in the liver (0.215% of administered dose). When 160 mg/kg was administered on gestation day 18, the pattern of distribution was similar, except greater accumulation occurred in the developing fetus and placenta. At 48 hours postexposure (the 20th day of gestation), the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

Spreafico et al. (1980) studied the distribution of 1,2-dichloroethane in rats following repeated oral administration (11 daily doses). They demonstrated that there was no difference between blood or tissue levels following either single or repeated exposure. This finding suggests that bioaccumulation of 1,2-dichloroethane does not occur with repeated oral exposure.

3.4.2.3 Dermal Exposure

1,2-Dichloroethane was detected in the breast milk of nursing mothers following dermal exposure (with probable concurrent inhalation exposure) to liquid 1,2-dichloroethane at the workplace (Urusova 1953). The concentration in milk gradually increased, with the maximum level (2.8 mg %) reached 1 hour after work ended. Eighteen hours later, the levels in milk ranged from 0.195 to 0.63 mg %. This study did not report the dermal exposure concentration of 1,2-dichloroethane. Because of the lack of details on methodology, the validity of these findings cannot be assessed.

No studies regarding distribution in animals following dermal exposure to 1,2-dichloroethane were located. Since the tissue distribution of this chemical did not appear to be route-dependent after either inhalation or oral exposure, and since it is well absorbed through the skin, the distribution pattern of 1,2-dichloroethane following percutaneous application may possibly resemble that observed following exposure via other routes.

3.4.2.4 Other Routes of Exposure

No studies were located regarding distribution in humans after parenteral exposure to 1,2-dichloroethane.

Mice exposed to radiolabeled 1,2-dichloroethane by a single intravenous injection had high levels of tightly bound radioactivity in the nasal mucosa and tracheo-bronchial epithelium within 1 minute of exposure; these levels persisted throughout the 4-day observation period (Brittebo et al. 1989). Lower

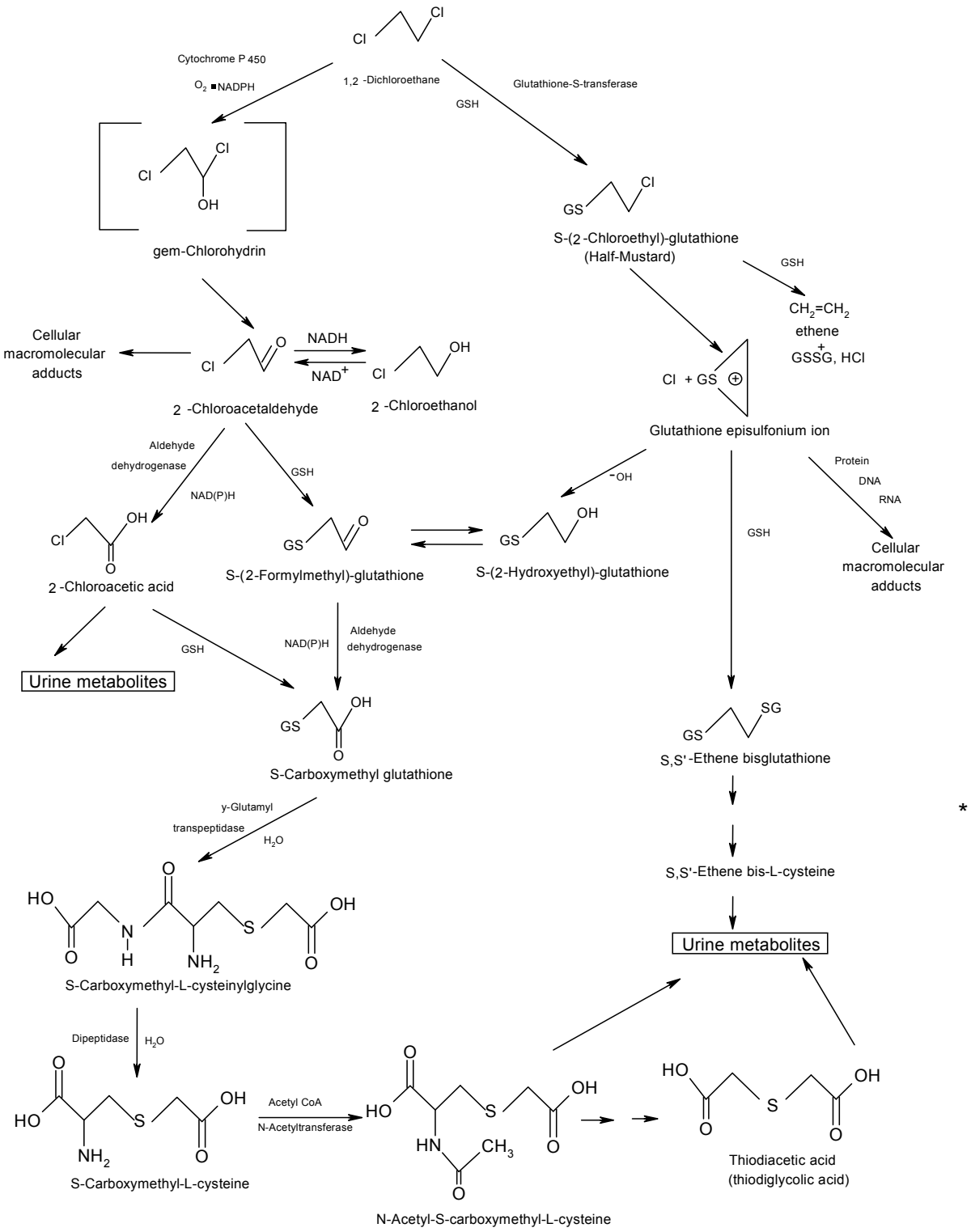
levels of radioactivity were bound to epithelia of the upper alimentary tract, eyelid, and vagina, as well as the liver, kidney, adrenal cortex, and submaxillary gland. The bound radioactivity was considered to represent nonvolatile reactive metabolites formed in the tissues where it was found. A study of tissue kinetics of 1,2-dichloroethane in rats after a single intravenous dose of 15 mg/kg reported preferential initial distribution to fat (Withey and Collins 1980) and first-order elimination from each tissue studied (except blood). The estimated initial concentration in fat was 36.9 µg/g, while for other soft tissues (including heart, lung, liver, spleen, kidney, and brain), the initial concentrations were relatively uniform, with estimates ranging from 4.2 to 9.2 µg/g. The study also showed that distributed 1,2-dichloroethane remained in fat longer than in other soft tissues, as indicated by a lower estimated elimination coefficient in fat (0.0088 min^{-1}) relative to other tissues (ranged from 0.0226 to 0.0514 $minute^{-1}$).

3.4.3 Metabolism

No studies regarding metabolism in humans following inhalation, oral, or dermal exposure to 1,2-dichloroethane were located. The biotransformation of 1,2-dichloroethane has been studied extensively in rats and mice both *in vivo* and *in vitro*. Proposed metabolic pathways for 1,2-dichloroethane are shown in Figure 3-3. The results of the *in vivo* studies indicate that 1,2-dichloroethane is readily metabolized in the body, the primary route of biotransformation involves conjugation with glutathione to yield nonvolatile urinary metabolites, and the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) (D'Souza et al. 1988; Reitz et al. 1982). Metabolic saturation appears to occur sooner after oral (gavage) administration than after inhalation exposure. This will be discussed further below. A proposed physiological pharmacokinetic model explains the route-of-exposure difference in quantifying the amount of 1,2-dichloroethane-glutathione conjugate produced in target organs after oral and inhalation exposures (D'Souza et al. 1987, 1988).

No studies were located regarding metabolism specifically in children. However, the expression of certain enzymes is known to be developmentally regulated. An N-acetyltransferase (NAT) is thought to be involved in 1,2-dichloroethane metabolism at a step subsequent to a glutathione (GSH) conjugation (see Figure 3-3). There are two NATs (NAT1 and NAT2) that are expressed in humans (Parkinson 1996) and one, NAT2, is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks. Activity is low in virtually 100% of infants, and reaches adult activity at 1 to 3 years of age (Leeder and Kearns 1997).

Figure 3-3. Proposed Pathways for 1,2-Dichloroethane Metabolism*



*

Derived from NTP 1991a

3.4.3.1 Inhalation Exposure

Reitz et al. (1982) studied the metabolism of 1,2-dichloroethane in male rats following a 6-hour exposure to 150 ppm of [^{14}C]-1,2-dichloroethane. The exact metabolic pathways were not determined, but an observed depression of hepatic nonprotein sulfhydryl groups may indicate that glutathione plays a major role in the metabolism of 1,2-dichloroethane following inhalation exposure. Saturation of biotransformation enzymes was not apparent at this dose since 84% of the administered ^{14}C was recovered as urinary metabolites and only 2% of the administered ^{14}C was recovered as parent compound in the expired air. However, the data of Spreafico et al. (1980) suggest that saturation does occur after inhalation exposure in rats, since peak blood levels of 1,2-dichloroethane rose 22-fold when the exposure concentration was increased from 50 to 250 ppm. Based on the data of these 2 groups of investigators, it appears that saturation of 1,2-dichloroethane metabolism occurs when blood levels reach 5–10 µg/mL blood or after exposure to 150–250 ppm 1,2-dichloroethane. When blood concentrations of 1,2-dichloroethane exceed these levels (i.e., at exposure concentrations $150 ppm), manifestations of toxicity became more apparent. For example, Maltoni et al. (1980) reported that most of the toxicity associated with inhalation exposure to 250 ppm 1,2-dichloroethane in rats and mice was alleviated when exposure levels were reduced to 150 ppm, and no treatment-related effects were noted at 50 ppm. These findings suggest that 1,2-dichloroethane-induced toxicity occurs once a threshold blood level has been exceeded.

3.4.3.2 Oral Exposure

Reitz et al. (1982) also studied the metabolism of 1,2-dichloroethane following the administration of single oral doses of 150 mg/kg [^{14}C]-1,2-dichloroethane. Again, the exact metabolic pathways were not determined, but the observation that hepatic nonprotein sulfhydryl groups were depressed indicated that glutathione may also play a major role in the metabolism of 1,2-dichloroethane following oral exposure. Saturation of biotransformation enzymes was apparent at this dose since only 60% of the administered radiolabel was recovered as urinary metabolites, and 29% of the administered radiolabel was associated with unchanged parent compound in the expired air. As with inhalation, it appeared that saturation of 1,2-dichloroethane metabolism occurred when blood levels reached 5–10 µg/mL blood or after administration of $25 mg/kg 1,2-dichloroethane (D'Souza et al.1988; Reitz et al. 1982; Spreafico et al. 1980). This blood threshold level again correlated with observed toxicity in animal studies (NCI 1978), as discussed above.

Although the saturable pathways appear to be the same for both oral and inhalation exposure, oral administration of 1,2-dichloroethane by gavage results in saturation at lower administered doses than inhalation exposure. Reitz et al. (1982) demonstrated that administration of 150 mg/kg 1,2-dichloroethane by gavage resulted in a 1.3-fold higher absolute dose to the animals than 150 ppm via inhalation (which is approximately equal to 502 mg/kg). Gavage administration produced approximately twice as much total metabolite as inhalation, and peak levels of 1,2-dichloroethane in blood were almost five times higher following gavage versus inhalation. Gavage administration may not represent typical oral exposure in humans. Gavage administration results in large bolus doses absorbed at one time thereby leading to spikes in blood levels and a more pronounced expression of toxicity. Oral exposure to 1,2-dichloroethane by humans will most likely occur via ingestion of contaminated drinking water in small doses spread out over the course of a day. In such instances, biotransformation processes will probably not become saturated; thus, the risk for adverse effects is not as high as would be predicted from gavage administration of equivalent doses.

3.4.3.3 Intraperitoneal Exposure

In female albino mice given 1,2-dichloroethane intraperitoneally, the metabolism of 1,2-dichloroethane appeared to be initiated by hydrolytic dehalogenation followed by reduction to yield 2-chloroethanol (Yllner 1971b). This was then converted to 2-chloroacetic acid by microsomal oxidation. Final metabolites identified in the urine of these animals in percent radioactivity recovered included *S*-carboxymethyl-L-cysteine (44–46% free; 0.5–5% conjugated), thiodiacetic acid (33–34%), *S,S'*-ethylene-*bis*-cysteine (1.0%), which are indicative of glutathione conjugation, in addition to chloroacetic acid (6–23%) and 2-chloroethanol (0–0.8%) (see Figure 3-3).

3.4.3.4 Other Routes of Exposure

The pathways of 1,2-dichloroethane metabolism have been elucidated primarily by *in vitro* studies in isolated rat hepatic microsomes.

In one *in vitro* study, 1,2-dichloroethane was metabolized mainly to chloroacetaldehyde by hepatic nuclear cytochrome P-450 (Casciola and Ivanetich 1984). Guengerich et al. (1980) proposed a pathway involving microsomal cytochrome P-450 (in the presence of oxygen and nicotinamide adenine dinucleotide phosphate [reduced form] [NADPH]) and MFO to explain the production of chloroacetaldehyde. 1,2-Dichloroethane undergoes oxygen insertion to yield an unstable chlorohydrin,

which spontaneously dechlorinates to form 2-chloroacetaldehyde that can react with macromolecules. 2-Chloroacetaldehyde can also be reduced to chloroethanol or be further oxidized to chloroacetic acid. Guengerich et al. (1991) demonstrated that cytochrome P-450 2E1 is the primary oxidation catalyst of 1,2-dichloroethane in humans.

Conjugation of 1,2-dichloroethane with glutathione is proposed to be a major metabolic pathway *in vivo* (Yllner 1971b); this has been confirmed by the *in vitro* studies of Livesey and Anders (1979), Anders and Livesey (1980), and Jean and Reed (1989). This pathway is outlined on the right side of Figure 3-3. The depletion of hepatic glutathione by 1,2-dichloroethane has been demonstrated *in vitro* (Albano et al. 1984). Johnson (1967) demonstrated that, *in vitro*, conjugation of 2-chloroacetic acid with glutathione also proceeded by a nonenzymatic process, yielding *S*-carboxymethylglutathione. This compound subsequently degraded to yield glycine, glutamic acid, and *S*-carboxymethylcysteine. *S*-carboxymethylcysteine may then be further oxidized to thiodiglycolic acid. Both *S*-carboxymethylcysteine and thiodiglycolic acid were found as urinary metabolites in rats and mice given 1,2-dichloroethane *in vivo* (Spreafico et al. 1980; Yllner 1971b). This scheme is also supported by studies with 1,2-dibromoethane (Nachtomi et al. 1966; Van Bladeren 1983).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Women inhaling approximately 15.6 ppm 1,2-dichloroethane present in the workplace air eliminated the compound unchanged in the expired air. Similar observations were also reported in women exposed via dermal contact to liquid 1,2-dichloroethane. In both cases, the amount of 1,2-dichloroethane in the expired air was greater immediately following exposure and decreased gradually with time (Urusova 1953).

Elimination of 1,2-dichloroethane following inhalation exposure in rats occurred primarily via the excretion of soluble metabolites and unchanged parent compound in the urine and carbon dioxide in the expired air (Reitz et al. 1982; Spreafico et al. 1980). Urinary metabolites accounted for 84% of the absorbed dose, unchanged fecal 1,2-dichloroethane accounted for 2%, and carbon dioxide accounted for 7% of the absorbed dose following the inhalation of 150 ppm by rats (Reitz et al. 1982). The primary urinary metabolites identified in rats following inhalation exposure were thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). The rapidity of elimination is demonstrated by the fact that a few

hours after exposure, 1,2-dichloroethane was not detected in blood and was detected only to a small extent 48 hours after exposure in various tissues (liver, kidney, lung, spleen, forestomach, stomach, carcass) (Reitz et al. 1982).

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following inhalation exposure of 50 or 250 ppm 1,2-dichloroethane for 5 hours. They determined that elimination was monophasic with the half-times of 12.7 and 22 minutes at 50 and 250 ppm exposure, respectively. The disappearance of 1,2-dichloroethane was dose-dependent since the percentage of parent compound recovered in the expired air increased exponentially with dose. This was presumably a reflection of the saturable metabolic processes. Spreafico et al. (1980) also determined that elimination of 1,2-dichloroethane from adipose tissue was slower than elimination of 1,2-dichloroethane from the blood, liver, and lung.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to 1,2-dichloroethane.

Elimination of 1,2-dichloroethane following oral administration in rats was also rapid and occurred primarily via excretion of soluble metabolites in the urine, and unchanged parent compound and carbon dioxide in the expired air (Mitoma et al. 1985; Payan et al. 1993; Reitz et al. 1982; Spreafico et al. 1980). Reitz et al. (1982) conducted a complete ^{14}C-balance study in male Osborne-Mendel rats and found that urinary metabolites accounted for 60% of the radioactivity administered as a single oral dose of 150 mg ^{14}C-1,2-dichloroethane/kg body weight. Unchanged 1,2-dichloroethane in the breath accounted for 29% and carbon dioxide in the breath accounted for 5% of the administered radioactivity. The remaining 6% of the administered radioactivity was recovered in the carcass, feces, and cage washes. The primary urinary metabolites identified were the same as those seen following inhalation exposure—thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). Elimination of 1,2-dichloroethane was 96% complete within 48 hours. The results were similar in rats given a single gavage dose of 150 mg/kg following 2 years of intermittent inhalation exposure to 50 ppm of 1,2-dichloroethane (Cheever et al. 1990).

Mitoma et al. (1985) studied the elimination of single gavage doses of ^{14}C-labeled 1,2-dichloroethane from rats and mice (doses of 100 and 150 mg/kg, respectively, in corn oil) after pretreatment with unlabeled compound 5 days per week for 4 weeks. At 48 hours after administration of the radiolabeled

compound, expired volatile metabolites, CO_2, excreta (feces and urine), and the carcass accounted for approximately 11.5, 8.2, 69.5, and 7% of administered radioactivity in rats, and 7.7, 18.2, 81.9, and 2.4% of the administered dose in mice.

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following the oral administration of 50 mg/kg 1,2-dichloroethane (in corn oil), and found that kinetics were best described by a two-compartment model. Withey et al. (1983) reported that administration in water resulted in a shorter elimination half-time than administration in vegetable oil. Reitz et al. (1982) also reported a two-compartment model of elimination following the gavage administration of 150 mg/kg 1,2-dichloroethane. The initial elimination phase had a half-time of .90 minutes, but elimination became more rapid when blood levels fell to 5–10 µg/mL, characterized by a half-life of approximately 20–30 minutes. This is in contrast, however, to what was observed following inhalation exposure. Spreafico et al. (1980) suggested that the oral profile represented both an absorption-distribution phase and an elimination phase, whereas the inhalation profile reflected only elimination. This elimination of 1,2-dichloroethane was also dose-dependent following oral administration in rats, as the percentage of parent compound recovered in the expired air increased exponentially with dose. Again, this is a reflection of saturable metabolic processes. The rate of elimination from adipose tissue was similar to that from blood and other tissues, in contrast to the results for inhalation exposure.

These results indicate that 1,2-dichloroethane will most likely not accumulate in nonlipid components of the human body following repeated exposure by any route, as elimination of the compound is rapid and complete. Available data also suggest that 1,2-dichloroethane is not particularly persistent in adipose tissue following oral exposure (Spreafico et al. 1980), but it may accumulate to some extent in adipose tissue after inhalation exposure (Spreafico et al. 1980) and/or in breast milk of nursing women (Urusova 1953).

3.4.4.3 Dermal Exposure

1,2-Dichloroethane was eliminated unchanged in the expired air following dermal exposure of nursing mothers to liquid 1,2-dichloroethane in the workplace (Urusova 1953). The amount of 1,2-dichloroethane in the expired air was greatest immediately after skin contact and gradually decreased with time.

No studies were located regarding excretion in animals after dermal exposure to 1,2-dichloroethane.

3.4.4.4 Other Routes of Exposure

Studies conducted in animals in which 1,2-dichloroethane was administered via other routes (e.g., intraperitoneal or intravenous) support the findings of the studies discussed above; excretion of 1,2-dichloroethane via urine and expired air was rapid and complete, and the route of excretion as well as the form of the chemical excreted were dose-dependent (Spreafico et al. 1980; Yllner 1971b).

Estimates of an elimination constant (k_e) for 1,2-dichloroethane were similar between two- and three-compartment pharmacokinetic models fitted to a time-series of blood concentration data that were obtained from rats given single intravenous doses (Withey and Collins 1980). The k_e values for elimination from blood were roughly inversely related to dose; mean values of 0.143, 0.122, 0.091, 0.096, or 0.097 were obtained at dose levels of 3, 6, 9, 12, or 15 mg/kg, respectively.

3.4.5 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.

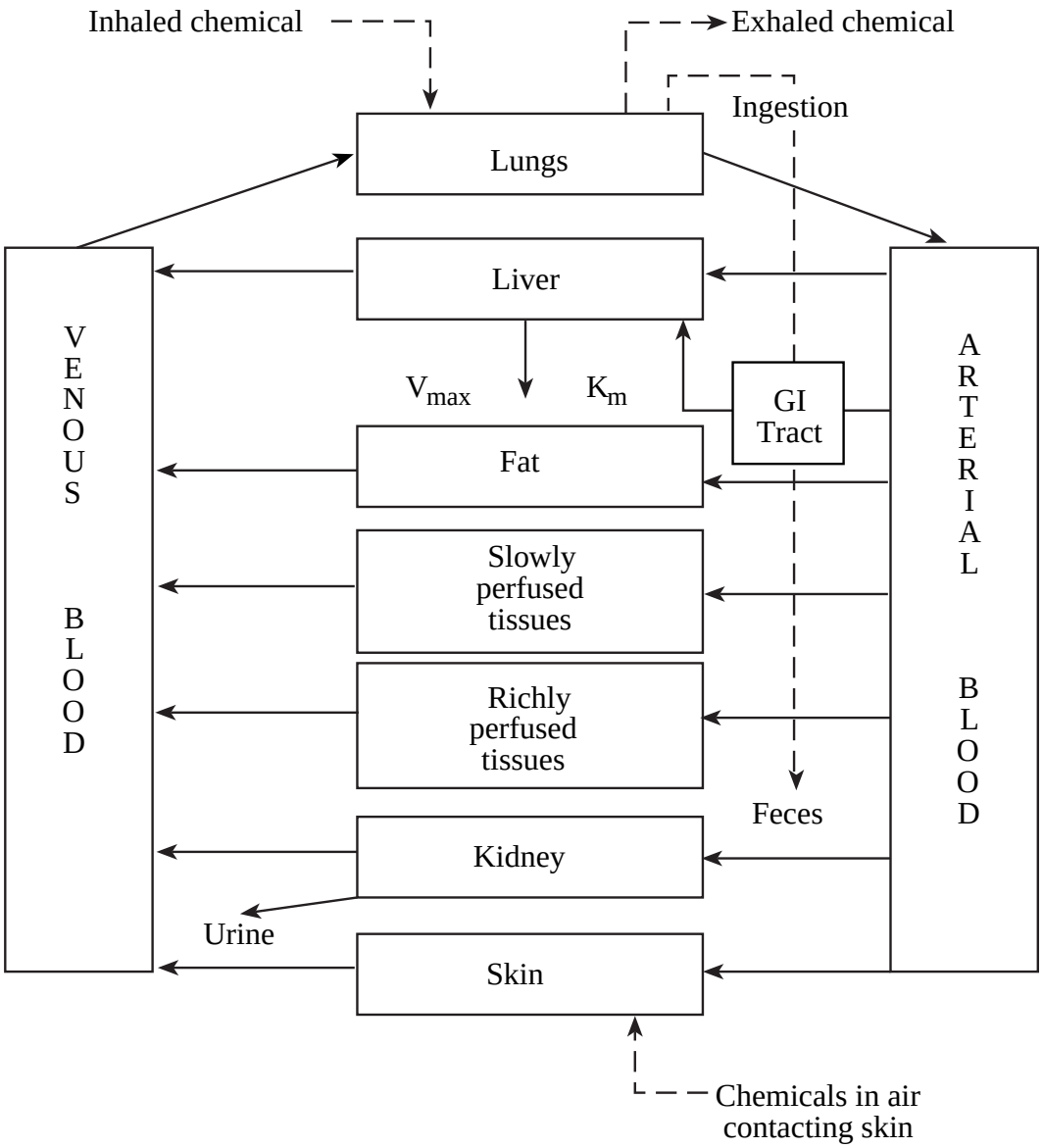
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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 3-4 shows a conceptualized representation of a PBPK model.

A PBPK model has been developed that quantitates the amount of 1,2-dichloroethane and its metabolites that reach the blood and target tissues following different exposure routes (D'Souza et al. 1987, 1988). As discussed in Section 3.4.3, 1,2-dichloroethane is metabolized by a saturable oxidation pathway and direct conjugation with glutathione. The model predicts that inhalation exposures to 1,2-dichloroethane produce less glutathione-conjugate metabolites in the liver and lung of rats than equivalent oral exposures. This prediction offers a possible explanation for why 1,2-dichloroethane is carcinogenic in rats by the oral route (NCI 1978), but not following inhalation exposures (Maltoni et al. 1980). This may have important implications for extrapolating cancer risk from high doses (above MFO saturation) to environmental exposures (below MFO saturation). The PBPK model may also be useful for extrapolating toxicity data

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

from animals to humans because the level of glutathione in the liver appears to modulate the toxic effects of 1,2-dichloroethane (see discussion in Section 3.5). However, this model needs to be tested and validated.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The physical properties of 1,2-dichloroethane, particularly its lipophilic nature, high vapor pressure, and high serum/air partition coefficient, suggest that it is likely to be absorbed across the alveolar membranes of the lung, mucosal membranes of the gastrointestinal tract, and the skin by passive diffusion. Once in the body, it is widely distributed, with the greatest amounts accumulating in the more lipophilic tissues; this probably also occurs by passive diffusion.

There is compelling evidence that the toxicity and carcinogenicity of 1,2-dichloroethane are associated with its metabolism to active intermediates. Studies in rats and mice indicate that 1,2-dichloroethane is metabolized to 2-chloroacetaldehyde, *S*-(2-chloroethyl)glutathione, and other putative reactive intermediates capable of binding covalently to cellular macromolecules (Fabricant and Chalmers 1980; Jean and Reed 1989). The ability of a chemical to bind covalently to cellular macromolecules is often correlated with the induction of toxic and carcinogenic effects. In addition, 1,2-dichloroethane has been shown to promote lipid peroxidation *in vitro* (Sano and Tappel 1990; Tse et al. 1990). Lipid peroxidation is also associated with tissue damage. The lag time between inhalation exposure and onset of effects reported by Nouchi et al. (1984) in an occupationally exposed 51-year-old male may have been a reflection, in part, of the time required to metabolize 1,2-dichloroethane to active intermediates.

The level of glutathione present in the liver appears to modulate effects of 1,2-dichloroethane in animals. Glutathione is believed to be heavily involved in the biotransformation of 1,2-dichloroethane (Anders and Livesey 1980; Yllner 1971b). The metabolic pathway of 1,2-dichloroethane is linear at low doses, but at higher concentrations, as the P-450 enzymes become saturated, the amount of glutathione conjugate produced rises disproportionately with increasing administered dose; at very high doses, the GSH pathway is also saturated, and the glutathione conjugate produced declines disproportionately with increasing dose (D'Souza et al. 1987). It has been suggested that 1,2-dichloroethane-induced toxicity occurs when the biotransformation processes are saturated, thereby allowing higher levels of

1,2-dichloroethane to circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated (D'Souza et al. 1987; Reitz et al. 1982).

This might explain the observation that large drinking water doses fail to produce the same toxic effects as smaller gavage doses (Munson et al. 1982). Gavage administration involves the placement of large bolus doses in the stomach that are absorbed at one time, thereby leading to spikes in blood levels and the subsequent expression of toxicity. However, drinking water exposure results in ingestion of contaminated water in small doses spread out over the course of a day. In such instances, biotransformation processes are not as likely to become saturated, and the risk of adverse effects is not as high as would be predicted from gavage administration of equivalent doses. The time required for saturation of biotransformation processes to occur might have contributed to the lag time, observed by Nouchi et al. (1984), between exposure and onset of toxic effects in an exposed human male, since the exposure dose (unknown) was undoubtedly high.

3.5.2 Mechanisms of Toxicity

Specific mechanisms for 1,2-dichloroethane-induced toxicity have not been elucidated. Studies in rats and mice indicate that 1,2-dichloroethane may be metabolized to 2-chloroacetaldehyde, *S*-(2-chloroethyl)glutathione, and other putative reactive intermediates capable of binding covalently to cellular macromolecules in the liver, kidney, and other tissues (Fabricant and Chalmers 1980; Jean and Reed 1989; Lock 1989). 1,2-Dichloroethane promoted lipid peroxidation in rat liver cells (Sano and Tappel 1990) and arterial endothelial and aortic smooth muscle cells (Tse et al. 1990) *in vitro*, suggesting another possible mechanism by which this chemical might produce toxic effects.

Available evidence suggests that toxicity of 1,2-dichloroethane in various tissues is largely mediated by reactive intermediates formed by conjugation with glutathione (Lock 1989). High levels of glutathione-*S*-transferases, the family of enzymes that catalyze the conjugation of xenobiotics with glutathione, are present in liver, kidney, intestine, testis, adrenal, and lung, primarily (>95%) in the cytoplasm (Parkinson 1996). Putative glutathione-dependent metabolites, such as *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine, are thought to spontaneously rearrange to form electrophilic episulfonium ions that can bind to cellular macromolecules (Peterson et al. 1988). Rapid depletion of hepatocellular glutathione and binding of *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine to liver DNA and protein have been demonstrated *in vitro* (Jean and Reed 1989). Similarly, the renal cortex contains substantial amounts and high activity of glutathione *S*-transferases that perform the initial conjugation

reaction (Lock 1989), and the conjugates *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine have been identified as nephrotoxic in rats. Cytochrome P-450, which catalyzes competing metabolic reactions, has relatively low activity in the kidney, thus shifting the metabolism of 1,2-dichloroethane in the kidney toward production of toxic metabolites.

Differences in carcinogenic response have been observed between the positive oral gavage study (NCI 1978) and the negative inhalation study (Maltoni et al. 1980) summarized in Sections 3.2.1.7 and 3.2.2.7. These inconsistent cancer findings could be attributed to a number of factors, including different strains of rats and inhalation study limitations, including intermittent exposures, an MTD that was exceeded at the highest dose tested, and poor survival rates. The route-related difference in carcinogenic response may also be explained on the basis of metabolic differences and the saturation of the detoxification/ excretion mechanism occurring between the gavage dose and the longer-term inhalation dose, as proposed by Reitz et al. (1982) and discussed in Section 3.5.1. At lower doses, metabolic saturation appeared to occur sooner after oral administration than after inhalation exposure. Reitz et al. (1982) also suggested that the expression of 1,2-dichloroethane-induced toxicity occurred when the biotransformation processes were saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body instead of being detoxified and eliminated. The 1,2-dichloroethane inhalation study therefore may not have produced peak blood levels high enough to saturate the detoxification mechanisms and produce a detectable incidence of tumors. Route-related differences in immunologic and several other toxic responses have similarly been observed, which may also be due to the saturation of the detoxification/ excretion mechanism as a result of the bolus gavage dosing.

3.5.3 Animal-to-Human Extrapolations

The metabolism of 1,2-dichloroethane has not been studied in humans. The lack of this information precludes a nonspeculative attempt to discuss potential interspecies differences or similarities in the toxicity of 1,2-dichloroethane, as well as a determination of which animal species is the most appropriate model for humans. Extrapolations of 1,2-dichloroethane oral toxicity data from animals to humans should consider the type of exposure because, as discussed in Section 3.5.1, some of the differences in toxic and carcinogenic responses in animal studies can be explained on the basis of saturation of the detoxification/excretion mechanism due to bolus (gavage) administration.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies regarding endocrine disruption in humans and animals after exposure to 1,2-dichloroethane were located.

No *in vitro* studies regarding endocrine disruption of 1,2-dichloroethane were located.

3.7 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 resulting from 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 6.6 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 prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining 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, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Data on the health effects of 1,2-dichloroethane exposure in children are limited to a single case report of a 14-year-old boy who swallowed 15 mL of the compound (Yodaiken and Babcock 1973). The most immediate signs of toxicity were headache and staggering gait within 2 hours of exposure, followed soon after by lethargy and vomiting. During the next few days, the boy developed symptoms of toxicity, increasing in variety and severity, that involved several organ systems, including adverse hematological effects, pulmonary edema, cardiac arrest (he was resuscitated), and eventual death on the 5th day after exposure from massive hepatic necrosis and renal tubular necrosis. Data from this case report and from reports of adult humans who died following acute exposure to high levels by inhalation or ingestion are consistent with animal studies indicating that the main targets of acute toxicity include the central nervous system, respiratory tract, stomach, liver, and kidneys. Considering the consistency of effects in acutely exposed humans and animals, and data showing that the liver, kidney, and immune system are sensitive targets of lower-dose and longer-term inhalation and oral exposures in animals, it is reasonable to assume that effects in these tissues would also be seen in similarly exposed adults and children.

No studies that provide reliable information on adverse developmental effects in humans exposed to 1,2-dichloroethane are available. A cross-sectional epidemiologic study that investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995) was located. A number of associations between various chemicals and birth outcomes were found, including a positive association between ingestion of 1,2-dichloroethane in drinking water and major cardiac birth defects; however, the mixed chemical exposures indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

Studies in rats, mice, and rabbits indicate that 1,2-dichloroethane is not developmentally toxic following inhalation or oral gestational exposure, although indications of embryolethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980).

Evidence from mouse studies suggests that the specific nature of oral exposure may play a role in the degree of immunotoxicity expressed in young animals. Bolus doses of 1,2-dichloroethane appear to be more effective in eliciting an immunotoxic response than drinking-water exposures in 5-week-old mice. There was a significant, dose-related reduction in IgM response to sheep erythrocytes, and a significant,

but not dose-related, reduction in delayed-type hypersensitivity response to sheep erythrocytes in 5-week-old CD-1 mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day (Munson et al. 1982). In mice provided 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number. In contrast, mice given drinking water containing 189 mg/kg/day of 1,2-dichloroethane for 90 days beginning at 5 weeks of age displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982). The fact that the animal evidence for oral immunotoxicity of 1,2-dichloroethane includes decreased immune responses in 5-week-old mice provides a limited indication of the potential susceptibility of children to immunotoxic effects, particularly after bolus ingestion by children, that could occur, for example, with accidental ingestion of older household products that contain 1,2-dichloroethane.

Young mice were also susceptible to reduced immune function after brief inhalation exposure to 1,2-dichloroethane. A single 3-hour exposure to 5–11 ppm of 1,2-dichloroethane induced increased susceptibility to *S. zooepidemicus* (i.e., increased mortality following infection) in 4- to 5-week-old female mice, suggesting reduced pulmonary immunological defenses in the exposed mice (Sherwood et al. 1987). No immunological effects were observed at 2.3 ppm. Young female mice exposed to 11 ppm also had reduced bactericidal activity in the lungs 3 hours after inhalation challenge with *K. pneumoniae*. In contrast, young male rats (ages ranging from 4 to 5 weeks) that were exposed once to 200 ppm for 5 hours or 100 ppm 5 hours/day for 12 days did not exhibit any increased susceptibility to infection from these microbes, suggesting that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females (Sherwood et al. 1987). The relevance of the young mouse inhalation data to child susceptibility is unknown, particularly in the light of the observed interspecies differences. However, the data do suggest that it would be prudent to prevent 1,2-dichloroethane inhalation exposures in children such as those that might occur during, and for several days after, using old wallpaper or carpet adhesives that contain 1,2-dichloroethane.

No studies that evaluated for the distribution of 1,2-dichloroethane or its metabolites across the placenta in humans were located. However, there is some evidence that 1,2-dichloroethane and/or its metabolites crosses the placenta after inhalation and oral exposures in animals. 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977). Additional evidence of transplacental distribution of 1,2-dichloroethane after inhalation exposure is provided by Withey and Karpinski (1985), who found that

the geometric mean concentration of 1,2-dichloroethane in the fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level. However, the reliability of the Vozovaya data is unclear, and the methods for evaluating 1,2-dichloroethane tissue concentrations were not reported in Withey and Karpinski (1985).

There is clearer evidence for transplacental distribution of 1,2-dichloroethane and/or its metabolites after maternal oral exposure. Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on gestation day 12 or 18. In both cases, transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus. A greater accumulation occurred in the developing fetus and placenta 48 hours after the gestation-day 18 administration than after the gestation-day 12 administration. At 48 hours after the gestation-day 18 dosing, the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

No studies regarding 1,2-dichloroethane metabolism in children were located. The metabolism of 1,2-dichloroethane is well described (see Figure 3-3), and it is reasonable to assume that the metabolic pathways are, for the most part, the same between adults and children. However, the expression of certain enzymes is known to be developmentally regulated, and one of these enzymes may be involved in 1,2-dichloroethane metabolism. NAT is involved in 1,2-dichloroethane metabolism at a step subsequent to GSH conjugation (see Figure 3-3). NAT performs the N-acetylation of S-carboxymethyl-L-cysteine to N-acetyl-S-carboxymethyl-L-cysteine, a major urinary metabolite. There are, however, two NATs (NAT1 and NAT2) that are expressed in humans with separate but overlapping substrate specificities (Parkinson 1996). NAT2 is apparently expressed only in the liver and the gut (Parkinson 1996), and is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks, but NAT2 activity is low in virtually 100% of infants, not reaching adult activity levels until 1 to 3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991a), the source of the metabolism information in Figure 3-3, whether the NAT involved in 1,2-dichloroethane metabolism is NAT1 or NAT2, although both enzymes N-acetylate some xenobiotics equally well (Parkinson 1996).

1,2-Dichloroethane has been detected in human milk (EPA 1980a; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane also accumulated in the adipose tissue of rats after inhalation exposure and was eliminated from fat more slowly than from blood,

liver, and lung (Spreafico et al. 1980), suggesting the possibility that the maternal body burden of 1,2-dichloroethane in fat could be available for exposure to the fetus or nursing infant for a somewhat extended period after maternal exposure. Supporting data for relatively slow elimination of 1,2-dichloroethane from fat are provided in an intravenous exposure study in rats (Withey and Collins 1980).

3.8 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 1,2-dichloroethane are discussed in Section 3.8.1.

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 1,2-dichloroethane are discussed in Section 3.8.2.

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 3.10. "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,2-Dichloroethane

Levels of 1,2-dichloroethane in breath, blood, and urine may be used to indicate exposure to this chemical. However, these measurements would have to be made soon after exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.4.4). In addition, it is not possible to establish from such measurements the precise environmental levels of 1,2-dichloroethane to which these individuals were exposed. A number of studies have investigated the relationship between tissue and environmental levels of 1,2-dichloroethane. In general, small amounts of 1,2-dichloroethane detected in the breath and urine (trace–0.2 ppb and 50–140 ng/L, respectively) were associated with exposure to 1,2-dichloroethane in air and water (Barkley et al. 1980; Conkle et al. 1975). In 2 studies conducted by Wallace et al. (1984, 1986), levels of 1,2-dichloroethane in breath samples from 350 residents of New Jersey were consistently below the detection limit; therefore, no conclusions could be drawn from these studies. 1,2-Dichloroethane was also detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg %) of nursing women working in factory premises containing 15.6 ppm 1,2-dichloroethane in air (Urusova 1953). These data are insufficient to characterize the relationship between environmental exposure to 1,2-dichloroethane and resultant tissue and fluid levels.

Urinary excretion of thioethers is another potentially useful biomarker of exposure to 1,2-dichloroethane. Payan et al. (1993) showed that total excreted urinary thioethers increased linearly with increasing oral dose (for doses between 0.25 and 4.04 mmol/kg [11.9 mg/kg/d and 400 mg/kg/d, respectively]) in male Sprague-Dawley rats during a 24-hour postadministration period, at a rate of 0.028 mmol thiol group eliminated per millimole of 1,2-dichloroethane administered. This occurred in spite of the fact that the total percentage of orally administered radioactivity excreted in the urine decreased with increasing dose (possibly due to saturation of certain metabolic pathways leading to urinary metabolites). Thioethers are commonly produced by conjugation reactions involving glutathione and comprise the primary urinary metabolites of 1,2-dichloroethane (see Sections 3.4.3 and 3.4.4). Increased urinary excretion of thioethers following exposure to 1,2-dichloroethane has been demonstrated in rats (Igwe et al. 1988; Payan et al. 1993), showing that this end point is sensitive to 1,2-dichloroethane exposure. As discussed above for the

parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made soon after exposure to be of any value. There is an additional problem with use of increased urinary thioether excretion as a biomarker for 1,2-dichloroethane exposure. Since many xenobiotics form conjugates with glutathione, exposure to any number of compounds may increase urinary excretion of total thioethers (Monster 1986). Therefore, its use as a biomarker of 1,2-dichloroethane exposure is limited unless exposure to other compounds can be ruled out. Payan et al. (1993), however, found that urinary thiodiglycolic acid (measured by gas chromatography), a thioether compound that is not extractable by alkaline hydrolysis, is a more sensitive marker of 1,2-dichloroethane exposure than total thioethers.

Kim and Guengerich (1989) found that urinary mercapturic acid was linearly dose-related to intraperitoneally injected 1,2-dibromoethane in rats, and the urinary excretion of mercapturic acid was correlated with formation of hepatic and renal DNA adducts. It is possible that a similar relationship exists for relevant 1,2-dichloroethane exposures, although the methods proposed by Kim and Guengerich (1989) would not discriminate between the halogens.

Erve et al. (1996) investigated whether human hemoglobin, alkylated with the episulfonium ion of *S*-(2-chloroethyl)glutathione (a 1,2-dichloroethane metabolite via the glutathione-conjugation metabolic pathway), could be a useful biomarker for human exposure to 1,2-dichloroethane. They found that the method was not a very sensitive indicator for exposure, since an approximately 100-fold molar excess of *S*-(2-chloroethyl)glutathione over the hemoglobin concentration was required before alkylation was detectable *in vitro*.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,2-Dichloroethane

The health effects observed in humans exposed to 1,2-dichloroethane are all nonspecific effects and may be produced from any number of causes, including other causes that do not involve environmental exposure to xenobiotics such as 1,2-dichloroethane. Therefore, these effects would not be useful as indicators of exposure to 1,2-dichloroethane. Even if other causes could be ruled out, the specific levels that produce the various effects in humans are not known, so it would not be possible to quantify exposure based on the observed effects.

The primary targets of 1,2-dichloroethane identified in humans are probably the central nervous system, liver, and kidney (for a detailed description of the health effects of 1,2-dichloroethane, see Section 3.2).

Another likely target is the immune system, for which very limited information was available in humans but was the most sensitive target of 1,2-dichloroethane in animals. The effect on the immune system is immunosuppression. The observed biomarkers for this effect are reduced ability to fight induced bacterial infection, reduced immunoglobulin response to sheep erythrocytes, and reduced delayed-type hypersensitivity response to sheep erythrocytes, all of which show reduced immune system response to a challenge. The neurological effects observed included a variety of symptoms such as headache, irritability, drowsiness, tremors, partial paralysis, and coma. These effects were accompanied by histopathological changes in the brain in both humans and animals. The symptoms that occur at the lowest levels (such as headache, irritability, drowsiness, and tremors) may be considered biomarkers for the neurological effects of 1,2-dichloroethane. However, these suggested biomarkers of effects are nonspecific to 1,2-dichloroethane-induced toxicity.

Liver damage is a prominent feature of 1,2-dichloroethane exposure. Biomarkers for hepatotoxicity observed in humans and animals were alkylation of hepatocellular macromolecules, increased liver weight, and elevated levels of serum enzymes (ALT, AST, SDH). Kidney damage is another major effect of 1,2-dichloroethane; kidney failure has been reported in humans following high-level exposure. Biomarkers of renal effects in humans and animals included binding of macromolecules in renal cells and increased kidney weight. Glomerular involvement may be indicated by urinary excretion of the glomerular structural protein fibronectin (Bundschuh et al. 1993). Discussions of additional biomarkers of immunological, neurological, hepatic, and renal effects that may be relevant for 1,2-dichloroethane-induced toxicity can be found in the CDC/ATSDR (1990) and OTA (1990) reports referenced in Chapter 9.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies regarding interactions of 1,2-dichloroethane with other chemicals in humans were located. Based on metabolic data resulting from animal studies, various interactions can be expected to occur. Inducers and inhibitors of cytochrome P-450 enzymes, glutathione precursors and depleting agents, and dietary/nutritional status can all influence the rate of formation and excretion of the various toxic intermediates resulting from exposure to 1,2-dichloroethane.

Induction of hepatic cytochrome P-450 enzymes by phenobarbital and/or Aroclor 1254 increases the rate of MFO metabolism of 1,2-dichloroethane *in vitro* (Hayes et al. 1973; Sipes and Gandolfi 1980). Alterations in metabolism could potentially produce profound effects on toxicity. Enhanced enzymatic

metabolism of 1,2-dichloroethane also occurs after treatment with ethanol *in vitro* (Sato et al. 1981). Ethanol is an inducer of cytochrome P-450 2E1, the major MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991). However, the effect of the consumption of ethanol before *in vitro* exposure to 1,2-dichloroethane varies greatly depending on the actual tissue concentration of ethanol reached during the metabolism of 1,2-dichloroethane (Sato et al. 1981). At low tissue ethanol concentration, cytochrome P-450 activity is stimulated. At high tissue ethanol concentrations, especially just before exposure to 1,2-dichloroethane, suppression of 1,2-dichloroethane metabolism occurs (Sato et al. 1981). Metabolism of 1,2-dichloroethane (50 ppm in air) was unaffected by chronic co-exposure to ethanol (5% in drinking water) in a 2-year study in rats (Cheever et al. 1990). Toxicity was also unaffected in this study.

Concurrent administration of 0.15% disulfiram in the diet and inhaled 1,2-dichloroethane (10, 153–304, 455 ppm) in animals markedly increased hepatotoxicity much more than would occur with exposure to 1,2-dichloroethane alone (Igwe et al. 1986a, 1988). Similarly, after chronic co-treatment with 50 ppm of 1,2-dichloroethane by inhalation and 0.05% disulfiram in the diet for 2 years, a series of neoplastic lesions were produced in rats that were not produced by 1,2-dichloroethane (or disulfiram) alone (Cheever et al. 1990). The lesions included intrahepatic bile duct cholangiomas, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumors in the testes, and mammary adenocarcinomas.

Metabolism studies on rats co-exposed to 1,2-dichloroethane and disulfiram for 2 years showed that following a 7-hour exposure, blood levels of 1,2-dichloroethane were elevated five-fold by co-treatment with disulfiram (Cheever et al. 1990). In addition, the amount of ^{14}C eliminated as unchanged 1,2-dichloroethane in the breath was elevated by disulfiram co-treatment, with a corresponding decrease in the amount of radioactivity excreted as metabolites in the urine. These results support the suggestion that disulfiram reduces the MFO metabolism of 1,2-dichloroethane, leading to accumulation of 1,2-dichloroethane in the blood and toxic effects. Diethyldithiocarbamate, the reduced form of disulfiram, is a relatively selective inhibitor of cytochrome P-450 2E1, the primary MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991).

Conjugation with glutathione is an important metabolic pathway for 1,2-dichloroethane. However, glutathione conjugation with 1,2-dichloroethane has also been hypothesized to produce reactive sulfur half-mustard metabolites, such as *S*-(2-chloroethyl) glutathione (D'Souza et al. 1987; Igwe et al. 1986b; Jean and Reed 1989; Lock 1989; Reitz et al. 1982). There is considerable evidence supporting the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloro-

ethane toxicity. However, studies also show a protective effect of glutathione. The administration of glutathione, precursors of glutathione, or amino acids capable of donating a sulfhydryl group for the biosynthesis of glutathione all decrease the toxic effects and mortality in rats given 1,2-dichloroethane orally (Heppel et al. 1947). This protective action of glutathione and precursors also occurs in young rats exposed to 1,2-dichloroethane by inhalation (Johnson 1967). It is not clear how the protective effect of glutathione reported in these studies may be reconciled with the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity. By analogy to 1,2-dibromoethane, however, the protective effect of co-administered glutathione in 1,2-dichloroethane exposures might be explained by the reaction of S-(2-chloroethyl)glutathione with glutathione, which is a nonenzymatic reaction occurring at physiological glutathione concentrations (Cmarik et al. 1990), although work with 1,2-dibromoethane indicates that levels of DNA adducts are correlated with glutathione content (Kim and Guengerich 1990). Methionine, p-aminobenzoic acid, aniline, and sulfanilamide have been shown to protect against toxicity of 1,2-dichloroethane (Heppel et al. 1945). A good correlation has been found between the urinary excretion of mercapturic acid and the formation of DNA adducts in liver and kidney DNA of 1,2-dibromoethane-treated rats (Kim and Guengerich 1989). This finding suggests that the extent of formation of adducts may be correlated with the toxic effects of 1,2-dichloroethane.

Nutritional status affects the rate of metabolic formation of toxic intermediates; liver from fasted animals showed an increased rate of 1,2-dichloroethane metabolism *in vitro* (Nakajima and Sato 1979) because fasting induces the formation of cytochrome P-450 2E1 (Johansson et al. 1988), the primary MFO enzyme involved in oxidation of 1,2-dichloroethane (Guengerich et al. 1991). Fasting also may lower hepatic levels of glutathione. According to the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity, toxicity would be reduced under these conditions. However, the actual effect of fasting on 1,2-dichloroethane toxicity is unknown.

A few studies that investigated the toxic interactions between 1,2-dichloroethane and other xenobiotic toxicants were located. Pretreatment with orally administered 2-hexanone did not potentiate the nephrotoxicity of 1,2-dichloroethane administered by intraperitoneal injection in rats (Raisbeck et al. 1990). Co-treatment with 1,1-dichloroethylene produced only a slightly greater-than-additive effect on lipid droplet changes in rat hepatocytes (EPA 1989b). A mixture of 1,2-dichloroethane (80 mg/kg) and carbon tetrachloride (200 mg/kg) administered in a single oral dose to rats produced lower liver triglyceride levels than observed with carbon tetrachloride alone. These levels were still increased above

1,2-dichloroethane-only levels (Aragno et al. 1992). Studies of *in vitro* interactions produced more positive results. *tert*-Butyl hydroperoxide potentiated lipid peroxidation induced by 1,2-dichloroethane in rat liver slices *in vitro* (Sano and Tappel 1990). The occurrence of lipid peroxidation is associated with physical damage to tissues. There was a synergistic inactivation of plasma alpha-1 proteinase inhibitor when 1,2-dichloroethane was tested together with the cigarette smoke components acrolein and pyruvic aldehyde *in vitro* (Ansari et al. 1988b). Inactivation of plasma alpha-1 proteinase inhibitor has been proposed as an important factor in the development of lung emphysema.

Oral administration of 1,2-dichloroethane in drinking water for 16 weeks together with 3 other chemical carcinogens commonly found at hazardous waste sites (arsenic, vinyl chloride, and trichloroethylene) resulted in inhibition of the promotion of preneoplastic hepatic lesions and pulmonary hyperplasia and adenomas (Pott et al. 1998). The four chemicals, including 1,2-dichloroethane, have been shown to be individually carcinogenic in laboratory animals, yet they interacted antagonistically to inhibit promotion of precancerous lesions. The study is limited, however, by a short exposure duration, small numbers of test animals, and the use of only male rats; the interactive effect of lifetime exposure to the four chemicals cannot be inferred with confidence from these results. The mechanism for this interactive effect has not been elucidated, but Pott et al. (1998) hypothesized that decreased cell proliferation, increased apoptosis, or enhanced remodeling of preneoplastic lesions may play a role.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,2-dichloroethane than will most persons exposed to the same level of 1,2-dichloroethane 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 result in reduced detoxification or excretion of 1,2-dichloroethane, or compromised function of organs affected by 1,2-dichloroethane. Populations who are at greater risk due to their unusually high exposure to 1,2-dichloroethane are discussed in Section 6.7, Populations With Potentially High Exposures.

The synergistic effect of disulfiram (tetraethylthiuram disulfide) on 1,2-dichloroethane hepatotoxicity and carcinogenicity in animal studies suggests that individuals exposed concurrently to 1,2-dichloroethane and disulfiram, either in the rubber industry or medically (disulfiram is used as an anti-alcohol-abuse drug), have increased risk for liver toxicity (Cheever et al. 1990; Igwe et al. 1986a). Disulfiram and its reduced form, diethyldithiocarbamate, are known inhibitors of microsomal MFO enzyme, particularly

cytochrome P-450 2E1 (Guengerich et al. 1991; Igwe et al. 1985). It is possible that people exposed to other MFO inhibitors of like specificity would be at similar risk.

Inactivation of plasma alpha-1-proteinase inhibitor has been proposed to be an important factor in the development of lung emphysema. The occurrence of a synergistic inactivation of plasma alpha-1 proteinase inhibitor by 1,2-dichloroethane and cigarette smoke components (acrolein and pyruvic aldehyde) *in vitro* suggests that smokers as well as those exposed to passive smoke may be more susceptible to lung emphysema following repeated exposure to 1,2-dichloroethane (Ansari et al. 1988b). Further, those with genetically reduced plasma alpha-1-proteinase inhibitor, who are predisposed to emphysema, may be at increased risk.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,2-dichloroethane. 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 1,2-dichloroethane. 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 1,2-dichloroethane:

> Ellenhorn, M.J. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisons. (2^{nd} ed). Williams and Wilkins, Baltimore. 2047 pp.

The following discussion is based on suggested treatments provided in Ellenhorn (1997) for patients who were exposed to halogenated solvents, including 1,2-dichloroethane. Treatment is largely supportive. After dermal or ocular exposure, the exposed surface should be washed immediately with large amounts of water; for the eye, a 15- to 20-minute rinse is suggested. Appropriate and timely administration of ipecac to induce vomiting may help to reduce absorption from the gut if administered within 1 or 2 hours after the halogenated solvent is ingested. However, the risk of aspiration of the chemical during vomiting should be considered, particularly for infants and small children. After inhalation exposure, provide oxygen and watch for the need to provide mechanical respiration.

After exposures to high levels of a halogenated solvent, including 1,2-dichloroethane, the patient should be monitored for respiratory depression, hypoxic encephalopathy, cardiac dysrhythmias, hepatotoxicity, and renal toxicity (Ellenhorn 1997). Blood gases should be monitored and good ventilation maintained.

Observe for cardiac arrhythmias for a minimum of 24 hours. In the event of a ventricular arrhythmia, lidocaine or beta-blockers could be administered. Monitor serum creatinine, hepatic aminotransferase, electrolytes, and fluid balance for signs of hepatic or renal failure. Dialysis may be helpful in the event of renal failure. Hepatic failure may be treated with fresh frozen plasma, vitamin K, low protein diet, neomycin, and lactulose.

A major metabolic pathway of 1,2-dichloroethane involves conjugation with glutathione. In apparent opposition to the observation that conjugation with glutathione mediates 1,2-dichloroethane toxicity, some evidence from animal studies (Heppel et al. 1947; Johnson 1967) suggests that, after acute oral or inhalation exposure to 1,2-dichloroethane, prompt oral administration of glutathione, precursors of glutathione, or amino acids involved in donating a sulfhydryl group for the biosynthesis of glutathione may help to reduce the toxic effects of 1,2-dichloroethane exposure (further details of the animal studies are provided in Section 3.9). Ellenhorn (1997) suggested that treatment with N-acetylcysteine may help to restore depleted glutathione after exposure to a halogenated solvent, although he noted that no clinical trials had been conducted to confirm the efficacy or safety of this treatment.

3.11.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption of 1,2-dichloroethane after oral exposure include gastric lavage with activated charcoal, administration of ipecac to induce emesis, and the use of cathartics (Ellenhorn and Barceloux 1988). No information regarding ways to reduce absorption after exposure by other routes was located.

3.11.2 Reducing Body Burden

1,2-Dichloroethane is rapidly eliminated from the body after exposure. In animals, excretion of 1,2-dichloroethane and its metabolites was essentially complete within 48 hours of exposure (see Section 3.4.4). Following inhalation or oral exposure, elimination of 1,2-dichloroethane occurred primarily via excretion of soluble metabolites in the urine and excretion of unchanged parent compound and carbon dioxide in the expired air (Reitz et al. 1982). Increasing the volume of urine production by consuming a large volume of fluids beginning shortly after exposure may enhance the rate of urinary excretion of soluble 1,2-dichloroethane metabolites. The available data suggest that 1,2-dichloroethane will not accumulate in nonlipid components of the human body, but that it may accumulate to some extent in adipose tissue and in the breast milk of nursing women. Excretion of 1,2-dichloroethane may be

facilitated in nursing women by removing milk using either manual expression or a breast pump. The expressed breast milk should be discarded and not fed to infants. Methods (not specified) to enhance removal of 1,2-dichloroethane from the body have not been successful (Ellenhorn and Barceloux 1988).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism by which 1,2-dichloroethane produces toxic effects is not entirely understood. The two important metabolic pathways for 1,2-dichloroethane both lead to the formation of potentially reactive intermediates—chloroacetaldehyde by MFO and *S*-(2-chloroethyl)glutathione by glutathione conjugation (see Section 3.4.3). These reactive intermediates could produce toxic effects by binding covalently to cellular macromolecules. The MFO biotransformation pathway is saturable, and it has been suggested that 1,2-dichloroethane-induced toxicity occurs when MFO metabolism is saturated and large amounts of 1,2-dichloroethane conjugate with glutathione (see Section 3.5.1).

If this hypothesis is correct, then stimulation of MFO metabolism might prove effective in reducing toxicity. Cytochrome P-450 2E1 is the specific MFO enzyme that catalyzes metabolism of 1,2-dichloroethane (Guengerich et al. 1991). Theoretically, a drug that very rapidly induces this enzyme and is administered in a timely manner might have the ultimate effect of reducing 1,2-dichloroethane toxicity. Although experimental data are lacking that show that rapid P-450 2E1 induction by another chemical reduces 1,2-dichloroethane toxicity, available data do provide indirect support of this argument. Co-treatment with disulfiram, an inhibitor of MFO metabolism (especially P-450 2E1), enhances the toxicity of 1,2-dichloroethane (see Section 3.10). Alternatively, administration of drugs that would compete for glutathione and reduce the amount of glutathione available to conjugate with 1,2-dichloroethane might also mitigate the toxicity of 1,2-dichloroethane.

However, as evidence of the complexity of 1,2-dichloroethane biotransformation and uncertainty regarding toxic mechanisms, it may be noted that co-administration of glutathione and precursors with 1,2-dichloroethane had a protective effect (Heppel et al. 1947; Jaeger et al. 1974; Johnson 1967). These results are the opposite of those expected from the hypothesis that glutathione-dependent metabolites are responsible for 1,2-dichloroethane-induced toxicity. Clearly, a greater understanding of 1,2-dichloroethane bioactivation is necessary to develop methods to interfere with the process.

3.12 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 1,2-dichloroethane 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 1,2-dichloroethane.

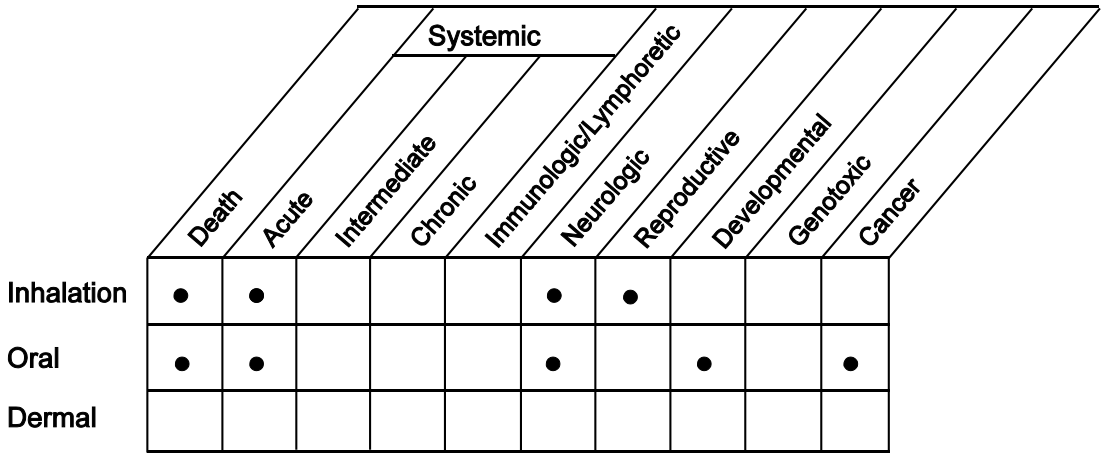
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

3.12.1 Existing Information on Health Effects of 1,2-Dichloroethane

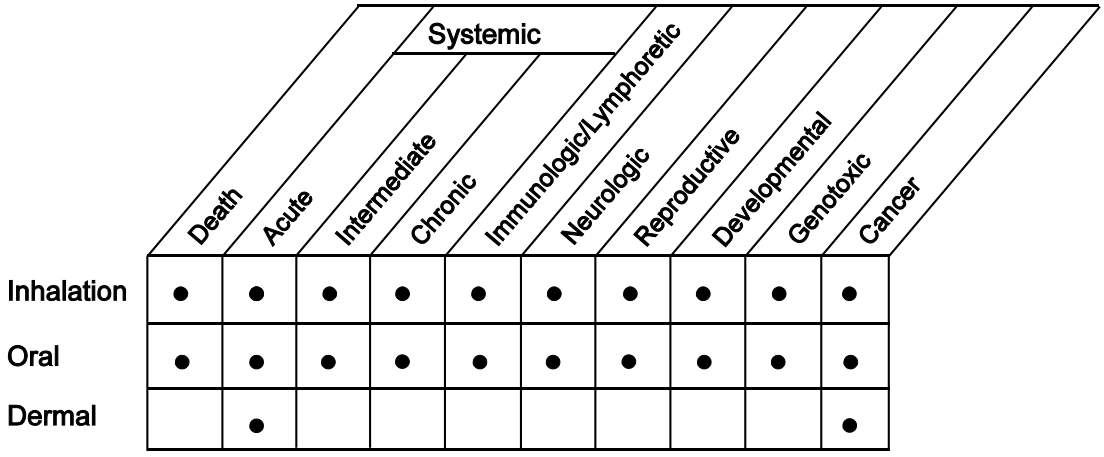
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloroethane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2-dichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Limited information is available on the effects of inhaled 1,2-dichloroethane in humans. Most of the information consists of case reports of accidental or occupational exposure to 1,2-dichloroethane vapor. These studies are difficult to interpret because exposure concentration usually was not quantified, dermal exposure to 1,2-dichloroethane was also likely to occur concurrently with inhalation exposure, thereby contributing to total dose, or co-exposure to other chemicals occurred. The human health effects associated with ingested 1,2-dichloroethane are reported in case studies of individuals who drank 1,2-dichloroethane either intentionally or accidentally. In almost all of the case studies, death occurred

Figure 3-5. Existing Information on Health Effects of 1,2-Dichloroethane



Human



Animal

● Existing Studies

within a few days following exposure, and many of the systemic effects observed were found upon autopsy. No evidence of a relationship between 1,2-dichloroethane and cancer has been reported in epidemiological studies of petrochemical and other chemical industry workers, but the relevance of these studies to 1,2-dichloroethane is limited because exposure to various other chemicals also occurred. Similarly, evidence that 1,2-dichloroethane in drinking water is associated with colon and rectal cancer is also limited by the co-exposure to other chemicals. No information regarding human health effects following dermal exposure to 1,2-dichloroethane, except for ocular effects produced by direct contact with the vapor during inhalation exposure was located.

The lethal and systemic effects of 1,2-dichloroethane following acute- and intermediate-duration inhalation exposures have been studied in a variety of species. Excessive mortality was noted in most species examined under these exposure durations. Health effects associated with chronic-duration inhalation exposure to 1,2-dichloroethane have been investigated only in rats. Lethal and systemic effects of oral exposure have been studied mainly in rats and mice exposed for acute, intermediate, and chronic durations. Animal health effects data for dermal exposure to 1,2-dichloroethane are only available for acute-duration exposure. The carcinogenic effects of 1,2-dichloroethane have been investigated in rats and mice following inhalation, oral, and dermal exposure. Based on the results of available animal studies, EPA has classified 1,2-dichloroethane as a possible human carcinogen (Group B2) (IRIS 2001).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Information on 1,2-dichloroethane toxicity in humans comes primarily from a few case reports of humans who died following acute exposure to high levels of 1,2-dichloroethane by inhalation or ingestion (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Information that may be obtained from such studies is limited, but for 1,2-dichloroethane, the data were sufficient to identify the central nervous system, liver, kidney, and possibly cardiovascular system as target organs of high-level exposure from both oral and inhalation exposure. Results from acute inhalation and oral exposure studies in animals generally support the observations in humans. The dose spacing in these animal studies, however, was wide and resulted in identification of NOAELs and serious LOAELs for these effects.

The immune system was identified as the most sensitive target in mice for acute gavage exposure (Munson et al. 1982) and acute inhalation exposure (Sherwood et al. 1987) to 1,2-dichloroethane, but was not affected in rats by acute inhalation exposure to up to 20-fold higher concentrations of 1,2-dichloroethane (Sherwood et al. 1987). The lack of species concordance in the inhalation study in mice and rats (Sherwood et al. 1987) suggested that extrapolation from animals to humans is uncertain. The massive streptococcal challenge and lethality end point used to measure immune response in the mice exposed by inhalation does not appear to be suitable as the basis for MRL derivation. Therefore, an acute-duration inhalation MRL was not derived. Only one end point showed a significant dose-related immunotoxic effect in the acute gavage study in mice (Munson et al. 1982), and the higher doses of 1,2-dichloroethane administered in the drinking water for 90 days were not immunosuppressive in mice (Munson et al. 1982). These findings precluded acute-duration oral MRL derivation. Additional studies are needed to characterize the thresholds for acute immunologic effects and for other end points (e.g., central nervous system, liver, kidney, cardiovascular) to determine the most sensitive effects of inhalation and oral exposure and to investigate whether the immunologic effects in mice can be extrapolated across species. The additional data would establish the most appropriate basis for deriving an acute inhalation or oral MRL.

In addition, the reason for the discrepancy in results for immunotoxicity between the acute gavage and the intermediate drinking water study (Munson et al. 1982) is unknown. Although the discrepancy may have been related to the methods of dosing (gavage versus drinking water), another possible explanation is that younger mice are more susceptible than fully adult mice. As discussed in more detail in the section on children's susceptibility, the mice in the acute study were much younger at the time of immune testing than were the mice in the intermediate study.

The primary exposure routes for populations surrounding hazardous waste sites are ingestion of contaminated water and inhalation of air contaminated by volatilization of 1,2-dichloroethane from waste sites and from contaminated water used as household water. Studies to determine acute thresholds for effects induced by oral exposure, especially via drinking water instead of gavage, and to determine acute thresholds for effects of inhalation exposure are needed as populations near hazardous waste sites may be exposed to this chemical for brief periods by these routes.

Very little information was located regarding acute toxicity following dermal exposure in humans or animals. 1,2-Dichloroethane is well absorbed by this route, both as undiluted chemical and from aqueous solution (Morgan et al. 1991), and is expected to produce effects in the same tissues affected by exposure

via other routes. Acute dermal toxicity data are needed because acute dermal exposure to 1,2-dichloroethane (in household water used for bathing and showering) is a likely route of exposure for humans who live near hazardous waste sites.

Intermediate-Duration. A data need to conduct additional studies via inhalation and dermal exposure has been identified. There is no information on the health effects of intermediate-duration exposure to 1,2-dichloroethane in humans. Available inhalation studies in animals (Heppel et al. 1946; Spencer et al. 1951) are adequate for identifying main target organs (essentially the same as those affected by acute inhalation and oral exposure in humans and animals), but do not provide a fully adequate basis for identifying the most sensitive end points. Limitations in the intermediate-duration inhalation studies preclude considering them in MRL derivation. Additional studies to identify toxicity thresholds following intermediate-duration inhalation exposure are needed to derive an inhalation MRL specifically for intermediate-duration exposure.

The MRL for intermediate oral exposure is based on a LOAEL of 58 mg/kg/day for kidney effects in rats from an adequate 13-week drinking water study in rats and mice (NTP 1991a). In the same drinking water study, the most sensitive effect in mice was also renal, but it occurred at a much higher exposure level, 249 mg/kg/day (NTP 1991a). A 90-day immunotoxicity study in mice of 1,2-dichloroethane in drinking water found no effects on the immune system and no effects on liver or kidney weight at the highest exposure level, 189 mg/kg/day. Thus, the rat appears to be more sensitive than the mouse to 1,2-dichloroethane exposure in drinking water. Although few immune-related end points were evaluated in the rat subchronic drinking water study (leukocyte counts, thymus histology), acute inhalation exposure did not result in immune effects in rats at exposure levels as much as 20-fold higher than the effect levels in mice in the same study (Sherwood et al. 1987). Additional oral studies could identify a NOAEL, as well as determine if the kidney is the most sensitive target for intermediate-duration exposure to 1,2-dichloroethane (see data needs sections for acute-duration exposure and for immunotoxicity). Because the data were adequate for derivation of an intermediate oral MRL, a data need is not identified for this route and duration.

Dermal data were not located, but are needed because absorption by this route is expected (Morgan et al. 1991), and intermediate-duration dermal exposure is a likely exposure scenario for humans who live in the vicinity of a hazardous waste site.

Chronic-Duration Exposure and Cancer. A data need to conduct additional studies via oral and dermal exposure has been identified. There is no information on the noncancer health effects of chronic-duration exposure to 1,2-dichloroethane by any route in humans. Chronic studies in animals are limited to one inhalation study in rats (Cheever et al. 1990) and one oral study in rats and mice (NCI 1978) that were primarily designed to assess carcinogenicity, but provided some information on systemic toxicity.

The inhalation study (Cheever et al. 1990) was used to derive an MRL for chronic-duration exposure but is limited by the use of a single exposure level (a NOAEL), use of a single species, and lack of sensitive immunotoxicity end points. Because the inhalation information was considered adequate for MRL derivation, there is no data need for additional chronic inhalation studies.

The oral study (NCI 1978) provided an insufficient basis for derivation of an MRL due to limitations such as dosage adjustments, possible contamination by other chemicals tested in the same laboratory, and poor survival and small numbers of control animals, as well as concerns regarding the method of exposure, since it may not be appropriate to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (bolus saturation of the detoxification/excretion mechanism, discussed elsewhere in this document). Additional chronic oral toxicity studies are needed because they could identify critical targets that are different than those detected in shorter-term studies and because toxicity levels may be considerably lower than in shorter-term studies.

The only chronic dermal study in animals was a carcinogenicity study that did not investigate noncancer end points (Van Duuren et al. 1979).

Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity of 1,2-dichloroethane in humans due to complicating co-exposures to various other chemicals, as discussed in the section on epidemiology. The carcinogenic potential of 1,2-dichloroethane has been examined in rats and mice following inhalation, oral, and dermal exposure. No tumors were produced in rats and mice exposed to 1,2-dichloroethane via inhalation (Cheever et al. 1990; Maltoni et al. 1980). Limitations of the inhalation studies included the use of a single, subthreshold exposure level in one study (Cheever et al. 1990) and exceedance of the maximum tolerated dose in rats, less-than-lifetime study duration, and poor survival in mice in the other study (Maltoni et al. 1980).

1,2-Dichloroethane was carcinogenic after gavage administration (of 97–195 mg/kg/day to rats and 97–299 mg/kg/day to mice), inducing statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice (NCI 1978). Limitations of this oral study include the nonnatural method of administration (gavage) and dosage adjustments during the study.

1,2-Dichloroethane induced lung papillomas following lifetime dermal exposure of female mice (Van Duuren et al. 1979). The results showed an apparent dose-response, with statistical significance at the high dose. This study appears adequate to demonstrate the carcinogenic potential of dermal exposure to 1,2-dichloroethane. In addition, pulmonary adenomas have been induced in mice by intraperitoneal injection (Stoner 1991; Theiss et al. 1977), and, as discussed previously, by oral administration of 1,2-dichloroethane.

It has been suggested that the route-related differences in carcinogenicity between inhalation and oral exposure may be associated with saturation of the detoxification/excretion mechanism by gavage dosing. Reitz et al. (1982) proposed that 1,2-dichloroethane-induced toxicity occurred when the biotransformation processes were saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body instead of being detoxified and eliminated. The 1,2-dichloroethane inhalation study, therefore, may not have produced peak blood levels that were high enough to saturate the detoxification mechanisms and produce a detectable incidence of tumors. Metabolic saturation apparently occurs at lower doses after oral administration (particularly by gavage) than after inhalation exposure. Additional information on 1,2-dichloroethane from well-conducted animal bioassays using the natural routes of exposure expected for populations surrounding hazardous waste sites (i.e., drinking water ingestion and inhalation exposure) are needed to better predict the likelihood of carcinogenicity in humans.

The positive and suggestive carcinogenicity results from animal bioassays (NCI 1978; Stoner 1991; Theiss et al. 1977; Van Duuren et al. 1979), along with data indicating that 1,2-dichloroethane and certain metabolites are mutagenic and capable of forming DNA adducts as discussed in the preceding section, provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well. The DHHS has

determined that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen (NTP 2000). IARC has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans) (IARC 2001). EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen) (IRIS 2001). This EPA category applies to chemical agents for which there is sufficient evidence of carcinogenicity in animals.

Genotoxicity. A data need to conduct additional genotoxicity studies has been identified. No information regarding the genotoxicity of 1,2-dichloroethane in humans following oral, inhalation, dermal, or parenteral exposure is available. However, a great deal of data are available regarding the genotoxic effects of 1,2-dichloroethane in human cells *in vitro*; prokaryotic organisms, fungi, and nonhuman mammalian cells *in vitro*; and insects, rats, and mice *in vivo*.

The ability of 1,2-dichloroethane to bind to DNA in rats and mice *in vivo* has been well established, not only in the liver, but also in other organs such as the kidney and lung (Baertsch et al. 1991; Banerjee 1988; Cheever et al. 1990; Hellman and Brandt 1986; Inskeep et al. 1986; Prodi et al. 1986). DNA binding has also been reported in *D. melanogaster in vivo* (Fossett et al. 1995). DNA damage has been demonstrated *in vivo* in mice (Sasaki et al. 1998; Storer and Conolly 1983, 1985; Taningher et al. 1991). Genotoxicity assays for clastogenic effects in mice *in vivo* obtained mixed results, with a positive effect on sister chromatid exchange in bone marrow cells (Giri and Hee 1988), but no effect on micronucleus formation (Armstrong and Galloway 1993; Jenssen and Ramel 1980; King et al. 1979; Sasaki et al. 1994), and in *D. melanogaster,* gave positive results for chromosomal aberration (Ballering et al. 1993) and a marginally positive response for chromosomal recombination (Rodriguez-Arnaiz 1998). Negative results were obtained in a cell transformation assay (Milmann et al. 1988).

The only *in vivo* assay for the mutagenicity of 1,2-dichloroethane in mammalian cells (mouse/spot test) produced a marginal response (Gocke et al. 1983), and a mouse host-mediated assay produced negative results in *Escherichia coli* (King et al. 1979). However, there is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in *D. melanogaster in vivo* (Ballering et al. 1994; King et al. 1979; Kramers et al. 1991; Nylander et al. 1978; Romert et al. 1990; Vogel and Nivard 1993). In addition, *in vitro* studies provide strong support for the mutagenicity of 1,2-dichloroethane. Results of *in vitro* assays for point mutations were positive in human cells (Crespi et al. 1985; Ferreri et al. 1983), marginally positive in a single assay in animal cells (Tan and Hsie 1981), and positive in nearly all of the assays in bacteria, with or without metabolic activation (Barber et al. 1981; Brem et al. 1974; Buijs et al. 1984; Cheh et al. 1980; Hemminki et al. 1980; Kanada and Uyeta

1978; King et al. 1979; Milman et al. 1988; Moriya et al. 1983; Nestmann et al. 1980; Rannug and Beije 1979; Rannug et al. 1978; Roldan-Arjona et al. 1991; Simula et al. 1993; Thier et al. 1993; Van Bladeren et al. 1981), although not in a single assay in fungi (Crebelli and Carere 1988). The results of these bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione *S*-transferases (DeMarini and Brooks 1992).

Additional evidence from *in vitro* studies supports the *in vivo* results regarding the DNA binding, DNA damaging, and clastogenic effects of 1,2-dichloroethane. Results were positive for DNA binding in animal cells (Banerjee 1988; Banerjee and Van Duuren 1979; Banerjee et al. 1980; Prodi et al. 1986), unscheduled DNA synthesis (i.e., DNA repair activity) in human (Perocco and Prodi 1981) and animal cells (Milman et al. 1988; Williams et al. 1989), and mitotic segregation aberrations leading to aneuploidy in fungi (Crebelli et al. 1984). Negative results were obtained for intrachromosomal recombination in a single assay in animal cells (Zhang and Jenssen 1994, but positive results were reported for micronucleus formation in human cells (Doherty et al. 1996; Tafazoli et al. 1998). Thus, both *in vitro* and *in vivo* genotoxic effects of 1,2-dichloroethane include gene mutations, DNA binding and damage, and clastogenic effects.

The DNA binding is an alkylation of DNA that occurs following biotransformation of 1,2-dichloroethane. Inhalation exposure of rats to very high concentrations of 1,2-dichloroethane for short durations produced greater amounts of DNA binding in liver and lung than do longer-duration inhalation to low concentrations (Baertsch et al. 1991), and oral gavage doses were more potent in causing DNA damage in liver than were comparable inhalation doses in mice (Storer et al. 1984). These observations are consistent with the hypothesis that the toxicity of 1,2-dichloroethane is associated with saturation of MFO enzymes. The major identified DNA adduct is *S*-[2-(N^7-guanyl)ethyl]glutathione in rat liver following a single intraperitoneal injection of ^{14}C-1,2,-dichloroethane, and it is one of several DNA adducts found in the kidney, after a single intraperitoneal injection (Inskeep et al. 1986).

Although genotoxicity in humans could be investigated directly by examining peripheral lymphocytes obtained from exposed workers for clastogenic effects, the utility of such studies is likely to be limited due to the workers' exposures to other chemicals. Additional *in vivo* studies examining the importance of the route of administration on 1,2-dichloroethane-induced quantitative genotoxicity data (i.e., adducts) in animals are needed since the available information indicates route-dependent effects (inhalation doses are less potent than oral gavage) (Storer et al. 1984). DNA adduct and monoclonal antibody dosimetry work

also are needed to provide quantitative genotoxicity data, and perhaps could be used as a biomarker of exposure to 1,2-dichloroethane.

Reproductive Toxicity. A data need to conduct additional reproductive studies via dermal exposure has been identified. A single study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a decrease in duration of gestation (Zhao et al. 1989), but should be interpreted with caution since co-exposure to other chemicals occurred in most cases and the adequacy of the study design could not be evaluated because of reporting deficiencies. Results of animal studies indicate that this chemical is unlikely to cause female reproductive impairment at doses that are not maternally toxic. Although some inhalation studies found that exposure to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryolethality in rats (Vozovaya 1974, 1977; Zhao et al. 1989), the methods used by these investigators were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed and reported study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study (Rao et al. 1980). In the absence of an apparent explanation for the discrepancy, greater credence should be given to the well-designed and reported study. One- and two-generation reproduction studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats (Alumot et al. 1976; Lane et al. 1982), but exposure to higher oral doses caused increases in nonsurviving implants and resorptions in rats that also experienced maternal toxicity (30% decreased body weight gain) (Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results (Cheever et al. 1990; Daniel et al. 1994; NCI 1978; NTP 1991a; van Esch et al. 1977), although reproductive performance was not evaluated in these studies.

Although 1,2-dichloroethane appears to have induced embryotoxic effects in one adequate animal study conducted by the oral route, the overall indication of the data is that this chemical is unlikely to impair reproduction at doses that are not highly toxic. No data are available regarding the potential reproductive toxicity of dermal exposure, so there is a need for studies.

Developmental Toxicity. A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes that found increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects)

(Bove 1996; Bove et al. 1995), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997). Primary routes of exposure in these epidemiologic studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water). The OR for cardiac defects for 1,2-dichloroethane (detected versus not detected in drinking water) was 2.8 (95% CI 1.11–6.65; 6 exposed cases) (Bove 1996; Bove et al. 1995). The crude odds ratio for neural tube defects was 2.8 (95% CI 1.0–7.2; 14 exposed cases) (Croen et al. 1997). In these studies, the study populations were also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryo and fetal lethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). The reliability of the reports of increased embryo and pup mortality following intermediate-duration inhalation of lower (not maternally toxic) concentrations of 1,2-dichloroethane (Vozovaya 1977; Zhao et al. 1989) is uncertain, due to the lack of statistical analysis, inadequate description of methods, and uncertainties in the reported results. The possibility of induction of cardiac malformations by 1,2-dichloroethane, as suggested by the epidemiologic data, was not adequately addressed in the animal studies because their conventional teratology protocols did not include detailed examinations of dissected hearts. Given the suggestive evidence of an association between exposure to 1,2-dichloroethane in drinking water and major cardiac defects in human offspring, and evidence of heart malformations in epidemiology and animal cardiac teratogenicity studies of dichloroethylene and trichloroethylene (Dawson et al. 1993; Goldberg et al. 1990), which are metabolized to some of the same reactive intermediates as is 1,2-dichloroethane, it would be informative to have studies specifically designed to investigate the potential for induction of developmental heart malformations by 1,2-dichloroethane. In addition, the possibility of neurodevelopmental effects, also suggested by the epidemiological data, needs to be investigated, particularly because 1,2-dichloroethane is known to affect the central nervous system.

Immunotoxicity. A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. Immunological effects reported in humans exposed to 1,2-dichloroethane are limited to splenic lesions in a single case of accidental ingestion (Hubbs and Prusmack 1955). In mice, this chemical had immunosuppressive effects following both acute inhalation and acute oral

exposure. A single 3-hour inhalation exposure to 5 or 11 ppm increased the susceptibility of female mice to bacterial infection, and to 11 ppm decreased the bactericidal activity of the lungs. No change in bactericidal activity was seen in male rats after a single 5-hour inhalation exposure to 200 ppm or 12 5-hour exposures to 100 ppm (Sherwood et al. 1987). Other immune function end points studied in the rats were also negative. The relevance of the end point (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain. Gavage administration of 4.9 and 49 mg/kg/day of 1,2-dichloroethane to mice for 14 days reduced humoral (immunoglobulin response to sheep red blood cells) and cell-mediated (delayed-type hypersensitivity response to sheep erythrocytes) immunity. Only the humoral response was dose-related. In addition, the leukocyte number was decreased by 30% at the high dose (Munson et al. 1982). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and gavage routes in mice, as compared with end points in other studies in mice and in other species. The other studies, however, had limitations including wide spacing of the exposure concentrations, such that only NOAELs and serious LOAELs were identified.

In contrast to the acute oral study, higher doses of 1,2-dichloroethane (189 mg/kg/day) administered to mice in their drinking water for 90 days did not affect humoral and cell-mediated immunity (Munson et al. 1982), as assessed by some of the Tier I and Tier II procedures from the immunotoxicity testing battery (Luster et al. 1988). Immune function has not been evaluated in chronic-duration studies of 1,2-dichloroethane, but histopathological examinations failed to detect immune system lesions or immune-related changes in rats and mice exposed to 1,2-dichloroethane by inhalation or oral (gavage or drinking water) routes for intermediate or chronic durations (Cheever et al. 1990; NCI 1978; NTP 1991a). Leucocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats (NTP 1991a). The acute data provide limited evidence that the immune system is a sensitive target of 1,2-dichloroethane in mice, but not rats. Because of the apparent interspecies differences in animal immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute exposure by inhalation or ingestion.

The mechanism by which 1,2-dichloroethane may produce immunological effects is not known, but it is possible that these effects were produced by reactive intermediates resulting from conjugation with glutathione (Reitz et al. 1982). Glutathione conjugation and MFO metabolism are the two primary pathways of 1,2-dichloroethane metabolism. It has been shown that MFO metabolism of 1,2-dichloroethane is saturable and that direct glutathione conjugation occurs to a much greater extent after saturation of MFO metabolism. Gavage administration, which involves the placement of large bolus doses in the

stomach that are absorbed at one time, could lead to saturation of MFO metabolism and the subsequent expression of toxicity. Drinking water exposure, which results in multiple daily ingestions of small doses, may not provide large enough doses to saturate MFO metabolism, even when the aggregate daily dose is fairly large. Therefore, even though immunological effects might be expected in humans ingesting large doses of undiluted 1,2-dichloroethane, it is uncertain whether immunological effects would occur in humans exposed to 1,2-dichloroethane in the drinking water at hazardous waste sites. Another possible explanation for the different outcomes of acute and intermediate oral exposure is that 1,2-dichloroethane may induce its own metabolism during the longer exposure period, thus reducing the dose to the immune cells. An additional possibility, related to age of the mice at the time of immune function testing, was mentioned in the section on acute exposure and is discussed in detail in the section on children's susceptibility.

Both the oral and the inhalation acute immunotoxicity studies found immunosuppressive effects at levels of 1,2-dichloroethane low enough to enable identification of the immune system as the most sensitive target for acute exposure by both routes of exposure, but neither study provided the data sufficient for deriving an MRL (the lethality assay in the inhalation study was not considered suitable, and the oral study showed a dose-response in only one end point and was limited by use of gavage). In addition, dose-response information for other potential targets of toxicity was not adequate. Additional studies are needed to determine the immunologic potential of acute inhalation and oral (drinking water) exposure and to better characterize the threshold for immunologic effects by both routes of exposure relative to thresholds for other effects in order to provide the data needed to establish the most appropriate basis for deriving acute inhalation and oral MRLs.

No data were located regarding the potential immunotoxicity of dermal exposure.

Neurotoxicity. A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. Neurological symptoms and signs in people acutely exposed to high levels of 1,2-dichloroethane by inhalation (Nouchi et al. 1984) or ingestion (Hubbs and Prusmack 1955; Lochhead and Close 1951; Yodaiken and Babcock 1973) included headache, irritability, drowsiness, tremors, partial paralysis, and coma. Autopsies of people who died following acute exposure to this chemical revealed morphological changes in the brain, such as hyperemia, edema, hemorrhage, myelin degeneration, diffuse changes in the cerebellum, shrunken appearance and pyknotic nuclei in the Purkinje cell layer of the cerebellum, and parenchymous changes in the brain and spinal cord (Hubbs and

Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984). The results of animal studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis, were observed after high-level acute vapor exposures (Heppel et al. 1945; NTP 1991a; Spencer et al. 1951). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks (NTP 1991a). No clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks (NTP 1991a), and no brain lesions were seen in rats intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). No studies regarding the potential neurotoxicity of dermal exposure were located. The discrepancy in results between gavage and drinking water administration may be due to saturation of the detoxification/excretion mechanism by the bolus gavage dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Intermediate-duration neurotoxicity studies in animals, using sensitive functional and neuropathological tests at inhalation and oral exposure levels significantly lower than those resulting in morbidity and death, would assist in the characterization of the neurotoxic potential of 1,2-dichloroethane.

Epidemiological and Human Dosimetry Studies. A data need has been identified. Most of the available information on the adverse noncancer effects of 1,2-dichloroethane in humans comes from cases of acute poisoning by inhalation or ingestion (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973) and epidemiological studies of exposure to drinking water contaminants, residence near hazardous waste sites, or employment in the chemical industry (discussed later in this section). Limitations inherent in the case studies include unquantified exposure and the high-dose nature of the exposures. Despite their inadequacies, the available human case studies indicate that 1,2-dichloroethane can cause neurotoxic, nephrotoxic, and hepatotoxic effects, and death due to cardiac arrhythmia. These observations are similar to those in high-dose animal studies, but other, more sensitive effects seen in animals at low levels of exposure have not been investigated in humans.

Epidemiologic investigations of adverse birth outcomes found an increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), and an increased OR for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997).

The study populations also were simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, and do not establish a cause-and-effect relationship. The animal data do not indicate that 1,2-dichloroethane is teratogenic, but conventional teratology protocols were used that do not include detailed examinations of dissected hearts. Increased rates of premature births were reported in workers exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). The study included women exposed throughout pregnancy and unexposed wives of men exposed for at least 1 year before their wives became pregnant, and included relatively small numbers of exposed workers. It was generally deficient in reporting of study design and accounting for possible confounders, including other chemicals in the factory. In general, the adequate one- and two-generation reproductive studies in animals did not report effects except at high, maternotoxic exposure levels.

Epidemiological studies of workers in the chemical industry suggest that exposure to chemical manufacturing processes that involve 1,2-dichloroethane is associated with an increased incidence of brain tumors (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), nonlymphatic leukemia (Ott et al. 1989), stomach cancer, and leukemia (Hogstedt et al. 1979), and with increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers (Benson and Teta 1993) among chemical plant workers. Increased risk of breast cancer was reported among men working at jobs associated with exposure to gasoline or gasoline combustion products containing 1,2-dichloroethane (Hansen 2000), and the risk of several cancer types was increased in residents living proximal to a Montreal municipal waste site that emitted volatile organic substances including 1,2-dichloroethane (Goldberg et al. 1995). These studies involved exposure to other chemicals and did not deal with 1,2-dichloroethane exposure exclusively. Isacson et al. (1985) reported an association between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon and rectal cancer in men aged 55 years or older, but other organic chemicals were present in the drinking water. Studies in animals are adequate to support the determination that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen.

Well-controlled epidemiological studies of people living in areas where 1,2-dichloroethane has been detected in water or near industries or hazardous waste sites releasing 1,2-dichloroethane, and/or of people exposed in the workplace, could add to and clarify the existing database on 1,2-dichloroethane-induced human health effects. In the United States, however, about 98% of the 1,2-dichloroethane produced is used (usually captively) to manufacture vinyl chloride (Anonymous 1998), which is a more

potent toxicant and carcinogen than is 1,2-dichloroethane. Other uses of 1,2-dichloroethane also involve manufacture of other chemicals. Therefore, it may not be possible to identify a cohort of workers exposed predominantly to 1,2-dichloroethane. Previous studies of 1,2-dichloroethane from hazardous waste sites or drinking water have not been able to establish anything more than a weak association between a health effect and 1,2-dichloroethane due to the presence of many other chemicals at the sites or in the water, small numbers of cases with the health effect, and difficulties in controlling for all of the variables that may confound the results for a general population study. At present, the only known health effects of 1,2-dichloroethane in humans, seen in cases of acute high exposure, are neurotoxicity, nephrotoxicity, hepatotoxicity, and effects on the cardiovascular system. A particularly sensitive end point of acute inhalation or gavage exposure to 1,2-dichloroethane in mice (but not rats) is immunological effects. No data regarding this end point are available for humans.

Biomarkers of Exposure and Effect.

Exposure. A data need has been identified. Proposed biomarkers for exposure to 1,2-dichloroethane include levels of parent compound in the breath, blood, urine, and breast milk; levels of thioethers in the urine; and levels of thiodiglycolic acid in the urine (Igwe et al. 1988; Payan et al. 1993; Spreafico et al. 1980; Urusova 1953). However, use of the parent compound as a biomarker would only be possible soon after exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane. If epidemiological studies are conducted in which there is a correlation between 1,2-dichloroethane exposure and specific adverse health effects, then it may be possible to correlate these health effects quantitatively with changes in tissue and/or body levels of 1,2-dichloroethane.

Effect. Biomarkers of effect for 1,2-dichloroethane include serum enzyme levels indicative of liver damage (ALT, AST, SDH), increased liver or kidney weight (size), and DNA adduct formation for liver and kidney effects (Brondeau et al. 1983; Inskeep et al. 1986; Nouchi et al. 1984; Prodi et al. 1986). Another potential biomarker would be tests for immunosuppression, but immune effects have been demonstrated only in mice in acute exposure studies (Munson et al. 1982; Sherwood et al. 1987). Because they have not been seen in humans, rats, or even mice exposed for an intermediate duration, the relevance of these effects to humans is uncertain. None of these biomarkers are specific for 1,2-dichloroethane. These biomarkers are indicative of effects, but dosimetry has not been worked out for any of them. Because immunological effects of 1,2-dichloroethane have been seen only in mice, it is uncertain whether immunosuppression would occur in humans exposed to this chemical.

Absorption, Distribution, Metabolism, and Excretion. A data need to assess the toxicokinetics of 1,2-dichloroethane following inhalation, oral, and dermal exposure has been identified. Case reports of toxic effects subsequent to inhalation or oral exposure suggest that 1,2-dichloroethane is absorbed following exposure by these routes (Garrison and Leadingham 1954; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Inhalation exposure of lactating women in the workplace resulted in distribution of 1,2-dichloroethane to their milk (Urusova 1953). Animal studies were sufficient to characterize the rate and extent of absorption following inhalation, oral, and dermal exposure (Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Distribution, metabolism, and excretion have also been well studied in animals exposed by the inhalation or oral routes (D'Souza et al. 1987, 1988; Reitz et al. 1982; Spreafico et al. 1980), and are qualitatively similar across these routes. Metabolism is saturable in animals, but the precise levels at which saturation phenomena come into play have not been determined and appear to differ between oral (gavage) and inhalation exposures (Reitz et al. 1982). Additional studies investigating the saturation of MFO metabolism by inhaled and ingested 1,2-dichloroethane would enable better understanding of the metabolism of this compound. Based on the elimination of virtually all radiolabel from inhalation or gavage administration of 1,2-dichloroethane to rats within 48 hours, Reitz et al. (1982) concluded that the potential for 1,2-dichloroethane to accumulate with repeated exposure is minimal. The rate of elimination of the parent compound from adipose tissue was similar to that from blood following gavage administration to rats, but was slower following a single inhalation exposure or intravenous injection (Spreafico et al. 1980; Withey and Collins 1980), raising the possibility that 1,2-dichloroethane may accumulate to some extent in adipose tissue and in breast milk of nursing women. More quantitative information on the presence of 1,2-dichloroethane in fat and breast milk would be useful to assess the ability of 1,2-dichloroethane to accumulate in fat and the potential hazard to nursing infants. Further study into the long-term fate of low-level 1,2-dichloroethane exposure in humans and animals and the potential for accumulation in humans would also provide valuable information.

Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics across species is limited as most studies have been performed in rats (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Only one set of studies included mice (D'Souza et al. 1987, 1988), and these studies were conducted to validate PBPK modeling, primarily for levels of the direct GSH conjugate in selected tissues of concern for carcinogenicity (liver and lung). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure. The database with regard to

comparative toxicokinetics across routes does include comparative toxicokinetics across acute inhalation and gavage (oil) administration (Reitz et al. 1980; Spreafico et al. 1980). The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) reported that 1,2-dichloroethane is absorbed more rapidly by the gastrointestinal tract following gavage administration in water than in corn oil; the estimated area under the curve (based on data for up to 300 minutes postdosing) was also much greater for the water than the oil vehicle). Information on toxicokinetics for repeated or longer-term continuous exposure is not available.

Comparative Toxicokinetics. Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics consists primarily of studies in rodents (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure.

Methods of Reducing Toxic Effects. A data need has been identified. It appears that 1,2-dichloroethane is absorbed across the alveolar membrane, gastrointestinal epithelium, and skin by passive means. Methods to reduce absorption following oral and dermal exposure are available, but must be applied soon after exposure (Ellenhorn and Barceloux 1988). The available data suggest that 1,2-dichloroethane does not accumulate in the nonlipid components of the human body, but that it may accumulate to some extent in adipose tissue and in the breast milk of nursing women. Methods to enhance removal of 1,2-dichloroethane from the body have not been successful (Ellenhorn and Barceloux 1988); determination of successful methods is needed. The mechanism of action of 1,2-dichloroethane is not clearly understood but involves complex toxifying and detoxifying reactions with glutathione (Jaeger et al. 1974; NTP 1991a). Reactive metabolites of P-450 metabolism are detoxified by conjugation with glutathione, but direct conjugation of unmetabolized 1,2-dichloroethane with glutathione produces reactive and toxic intermediates, which are in turn detoxified through additional reaction or conjugation with glutathione. Nevertheless, limited evidence that administration of glutathione and its precursors may have a protective effect against 1,2-dichloroethane toxicity in animals has been reported (Heppel et al. 1947; Jaeger et al. 1974; Johnson 1967). Further elucidation of the toxic mechanisms might enable identification of methods for reducing the toxic effects.

Endocrine Disruption. A data need to conduct additional studies on the endocrine system via dermal exposure has been identified.

A human study that reported increased rates of premature births in female workers and in wives of male workers at a Chinese synthetic fiber factory (Zhao et al. 1989) should be viewed with caution because of the deficient reporting of design, apparent lack of control for possible confounding environmental and behavioral factors, small number of subjects, and co-exposure to other chemicals. No assays of endocrine function are available. Some studies in animals, however, provide data regarding a lack of effect of 1,2-dichloroethane on the histology of endocrine tissues and on reproduction. Histological examinations of endocrine tissues were performed in animals exposed by inhalation or oral administration with essentially negative results (Cheever et al. 1990; Daniel et al. 1994; Heppel et al. 1946; NCI 1978; NTP 1991a; Spencer et al. 1951; van Esch et al. 1977). The examinations in these studies were generally limited to the adrenal gland and/or pancreas, although the pituitary, thyroid, and parathyroid glands were also evaluated following chronic inhalation and oral exposures. The only endocrine-related finding was calcification of the adrenal medulla in one of two monkeys exposed to 1,2-dichloroethane by inhalation in an intermediate-duration study (Heppel et al. 1946), but no controls were examined, and adrenal effects have not been reported in other long-term inhalation studies by these and other investigators. Histological examinations of pertinent reproductive tissues in animals in inhalation and oral studies revealed no changes (Cheever et al. 1990; Daniel et al. 1994; NCI 1978; NTP 1991a; van Esch et al. 1977), and adequately conducted studies of reproductive function in animals exposed to 1,2-dichloroethane by inhalation or oral routes (Alumot et al. 1976; Lane et al. 1982; Rao et al. 1980), although not definitive, strongly indicate that 1,2-dichloroethane is unlikely to impair reproduction at levels that are not maternally toxic. In an early NCI (1978) bioassay that had a number of limitations including dosage adjustments, possible contamination by other chemicals tested in the same laboratory, poor survival, and small control groups, gavage treatment with 1,2-dichloroethane in corn oil was associated with statistically significant increases in multiple tumor types, including mammary gland adenocarcinoma in female rats and mice and endometrial tumors in female mice. The finding of tumors in two endocrine-sensitive tissues is suggestive. On the other hand, the mechanism of carcinogenicity for 1,2-dichloroethane appears to involve alkylation of DNA, and statistically significant increased incidences were also observed for tumors of the forestomach, circulatory system, subcutaneous tissue, liver, and lung in the NCI (1978) study. The oral and inhalation data for noncancer effects in animals do not suggest that 1,2-dichloroethane has endocrine disrupting activity. No data are available for the dermal route, so there is a need for screening data (e.g., reproductive and other endocrine histopathology in a dermal study).

Children's Susceptibility. A data need to conduct additional studies relevant to children's susceptibility via oral, inhalation, and dermal exposure has been identified. Data on the effects of 1,2-dichloroethane exposure in children are limited to a single case report of a 14-year-old boy who

swallowed 15 mL of the compound (Yodaiken and Babcock 1973). The most immediate signs of toxicity were headache and staggering gait within 2 hours of exposure, followed soon after by lethargy and vomiting. During the next few days, the boy developed symptoms of toxicity, increasing in variety and severity, that involved several organ systems, including adverse hematological effects, pulmonary edema, cardiac arrest (he was resuscitated), and eventual death on the 5th day after exposure from massive hepatic necrosis and renal tubular necrosis. Data from this case report and from reports of adult humans who died following acute exposure to high levels by inhalation or ingestion are consistent with animal studies indicating that main targets of acute toxicity include the central nervous system, respiratory tract, stomach, liver, and kidneys. Considering the consistency of effects in acutely exposed humans and animals, and data showing that the liver and kidney are sensitive targets of lower-dose and longer-term inhalation and oral exposures in animals, it is reasonable to assume that effects in these tissues would also be seen in similarly exposed adults and children.

Evidence from mouse studies suggests that the specific nature of oral exposure or the age of the animals at the time of the immune testing may play a role in the degree of immunotoxicity expressed in young animals. Repeated gavage administration for 14 days of 1,2-dichloroethane appears to be more effective in eliciting an immunotoxic response than 90-day drinking-water exposure in 5-week-old mice (Munson et al. 1982). While this difference could be due to the saturation of detoxifying/excretion pathways by bolus gavage dosing, an alternative explanation is that young mice may be more sensitive to 1,2-dichloroethane than adult mice. The mice used for both the acute (14-day) and the 90-day studies were 5 weeks old at the start of dosing, so at the time of testing, the mice in the 14-day study were 7 weeks old, but the mice in the 90-day study were 17 weeks old. The decreased immune response in mice exposed at 5–7 weeks of age provides a limited indication of the potential susceptibility of children to immunotoxic effects. Because no immunotoxic effects were seen in young rats exposed to much higher inhalation concentrations of 1,2-dichloroethane than those that produced immunosuppression in mice (Sherwood et al. 1987), and because there are no reports of immune effects in humans exposed to this chemical, the relevance of the data in young mice to children is uncertain. Studies that also evaluate for other toxicological end points after exposures in immature animals are needed, particularly for known targets of toxicity such as the liver and kidney. Appropriate comparative studies are needed to document the toxicological potential and metabolism of 1,2-dichloroethane and to assess whether children and adults are equally susceptible, especially after longer-term exposures.

No studies that provide reliable information on adverse developmental effects in humans exposed to 1,2-dichloroethane are available. A cross-sectional epidemiologic study that investigated whether

elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995) was located. A number of associations between various chemicals and birth outcomes were found, including a positive association between ingestion of 1,2-dichloroethane in drinking water and major cardiac birth defects (but not neural tube defects). Similarly, a study that investigated residence within the census tract of NPL sites contaminated with 1,2-dichloroethane reported an association with neural tube (but not heart defects) (Croen et al. 1997). The mixed chemical exposures in these studies, and the lack of concordance on end point, indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

Studies in rats, mice, and rabbits indicate that 1,2-dichloroethane is not developmentally toxic following inhalation or oral gestational exposure, although fetolethality has been reported at maternolethal exposure levels following inhalation exposure (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). Embryolethality was reported at relatively low exposure levels in another inhalation study (Vozovaya 1977), but the reliability of these results cannot be evaluated due to limitations in reporting and data analysis.

No studies that evaluated for the distribution of 1,2-dichloroethane or its metabolites across the placenta in humans were located. However, there is some evidence that 1,2-dichloroethane and/or its metabolites crosses the placenta after inhalation and oral exposures in animals. 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977). Additional evidence of transplacental distribution of 1,2-dichloroethane after inhalation exposure is provided by Withey and Karpinski (1985), who found that the geometric mean concentration of 1,2-dichloroethane in the fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level. However, the reliability of the Vozovaya data is unclear, and the methods for evaluating 1,2-dichloroethane tissue concentrations were not reported in Withey and Karpinski (1985).

There is clearer evidence for transplacental distribution of 1,2-dichloroethane and/or its metabolites after maternal oral exposure. Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on gestation day 12 or 18. In both cases, transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus. A greater accumulation occurred in the developing fetus and placenta 48 hours

after the gestation day 18 administration than after the gestation day 12 administration. At 48 hours after the gestation day 18 dosing, the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

No studies regarding 1,2-dichloroethane metabolism in children were located. The metabolism of 1,2-dichloroethane is well described (NTP 1991a; WHO 1995), and it is reasonable to assume that the metabolic pathways are, for the most part, the same between adults and children. However, the expression of certain enzymes is known to be developmentally regulated, and one of these enzymes may be involved in 1,2-dichloroethane metabolism. NAT is involved in 1,2-dichloroethane metabolism at a step subsequent to GSH conjugation. NAT performs the N-acetylation of *S*-carboxymethyl-L-cysteine to N-acetyl-*S*-carboxymethyl-L-cysteine, a major urinary metabolite. There are, however, two NATs (NAT1 and NAT2) that are expressed in humans with separate but overlapping substrate specificities (Parkinson 1996). NAT2 is apparently expressed only in the liver and the gut (Parkinson 1996), and is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks, but NAT2 activity is low in virtually 100% of infants, not reaching adult activity levels until 1–3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991a) or WHO (1995) whether the NAT involved in 1,2-dichloroethane metabolism is NAT1 or NAT2, although both enzymes N-acetylate some xenobiotics equally well (Parkinson 1996). The impact of lower rates of N-acetylation of S-carboxymethyl-L-cysteine in terms of potential health effects also is unclear.

1,2-Dichloroethane has been detected in human milk (EPA 1980a; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane was also accumulated in the adipose tissue of rats after inhalation exposure and was eliminated from fat more slowly than from blood, liver, and lung (Spreafico et al. 1980), suggesting the possibility that the maternal body burden of 1,2-dichloroethane in fat could be available for exposure to the fetus or nursing infant for a somewhat extended period after maternal exposure. Supporting data for relatively slow elimination of 1,2-dichloroethane from fat are provided in an intravenous exposure study in rats (Withey and Collins 1980). Nevertheless, 1- and 2-generation reproductive studies of 1,2-dichloroethane, administered by inhalation or drinking water exposure to rats and mice, in which the pups were exposed through the milk of the treated dams, showed no adverse effects on survival, body weight, gross appearance of tissues and organs (Lane et al. 1982; Rao et al. 1980), or histological appearance of the liver, kidneys, ovaries, uterus, and testes (Rao et al. 1980) in the pups at 21 days of age.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The role of 1,2-dichloroethane and two other common groundwater contaminants, individually and in combination, in the development of hepatic angiosarcoma will be studied by Dr. Wendy A. Pott at the Foothills Campus of Colorado State University (FEDRIP 2000). The long-term objectives of this project are (1) to evaluate the carcinogenic effects of subchronic exposure to 1,2-dichloroethane, arsenic, and vinyl chloride, which are implicated as etiologic agents in the development of angiosarcoma; and (2) to use data from these studies with PBPK/PD models and statistical and mathematical modeling techniques for the purpose of health-risk characterization. Specific aims of the project include (1) evaluating whether synergistic carcinogenic activity may result when arsenic is combined with 1,2-dichloroethane; (2) developing PBPK/PD models for target tissue dosimetry of single chemicals and combinations of chemicals following exposure to arsenic, vinyl chloride, and/or 1,2-dichloroethane; and (3) developing cell turnover and carcinogenesis models and integrating them with PBPK/PD models to characterize cancer risks associated with exposure to arsenic, vinyl chloride, and/or 1,2-dichloroethane. These goals will be accomplished using a medium-term angiosarcoma bioassay to investigate the effects of each of the chemicals, alone and in combination, in inducing hepatic angiosarcoma. Data gathered from these experiments will be used to develop models to determine cancer risks and safe drinking-water levels of these chemicals.

4. CHEMICAL AND PHYSICAL INFORMATION

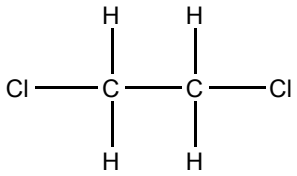
4.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for 1,2-dichloroethane are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2-dichloroethane are located in Table 4-2.

Table 4-1. Chemical Identity of 1,2-Dichloroethane

Characteristic	Information	Reference
Chemical Name	1,2-Dichloroethane	Budavari et al. 1996
Synonym(s)	Ethylene dichloride; dichloroethane; EDC; Dutch liquid	Budavari et al. 1996
Registered trade name(s)	No data	
Chemical formula	$C_2H_4Cl_2$	Budavari et al. 1996
Chemical structure		Budavari et al. 1996
Identification numbers:		
CAS registry	107-06-2	Lide 1998
NIOSH RTECS	KI0525000	HSDB 2001
EPA hazardous waste	U077	HSDB 2001
OHM/TADS	7216717	HSDB 2001
DOT/UN/NA/IMCO shipping	1184	HSDB 2001
HSDB	65	HSDB 2001
NCI	C00511	HSDB 2001

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

Table 4-2. Physical and Chemical Properties of 1,2-Dichloroethane

Property	Information	Reference
Molecular weight	98.96	Lide 1998
Color	Colorless	Lewis 1993
Physical state	Heavy liquid	Budavari et al. 1996
Melting point	-35.5 EC	Lide 1998
Boiling point	83.5 EC	Lide 1998
Density:		
at 20 EC	1.23 g/cm^3	Lide 1998
Odor	Pleasant odor	Budavari et al. 1996
Odor threshold:		
Water	20 mg/L	Verschueren 1996
Air	12 ppm 50 ppm 100 ppm	Verschueren 1996 Torkelson and Rowe 1981 Weiss 1980
Solubility:		
Water at 20 EC	8.69x10^3 mg/L	Verschueren 1996
Organic solvent(s)	Miscible with alcohol, chloroform and ether	Budavari et al. 1996
Partition coefficients:		
Log K_{ow}	1.48	Hansch et al. 1995
Log K_{oc}	1.28 1.52 1.62	Chiou et al. 1980 Sabljic et al. 1995 Borisover and Graber 1997
Vapor pressure	79.1 mmHg at 25 EC	Daubert et al. 1989
Henry's law constant at 20 EC	1.1x10^{-3}atm-m^3/mol	Staudinger and Roberts 1996
Autoignition temperature	413 EC	Weiss 1980

Table 4-2. Physical and Chemical Properties of 1,2-Dichloroethane *(continued)*

Property	Information	Reference
Flashpoint	13 EC (closed cup) 18 EC (open cup)	Budavari et al. 1996 Budavari et al. 1996
Conversion factors:		
ppm (v/v) to mg/m^3 in air (25 EC)	ppm(v/v)x4.05 = mg/m^3	Torkelson 1994
mg/m^3 to ppm (v/v) in air (25 EC)	mg/m^3x0.247 = ppm(v/v)	Torkelson 1994
Explosive limits	6-16% v/v in air	Lewis 1993

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

5.1 PRODUCTION

1,2-Dichloroethane does not occur naturally (IARC 1979). It is produced commercially either by direct chlorination or by oxychlorination. Direct chlorination is carried out in the liquid or vapor phase over iron, aluminum, copper, or antimony chloride catalysts at 60 EC. Oxychlorination is carried out in a fixed or fluidized bed reactor at 220 EC with a suitable solid chloride catalyst (Sundaram et al. 1994).

Currently, there are 12 domestic manufacturers of 1,2-dichloroethane; production occurs at 16 sites located predominantly in Texas, Kentucky, and Louisiana (Anonymous 1998; SRI 1998). Domestic producers and their annual capacities as of February 16, 1998 are listed in Table 5-1 (Anonymous 1998). U.S. production totals for 1,2-dichloroethane in 1984, 1985, 1986, 1990, 1992, 1993, and 1994 were 7.3, 12.1, 12.9, 13.8, 15.2, 17.9, and 16.8 billion pounds, respectively (USITC 1985, 1986, 1987, 1991, 1993, 1994, 1995). In 1986, sales were nearly 800 million pounds and were valued at .66 million dollars (USITC 1987). By 1994, sales had reached 2.8 billion pounds and were valued at .317 million dollars (USITC 1995). Sales of 1,2-dichloroethane on the open market in 1986 were .6% of the total 1,2-dichloroethane produced (USITC 1987), indicating that the producers captively consumed >90% of production (EPA 1985a). Currently, .85% of total production is used captively (USITC 1995).

According to the Toxics Release Inventory (TRI), 41 facilities manufactured or processed 1,2-dichloroethane in 1999 (TRI99 2001). All of these facilities reported the range of the maximum amounts of 1,2-dichloroethane that they have on site. A summary of these data are presented in Table 5-2. The data listed in the TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2 IMPORT/EXPORT

In 1996, 2.5 billion pounds of 1,2-dichloroethane were exported while 316 million pounds were imported to the United States (Anonymous 1998). This trend in import/export volume was also observed from 1992 to 1996 when the average amount of 1,2-dichloroethane exported was 2.1 billion pounds annually and the average amount imported was 267 million pounds annually (Anonymous 1998).

Table 5-1. United States Production of 1,2-Dichloroethane[a,b]

Manufacturer	Location	Annual capacity (millions of pounds)
Borden Chemicals and Plastics	Geismar, Louisiana	745
CONDEA Vista Company	Lake Charles, Louisiana	1,400
Dow Chemical U.S.A.	Freeport, Texas Plaquemine, Louisiana	4,500 2,300
Formosa Plastics Corporation U.S.A.	Baton Rouge, Louisiana Point Comfort, Texas	525 1,900
Geon Company	LaPorte, Texas	4,000
Georgia Gulf Corporation	Plaquemine, Louisiana	1,760
Occidental Chemical Corporation Electrochemicals and Proprietary Products Division	Convent, Louisiana Deer Park, Texas	1,500 1,950
Electrochemicals	Ingleside, Texas	1500
Oxymar	Ingleside, Texas	3,000
PHH Monomers	Lake Charles, Louisiana	1,400
PPG Industries, Inc. Chemicals Group	Lake Charles, Louisiana	1,600
Vulcan Materials Company Vulcan Chemicals Division	Geismar, Louisiana	500
Westlake Monomers Corporation	Calvert City, Kentucky	1,950
Total		30,530

[a]Derived from Anonymous 1998
[b]Estimates as of February 16, 1998

Table 5-2. Facilities that Produce, Process, or Use 1,2-Dichloroethane

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
CA	2	100–99,999	10
IA	1	1,000–9,999	1
KY	3	1,000–49,999,999	1, 2, 3
LA	11	1,000–999,999,999	1, 3, 4, 10
MI	3	1,000–99,999	1, 8
MO	3	100–9,999,999	1, 3, 8
PA	2	10,000–999,999	1
PR	2	10,000–99,999	2, 3
SC	1	100,000–999,999	1
TX	13	0–999,999,999	1, 2, 3, 4, 8, 10

Source: TRI99 2001

[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

5.3 USE

1,2-Dichloroethane is currently used as a chemical intermediate and as a solvent in closed systems (Dow Chemical Company 1989b). It is also added to leaded gasoline as a lead scavenger; however, this use has declined significantly as leaded gasoline use has attenuated (Vulcan Materials Company 1989). In the United States, about 98% of the 1,2-dichloroethane produced is used to manufacture vinyl chloride (Anonymous 1998). Smaller amounts of 1,2-dichloroethane are used in the synthesis of vinylidene chloride, 1,1,1-trichloroethane, trichloroethene, tetrachloroethene, aziridines, and ethylene diamines and in chlorinated solvents (Anonymous 1998; EPA 1985a).

Formerly, 1,2-dichloroethane was used in varnish and finish removers, in soaps and scouring compounds, in organic synthesis for extraction and cleaning purposes, in metal degreasers, in ore flotation, and in paints, coatings, and adhesives (Archer 1979; Budavari et al. 1996; Dow Chemical Company 1989b; EPA 1985a). It was also formerly used as a grain, household, and soil fumigant (Archer 1979; CMA 1989; Dow Chemical Company 1989b; EPA 1985a; Vulcan Materials Company 1989).

5.4 DISPOSAL

1,2-Dichloroethane can be removed from water by treatment with granulated activated carbon, by aeration (air stripping), and by boiling. One of the main drawbacks of granulated activated carbon removal is that the spent carbon must be further processed by desorbing the chemical with steam or thermal carbon regeneration and concomitant incineration of the desorbed chemicals. Recently, granulated active carbon treatment has been combined with bioremediation technologies to increase the removal capacity of 1,2-dichloroethane from groundwater (Stucki and Thuer 1994). Boiling is an effective treatment on a short-term emergency basis when low concentrations are spilled in water. Air stripping removes 1,2-dichloroethane simply and inexpensively from water. However, these processes should be used with caution, as they result in the transfer of the contaminant directly to air (EPA 1985a, 1987d).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,2-Dichloroethane's production, storage, and use as a synthetic feedstock (Anonymous 1998; EPA 1985a), as a lead scavenger in leaded gasoline, and as a solvent in closed systems (Dow Chemical Company 1989b) may result in its release to the environment. The use of 1,2-dichloroethane as a lead scavenger has decreased significantly in recent years as leaded gasoline use has declined. The largest environmental releases of 1,2-dichloroethane occur to air. 1,2-Dichloroethane released to surface water and soil is expected to volatilize rapidly to the atmosphere where it will be degraded by photochemically-produced hydroxyl radicals. The half-life for this reaction is about 73 days, calculated from its measured rate constant (Arnts et al. 1989; Atkinson et al. 1989), and the overall atmospheric lifetime of 1,2-dichloroethane is >5 months (EPA 1993). Hydrolysis and photolysis do not appear to be significant in determining the environmental fate of 1,2-dichloroethane. Although biodegradation occurs slowly, it is the primary degradation process for 1,2-dichloroethane in soils and waters. 1,2-Dichloroethane has been detected in ambient air, surface water, groundwater, drinking water, human breath, urine, and milk samples. Concentrations in environmental media are generally greatest near source areas (e.g., industrial point sources, hazardous waste sites).

1,2-Dichloroethane has been identified in at least 570 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for 1,2-dichloroethane is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 569 are located within the United States and 1 is located in the Commonwealth of Puerto Rico (not shown).

Inhalation of 1,2-dichloroethane in ambient or workplace air is generally the main route of human exposure to the compound. Estimates of populations potentially exposed to 1,2-dichloroethane in workplace environments range from 80,000 to 1.4 million workers (NIOSH 1976a, 1984a). The estimated size of the general population potentially exposed to low levels of the compound through inhalation of polluted ambient air around industrial sites was . 15 million people (Kellam and Dusetzina 1980). Ingestion of contaminated drinking water and food may also be important routes of exposure.

Figure 6-1. Frequency of NPL Sites with 1,2-Dichloroethane Contamination

6.2 RELEASES TO THE ENVIRONMENT

There are no known natural sources of 1,2-dichloroethane. Releases of this compound to the environment may result from the manufacture, use, storage, distribution, and disposal of 1,2-dichloroethane. Older consumer goods containing 1,2-dichloroethane that are still in use or have been discarded as waste also represent potential emission sources. 1,2-Dichloroethane may also be released to the environment from the microbial degradation of other chlorinated alkanes. For example, 1,2-dichloroethane is a known product of the anaerobic biodegradation of 1,1,2,2-tetrachloroethane (Chen et al. 1996; Lorah and Olsen 1999).

6.2.1 Air

Emissions to the atmosphere comprise the largest component of all releases of 1,2-dichloroethane to the environment. According to the Toxics Release Inventory (TRI) (Table 6-1), an estimated total of 546,039 pounds of 1,2-dichloroethane, amounting to 88.8% of the total on-site environmental release, was discharged to air from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

1,2-Dichloroethane has been identified in air samples collected at 39 of the 570 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001).

6.2.2 Water

Industrial releases of 1,2-dichloroethane to surface waters are relatively minor compared to releases to the atmosphere. According to the TRI (Table 6-1), an estimated total of 904 pounds of 1,2-dichloroethane, amounting to 0.1% of the total on-site environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

In England and Wales, 1,2-dichloroethane was detected in 17% of industrial waste water effluent samples at an average concentration of 117 µg/L, and in 9.5% of treated sewage at an average concentration of 1.39 µg/L (Stangroom et al. 1998). 1,2-Dichloroethane has been identified in surface water samples

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethane

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	2	18	No data	No data	No data	18	10,453	10,471
AR	4	10,143	70	0	0	10,213	150,574	160,787
CA	2	264	No data	No data	No data	264	83	347
GA	1	No data	No data	No data	No data	No data	No data	No data
IA	2	307	No data	No data	No data	307	No data	307
IL	4	20,529	No data	No data	0	20,529	147	20,676
IN	2	26,070	5	No data	5	26,080	No data	26,080
KS	1	3,549	38	No data	No data	3,587	No data	3,587
KY	3	21,557	47	No data	0	21,604	255	21,859
LA	19	222,595	343	51,116	2,972	277,026	2,472	279,498
MA	1	1,178	No data	No data	No data	1,178	No data	1,178
MI	3	162	No data	No data	No data	162	No data	162
MO	3	28,815	25	No data	5	28,845	No data	28,845
MS	1	7,420	No data	1,040	No data	8,460	No data	8,460
NC	2	5,466	1	No data	No data	5,467	952	6,419

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethane (*continued*)

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
NE	1	255	No data	No data	0	255	No data	255
NJ	1	18	0	No data	0	18	2	20
NY	2	524	255	No data	No data	779	72,446	73,225
OH	3	86	1	No data	No data	87	49	136
PA	6	25,244	No data	No data	No data	25,244	No data	25,244
PR	3	470	No data	No data	No data	470	No data	470
SC	2	27,661	No data	No data	No data	27,661	0	27,661
TX	18	143,703	119	13,309	1	157,132	445,871	603,003
VA	1	5	No data	No data	No data	5	No data	5
WI	1	No data	No data	No data	No data	No data	No data	No data
Total	89	546,039	904	65,465	2,983	615,391	683,304	1,298,695

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are 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, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

collected at 89 sites and groundwater samples collected at 492 of the 570 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001).

6.2.3 Soil

Industrial releases of 1,2-dichloroethane to soil are relatively minor compared to releases to the atmosphere. According to the TRI (Table 6-1), an estimated total of 2,983 pounds of 1,2-dichloroethane, amounting to 0.5% of the total on-site environmental release, was discharged to land from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). An additional 65,465 pounds of 1,2-dichloroethane, amounting to 10.6% of the total on-site environmental release, was injected underground. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

1,2-Dichloroethane has been identified in soil samples at 166 sites and sediment samples at 42 of the 570 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001).

6.3 ENVIRONMENTAL FATE

1,2-Dichloroethane released to the environment partitions to the atmosphere. Reaction with photochemically produced hydroxyl radicals is the primary degradation mechanism of 1,2-dichloroethane in the atmosphere. 1,2-Dichloroethane released to soil or water surfaces is expected to volatilize quickly. Biodegradation occurs slowly in water and soil surfaces. Hydrolysis and photolysis are not expected to be important environmental fate processes for 1,2-dichloroethane.

6.3.1 Transport and Partitioning

Releases of 1,2-dichloroethane to the environment as a result of industrial activity are primarily to the atmosphere (see Section 6.2). 1,2-Dichloroethane released to the atmosphere may be transported long distances before being washed out in precipitation or degraded. For example, Pearson and McConnell (1975) attributed the presence of chlorinated organic compounds, including 1,2-dichloroethane, in upland waters to long-range aerial transport and deposition in precipitation.

Based on a Henry's law constant of 1.1×10^{-3} atm-m^3/mol at 20 EC (Staudinger and Roberts 1996), 1,2-dichloroethane is expected to volatilize rapidly from water surfaces. An estimated volatilization

half-life of 28–29 minutes was reported for 1,2-dichloroethane present at a concentration of 1 mg/L in an open water column held at 25 EC and stirred at 200 revolutions per minute (Dilling 1977; Dilling et al. 1975). Removal of 90% of the compound under the same conditions occurred in 96 minutes. However, an evaporation half-life of 10 days was estimated using the EXAMS model for a eutrophic lake. Volatilization losses were shown to be the dominant fate process following a chemical spill in the Rhine River in Germany (Brüeggemann et al. 1991).

No information was found regarding partitioning of 1,2-dichloroethane from the water column onto sediments. However, structural analogs of the compound (i.e., dichloromethane, trichloromethane, and 1,1,1-trichloroethane) do not concentrate selectively onto sediments (Dilling et al. 1975; Pearson and McConnell 1975). Based on log K_{oc} values of 1.28–1.62 (Borisover and Graber 1997; Chiou et al. 1980; Sabljic et al. 1995), 1,2-dichloroethane is not expected to adsorb to suspended solids and sediment in the water column. An experimental bioconcentration factor of 2 indicates that 1,2-dichloroethane will not bioconcentrate in fish and aquatic organisms (Banerjee and Baughman 1991) and is not expected to bioaccumulate in the food chain (Farrington 1991).

1,2-Dichloroethane released to land surfaces is expected to volatilize rapidly to the atmosphere or leach into groundwater. Volatilization losses occur at a much slower rate for 1,2-dichloroethane present in sub-surface soil. Jury et al. (1990) modeled the rate of volatilization of 1,2-dichloroethane from soil at a depth of 1 m to mimic the type of contamination that may occur from landfill leachate. When water evaporation was not taken into account, the yearly loss of 1,2-dichloroethane amounted to 7.1% from a sandy soil. Yearly volatilization losses increased to 30% when water evaporation was considered. Based on log K_{oc} values of 1.28–1.62 (Borisover and Graber 1997; Chiou et al. 1980; Sabljic et al. 1995), 1,2-dichloroethane is expected to have very high mobility in soil surfaces and should be available for transport into groundwater. In a laboratory experiment conducted with a sandy loam, approximately 50% of an initial concentration of 0.81 mg/L of 1,2-dichloroethane applied to the soil surface was volatilized. The remainder percolated through the soil column to a depth of 140 cm, suggesting that leaching into groundwater may occur (Wilson et al. 1981). Environmental surveys conducted by EPA have detected 1,2-dichloroethane in groundwater sources in the vicinity of contaminated sites (EPA 1985a). Large spills of 1,2-dichloroethane may contaminate groundwater because of the high density of this compound, which makes it sink into the aquifer in a vertical gravity-driven process (Corapcioglu and Hossain 1990).

6.3.2 Transformation and Degradation

6.3.2.1 Air

In the atmosphere, 1,2-dichloroethane is degraded by reaction with photochemically produced hydroxyl radicals. An experimental rate constant of 2.2×10^{-13} cm^3/molecule-second at 25 EC (Arnts et al. 1989; Atkinson et al. 1989) corresponds to a half-life of 73 days using an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm^3. The estimated atmospheric lifetime of 1,2-dichloroethane was reported to be >5 months with formyl chloride, chloroacetyl chloride, hydrogen chloride, and chloroethanol reported as degradation products (EPA 1993). 1,2-Dichloroethane is not expected to undergo significant atmospheric removal by oxidation with ozone or nitrate radicals, and it will not undergo removal by direct photolysis.

6.3.2.2 Water

In groundwater and surface water, biodegradation is the primary degradation process for the removal of 1,2-dichloroethane. Abiotic degradation processes, such as oxidation and hydrolysis, are too slow to be environmentally significant.

Bacteria isolated from a mixture of activated sludge from waste water treatment plants and 1,2-dichloroethane-polluted soils have used 1,2-dichloroethane as a sole carbon source (Janssen et al. 1984; Stucki et al. 1983). Approximately 14% degradation of 5 mg/L 1,2-dichloroethane occurred after 14 days incubation in laboratory experiments using a domestic waste water inoculum (Tabak et al. 1981). The reported loss was corrected for 27% volatilization loss in 10 days from control flasks. Reported degradation losses (corrected for volatilization) for 10 mg/L of the compound were 15% at 7 days and 30% at 14 days. Following a 24-hour incubation at 25 EC under aerobic conditions, 1,2-dichloroethane was degraded (approximately 10%) by a strain of *Pseudomonas fluorescens* bacteria isolated from soil and water contaminated with various chlorinated hydrocarbons, including 1,2-dichloroethane (Vandenbergh and Kunka 1988). 1,2-Dichloroethane was not biodegraded after 35 days under anaerobic conditions in sediment-water test systems (Jafvert and Wolfe 1987) and was not biodegraded by bacteria isolated from groundwater after 8–16 weeks incubation (Wilson et al. 1983). However, recent reviews indicate that the biodegradation of 1,2-dichloroethane to ethene in anaerobic waters is a probable fate process (Kuhn and Suflita 1989; Saint-Fort 1991). The biodegradation half-life of 1,2-dichloroethane in aerobic water was reported as 100 days and the half-life in anaerobic water was reported as 400 days, but

no details on the kinetic experiments used to establish these half-lives were reported (Capel and Larson 1995). The half-life represents the calculated time for loss of the first 50% of the substance, but the time required for the loss of half of that which remains may be substantially longer, and the rate of disappearance may decline further as time progresses. 1,2-Dichloroethane was 97% biodegraded in laboratory studies using aerobic groundwater microcosms obtained from a Superfund site in California over a 6-day incubation period (Cox et al. 1998). In the field, however, the biodegradation half-life of 1,2-dichloroethane in groundwater can range from less than a year to 30 years depending on the conditions (Bosma et al. 1998).

A growing body of evidence indicates that the co-metabolism of 1,2-dichloroethane (the biodegradation of 1,2-dichloroethane from which the degrading organism gains no energetic benefit) occurs under aerobic conditions (see Section 6.3.2.3). Pure cultures of methanotrophic (methane using) bacteria obtained from both polluted and nonpolluted sources degraded 1,2-dichloroethane in the presence of methane and oxygen (Oldenhuis et al. 1989). Aquifer solids obtained at an *in situ* biorestoration field study mineralized 1,2-dichloroethane to carbon dioxide in the presence of dissolved oxygen and methane (Lanzarone and McCarty 1990). Concentrated cell suspensions of methanogenic bacteria incubated at 37 or 55 EC for 24–96 hours reductively dechlorinated 1,2-dichloroethane to ethene, chloroethane, and ethane (Holliger et al. 1990).

The experimental first-order rate constants for the hydrolysis of 1,2-dichloroethane under neutral conditions were reported as 2.1×10^{-8} second^{-1} and 1.8×10^{-8} second^{-1} at 25 EC (Barbash and Reinhard 1989; Jeffers et al. 1989). These values correspond to half-lives of 65 and 72 years. A more recent study determined that the hydrolysis half-life of 1,2-dichloroethane was 4.9×10^{4} years at pH 9 and 15 EC (Miyamoto and Urano 1996). Barbash and Reinhard (1989) found that the presence of 5.1×10^{-4} molar (16 ppm) solution of hydrogen sulfide anion decreased the hydrolytic half-life to 6 years. Although still a slow process, this latter reaction may occur in hypoxic groundwater where hydrogen sulfide occurs naturally.

6.3.2.3 Sediment and Soil

As in surface water, direct photolysis of 1,2-dichloroethane on soil surfaces and hydrolysis in moist soil and sediment are not expected to be important environmental fate processes. The primary transformation process for 1,2-dichloroethane in sediment and soil is biodegradation.

Incubation of 1,2-dichloroethane at a starting concentration of 100 ppb with an unsaturated calcareous soil resulted in 15–23% mineralization to carbon dioxide after 4 weeks, under aerobic conditions, and 3.3–3.4% mineralization under anaerobic conditions (Watwood et al. 1991). 1,2-Dichloroethane (2 µmol) was completely dechlorinated to ethane by anaerobic microcosms and enrichment cultures derived from river sediment over a 2-week incubation period (Loffler et al. 1997). A first-order biodegradation rate constant of 0.013 day^{-1} was determined for 1,2-dichloroethane in an anaerobic sediment slurry (Peijnenburg et al. 1998). This rate constant corresponds to a biodegradation half-life of about 52 days. It was noted that degradation followed first-order kinetics for at least two successive half-lives in this study.

The presence of methane or increasing the proportion of methanotrophs can increase the rate of aerobic biodegradation of 1,2-dichloroethane in soil. In laboratory experiments conducted with different soil types (sand, sandy clay, silty loam, clay, and Lincoln fine sand), soils exposed to methane biodegraded 1,2-dichloroethane to carbon dioxide (Henson et al. 1988; Speitel and Closmann 1991). Based on these results, it was estimated that the bioremediation of soil contaminated with 100 ppm 1,2-dichloroethane could be complete within several months if methane is present (Speitel and Closmann 1991). Methane oxidizing cultures from soil of a California landfill readily biodegraded 1,2-dichloroethane, but toluene and phenol oxidizing cultures were not able to degrade this compound (Chang and Alvarez-Cohen 1995).

As the concentration of 1,2-dichloroethane increases in a soil surface, the degree of biodegradation that takes place may decrease due to microbial toxicity at the enhanced contaminant level. In a respirometer study of microbial toxicity to an agricultural soil, it was determined that a concentration of 0.51 mg of 1,2-dichloroethane per gram of soil resulted in a 50% respiratory inhibition (Regno et al. 1998).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

1,2-Dichloroethane has been detected at low levels (ppb) in ambient urban and rural air, in indoor air samples of residences located near hazardous waste disposal sites, and in surface water, groundwater, and drinking water. Quantitative concentration information is presented in the following sections.

6.4.1 Air

1,2-Dichloroethane has been detected in ambient air samples taken over the north Atlantic Ocean at concentrations of 0.061–0.12 $\mu g/m^3$ (0.015–0.030 ppb) (Class and Ballschmiter 1986) and in trace

amounts in the southern Black Forest in southwestern Germany (concentration unspecified) (Juttner 1986). The reported average surface level background concentration of the compound in ambient air at mid-latitudes is 0.168 μg/m^3 (Singh et al. 1982).

1,2-Dichloroethane has been found at higher concentrations in ambient air samples from urban areas of the United States. In a review of . 950 potential papers on volatile organic compounds (VOCs) in air published from 1970 to 1987, a database of median daily atmospheric concentrations by site type was compiled (EPA 1988b). The median daily atmospheric concentration of 1,2-dichloroethane in urban sites was 0.049 μg/m^3 (0.012 ppb) (1,214 samples) and 1.0 μg/m^3 (0.26 ppb) (182 samples) for source-dominated samples; it was not detected in 648 samples from suburban, rural, or remote sites. 1,2-Dichloroethane was detected at 83 urban locations across the United States at a median concentration of 0.04 μg/m^3 (0.01 ppb) (Kelly et al. 1994). The average concentration of 1,2-dichloroethane in seven urban locations in 1980–1981 ranged from 0.405 to 6.07 μg/m^3 (0.100 to 1.50 ppb) (Singh et al. 1982). The mean concentrations of 1,2-dichloroethane in 1,412 samples of ambient air from 23 sites in 12 Canadian cities from 1988–1990 ranged from 0.070 to 0.28 μg/m^3 (0.017 to 0.069 ppb) with an overall mean of 0.13 μg/m^3 (0.032 ppb) (WHO 1995). Mean urban air concentrations of 1,2-dichloroethane measured during field experiments in March 1984 in Downey, California, Houston, Texas, and Denver, Colorado were 0.40 μg/m^3 (0.010 ppb), 1.82 μg/m^3 (0.45 ppb), and 0.089 μg/m^3 (0.022 ppb), respectively (Singh et al. 1992). In a 1987 survey of 35 homes in the Kanawha Valley, West Virginia, the mean concentration of 1,2-dichloroethane was 20.8 μg/m^3 (5.15 ppb) with a maximum concentration of 140 μg/m^3 (34.6 ppb) (Cohen et al. 1989). A component of the Total Exposure Assessment Methodology (TEAM) compared the outdoor concentration of toxic substances to the corresponding overnight indoor concentration. The results of this monitoring study indicated that 1,2-dichloroethane was detected in 30% of the indoor samples (median concentration: 0.025 μg/m^3) and 37% of the outdoor samples (median concentration: 0.025 μg/m^3) in Greensboro, North Carolina (fall, 1980); 89% of the indoor samples (3.6 μg/m^3) and 100% of the outdoor samples (2.2 μg/m^3) in Baton Rouge, Louisiana (winter, 1981); 18% of the indoor (0.04 μg/m^3) and 40% of the outdoor samples (0.045 μg/m^3) in Houston, Texas (summer, 1981); 64% of the indoor (0.22 μg/m^3) and 54% of the outdoor samples (0.21 μg/m^3) in Los Angeles, California (winter, 1984); 4.3% of the indoor samples (0.03 μg/m^3) and none of the outdoor samples in Los Angeles, California (summer, 1984); 20% of the indoor (0.12 μg/m^3) and none of the outdoor samples in Antioch/Pittsburgh, California (summer, 1984) (Pellizzari et al. 1986). 1,2-Dichloroethane was detected in only 1 of the 349 samples drawn from 11 cities in the 1990 Urban Air Toxics Monitoring Program (UATMP) at a concentration of 0.32 μg/m^3 (0.080 ppb) (EPA 1991c). In a survey of homes in North Carolina, 1,2-dichloroethane was detected at a concentration of 0.40 μg/m^3 (0.10 ppb) in 1 out of

25 homes of smokers and was not detected in the homes of nonsmokers (Heavner et al. 1995). In a survey of New Jersey and Pennsylvania residences, 1,2-dichloroethane was detected in the homes of nonsmokers at a mean concentration of 0.03 μg/m^3 (0.007 ppb) and in the homes of smokers at a mean concentration of 0.32 μg/m^3 (0.079 ppb) (Heavner et al. 1996). The maximum concentration of 1,2-dichloroethane reported in nonsmoking households was 0.54 μg/m^3 (0.13 ppb), while the maximum concentration in households where at least one family member smoked was 9.72 μg/m^3 (2.40 ppb).

1,2-Dichloroethane has also been detected in samples of ambient air collected in the vicinity of hazardous waste disposal sites. Trace amounts of 1,2-dichloroethane were found in samples of outdoor ambient air from two of nine residences in the Love Canal area of Niagara, New York (Barkley et al. 1980). It was also detected in indoor ambient air samples from two of the nine residences surveyed, at concentrations of 0.10 μg/m^3 (0.025 ppb) and 0.13 μg/m^3 (0.032 ppb). In addition, it has been found in ambient air samples from three of five hazardous waste sites surveyed in New Jersey at average concentrations of 0.04, 1.1, and 0.12 μg/m^3 (0.01, 0.28, and 0.030 ppb) (LaRegina et al. 1986). Another possible source of indoor air pollution is through volatilization from contaminated potable water in domestic shower and bath systems (Andelman 1985). 1,2-Dichloroethane was detected at concentrations of 146 μg/m^3 (36 ppb) and 81 μg/m^3 (20 ppb) in the ambient air at municipal landfill sites in Canada (Brosseau and Heitz 1994). 1,2-Dichloroethane was detected in 11.4% of the vented air samples obtained from the Fresh Kills landfill in New York at an average concentration of 0.77 mg/m^3 (0.19 ppm) (EPA 1996).

6.4.2 Water

In a survey of 14 heavily industrialized river basins in the United States, 1,2-dichloroethane was detected at a frequency of 53% in 204 surface water samples collected (EPA 1977a); reported concentrations in domestic surface waters used as drinking water sources ranged from trace amounts to 4.8 μg/L (Brown et al. 1984). 1,2-Dichloroethane has also been found in samples of urban runoff from Eugene, Oregon, at a concentration of 4 μg/L (Cole et al. 1984). 1,2-Dichloroethane was detected in 26% of the river samples obtained from Osaka, Japan, at a mean concentration of 0.09 μg/L (Yamamoto et al. 1997). 1,2-Dichloroethane was detected in the Tees estuary in England in 1992 at concentrations of 0.72–4.02 μg/L, with the highest levels measured near an industrialized area where 1,2-dichloroethane and vinyl chloride monomer were produced (Dawes and Waldock 1994).

Groundwater samples taken from 178 hazardous waste disposal sites contained 1,2-dichloroethane at 29.1% frequency (Plumb 1987). 1,2-Dichloroethane was detected in the groundwater of the Du Pont

Necco Park Landfill in Niagara Falls, New York at concentrations of 14–4,250 µg/L (Lee et al. 1995). Reported concentrations of 1,2-dichloroethane in domestic groundwater supplies used for drinking water ranged from trace amounts to 400 µg/L (Brown et al. 1984). 1,2-Dichloroethane was detected in 10 of 943 groundwater samples across the United States at concentrations that ranged from 0.95 to 9.80 µg/L with median concentrations ranging from 0.57 to 2.9 µg/L (Westrick et al. 1984). The disposal of organic chemicals in trenches at a waste disposal site near Ottawa, Canada resulted in 1,2-dichloroethane groundwater concentrations ranging from 3.9 to 58.0 µg/L in 30% of samples taken from a 37-well monitoring network in 1988 (Lesage et al. 1990). The concentration of 1,2-dichloroethane in the leachate samples from hazardous waste landfills in Germany ranged from 40 to 830 µg/L (Först et al. 1989). 1,2-Dichloroethane was identified, not quantified, in groundwater wells of Eau Claire, Wisconsin (Canter and Sabatini 1994). 1,2-Dichloroethane was detected in 17% of groundwater samples obtained from 479 waste disposal sites in the United States (Barbee 1994). 1,2-Dichloroethane was detected in 27 of 82 samples of groundwater at the Darling Hill Dump, Vermont at an average concentration of 3.7 µg/L and a maximum concentration of 240 µg/L (EPA 1992a). The maximum concentration of 1,2-dichloroethane in groundwater at the Fallon Naval Air Station, Fallon, Nevada was 1,400 µg/L (Kelley et al. 1998). Groundwater from a former petro-chemical refinery in California contained 1,2-dichloroethane at concentrations ranging from 1 to 9 µg/L (EPA 1992b). 1,2-Dichloroethane was detected at concentrations of 0.8–32.8 µg/L in groundwater near the Lower Llobregat aquifer in Spain (Ventura et al. 1997).

1,2-Dichloroethane was found in drinking water samples from a number of urban and rural locations in the United States. This compound has been detected in drinking water samples from New Orleans, Miami, Philadelphia, and Cincinnati (Clark et al. 1986; Suffet et al. 1980). Private drinking water wells in Wisconsin contained >7 µg/L 1,2-dichloroethane in 2 of 7 wells surveyed (Krill and Sonzogni 1986); in Iowa, 3 public well water supplies contained concentrations of 4–19 µg/L (EPA 1985g), and in Kansas, 1 of 103 farmstead wells contained 1,2-dichloroethane at an average concentration of 1.25 µg/L during 1985–1986 (Steichen et al. 1988). 1,2-Dichloroethane was detected at concentrations of 1–64 µg/L in 56 private drinking water wells in Rhode Island (Rhode Island Department of Health 1989). It was also detected at 0.050 µg/L in drinking water samples from three of nine residences surveyed in the Love Canal area of Niagara, New York (Barkley et al. 1980). 1,2-Dichloroethane was detected in 0.5% of the drinking water wells studied between 1984 and 1990 in California at a maximum concentration of 24 µg/L (Lam et al. 1994b).

6.4.3 Sediment and Soil

The concentration of 1,2-dichloroethane in sediment samples obtained from the Southampton Water estuary, England over an 18-month period ranged from 0.070 to 11 ppb (Bianchi et al. 1991). 1,2-Dichloroethane was not detected in sediment downstream from two facilities in Canada that manufactured this compound (Oliver and Pugsley 1986). The mean concentration of 1,2-dichloroethane in soil near 20 homes in the Netherlands was 11 mg/kg, while samples in the vicinity of a garage and waste site contained <5 and 30 mg/kg, respectively (WHO 1995). 1,2-Dichloroethane was detected in soil from Claire, Michigan near seven industrial facilities at concentrations of 6–19 µg/kg (EPA 1992c).

6.4.4 Other Environmental Media

In a market basket survey of over 500 samples of table-ready and prepared foods (including cereals, oils/dressings, vegetables, baked goods, nuts, dairy products, jams/candy, meats/meat dishes, fruits, infant/toddler blends, and beverages), 1,2-dichloroethane was detected in a whiskey sample at a concentration of 30 ng/g (Daft 1988, 1989, 1991). 1,2-Dichloroethane has been detected in plain granola samples at 0.31 and 12 ng/g, shredded wheat cereal samples at 8.2 ng/g (Heikes 1987), wheat grain samples at 0–180 ng/g, and bleached flour samples at 0–6.5 ng/g (Heikes and Hopper 1986). 1,2-Dichloroethane has also been qualitatively detected as a volatile component in chickpeas (Rembold et al. 1989).

1,2-Dichloroethane was formerly used as a fumigant, but is not currently registered for use in agricultural products in the United States, Canada, and the United Kingdom. 1,2-Dichloroethane was not detected in 24 samples of rice analyzed in 1992 (WHO 1995) and was not detected in an FDA survey of 234 table ready foods (Heikes et al. 1995). In a survey of foods from Tokyo, Japan, 1,2-dichloroethane was not detected in bean sprouts, colas, juice, rice, lactic beverages, plain yogurt, tofu, or ice milk (Miyahara et al. 1995). It was detected at mean concentrations of 1.3 ng/g in butter, 0.2 ng/g (ppb) in cake, 0.03 ng/g in ice cream, and 0.03 ng/g in store-bought milk (Miyahara et al. 1995).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The greatest source of exposure to 1,2-dichloroethane for most of the U.S. population is inhalation of the compound in contaminated air. Other potential routes of human exposure include ingestion of 1,2-dichloroethane in contaminated drinking water or food items and dermal absorption (EPA 1985a; Gold 1980). Since 1,2-dichloroethane is not currently registered for use in agricultural products in the United States, the potential exposure from ingesting contaminated food sources has likely decreased. Ingestion of drinking water contaminated with 1,2-dichloroethane is expected to be an important route of exposure for only 4–5% of the population (HSDB 2001). However, for populations with drinking water supplies containing >6 µg/L of the compound, oral and dermal routes are expected to be more important than inhalation (EPA 1985a). The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day (Miyahara et al. 1995). Since the levels of 1,2-dichloroethane in food products of Japan are similar to those in the United States, the daily intake value may also be similar.

The National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, estimated that 1.35 million workers in 111,222 plants were potentially exposed to 1,2-dichloroethane in the workplace in 1970 (NIOSH 1976a). These estimates were derived from observations of the actual use of 1,2-dichloroethane (5% of total estimate), the use of trade-name products known to contain 1,2-dichloroethane (3%), and the use of generic products suspected of containing the compound (92%). The largest numbers of exposed workers were employed in medical and other health services, automotive dealerships and service stations, and wholesale trade industries. The occupational groups with the largest numbers of exposed workers were automobile mechanics, registered nurses, heavy equipment mechanics, janitors, and machinists.

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 77,111 workers (including 32,891 females) in 1,526 plants were potentially exposed to 1,2-dichloroethane in the workplace in 1980 (NIOSH 1984a). The largest numbers of exposed workers were employed in the apparel and other textile products, chemical and allied products, business services, and petroleum and coal products industries as machine operators, assemblers, production inspectors, checkers, and examiners. The estimates were based on direct observation by the surveyor of the actual use of the compound (68%) and observation of the use of trade name products known to contain 1,2-dichloroethane (32%).

Neither the NOHS database nor the NOES database contains information on the frequency, level, or duration of exposure of workers to any of the chemicals listed therein. They provide only estimates of workers potentially exposed to the chemicals. There was a large potential for exposure to 1,2-dichloroethane in the workplace during its previous use as a grain fumigant, solvent, and diluent in open-system operations (NIOSH 1978a).

1,2-Dichloroethane was detected at a mean concentration of 0.09 μg/m^3 in workplaces where smoking is not permitted and at a mean concentration of 0.03 μg/m^3 in workplaces where smoking is permitted (Heavner et al. 1996). These data are in contrast with the findings from the same study that showed a significantly higher concentration of 1,2-dichloroethane in the air of homes in which at least one family member smoked (see Section 6.4.1).

Exposure of the population to 1,2-dichloroethane through releases to ambient air from a number of specific emission sources has been estimated (Kellam and Dusetzina 1980). The estimates, which are probably too high because of the current limited use of leaded fuels, are presented in Table 6-2. The EPA Total Exposure Assessment Methodology (TEAM) studies measured personal and outdoor exposures of about 800 people to 25 volatile organic compounds, including 1,2-dichloroethane (Wallace 1991). The people were selected to represent more than one million residents in a wide variety of urban, suburban, and rural areas. The mean measured exposure to 1,2-dichloroethane, which was based on a 24-hour exposure of . 750 people in 6 urban areas, was reported to be 0.5 μg/m^3. The outdoor air concentration based on backyard measurements in 175 homes in 6 urban areas was 7 μg/m^3 (Wallace 1991).

In addition to industrial releases of 1,2-dichloroethane to ambient air, the general population may have been exposed to this compound in indoor air through volatilization from consumer products and from potable water (Andelman 1985). 1,2-Dichloroethane was detected in the volatile emissions of cleaning agents and pesticides, recently glued wallpaper, and recently glued carpet at concentrations of 236 μg/m^3 (58.2 ppb), 48±7.3 μg/m^3 (12±1.8 ppb), and 15±1 μg/m^3 (3.7±0.25 ppb), respectively (Wallace et al. 1987). Since 1,2-dichloroethane is no longer used in consumer products like cleaning agents and adhesives, this route of exposure is expected to be low today.

1,2-Dichloroethane has been detected in the expired breath and urine of humans in a number of studies, following exposure of the test subjects to the compound in ambient air and drinking water (Barkley et al. 1980; EPA 1982a; Wallace et al. 1984).

Table 6-2. Estimated Population Exposure to 1,2-Dichloroethane Through Releases to Ambient Air From a Number of Specific Emission Sources[a]

Emission source	Estimated population exposed	Ambient air concentration (ppb)
1,2-Dichloroethane manufacturing plants	12,500,000	0.01 to $10
Chemical production facilities	2,621,000	0.01–0.99
Gasoline service stations[b]	1,000,000	0.01–0.029
Automobile emissions	13,000,000	0.01–0.029
Automobile refueling	30,000,000	<0.01

[a]Derived from Kellam and Dusetzina 1980
[b]Emissions from gasoline stations are in decline.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 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, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

There are no exposure studies or body burden measurements of 1,2-dichloroethane in children. 1,2-Dichloroethane has been detected in both ambient outdoor and indoor air as discussed in Section 6.4.1 and inhalation of contaminated air likely represents the greatest route of potential exposure for children. 1,2-Dichloroethane has also been detected in drinking water, and therefore, ingestion of contaminated water is a possible source of exposure. 1,2-Dichloroethane been detected in human milk at concentrations ranging from 0.195 to 0.63 mg/100 mL of milk (EPA 1980a; Urusova 1953). Therefore, it is possible that children may be exposed to 1,2-dichloroethane from breast-feeding mothers, although no details of the analytical methodology were reported and, the sample size was not provided in this study. Current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane was formerly used in certain consumer household products such as cleaning agents and adhesives. The use of any household products that contained 1,2-dichloroethane to clean floors or glue carpets may result in exposure since children often crawl on floors and play on carpets. The potential for exposure is expected to diminish with time since 1,2-dichloroethane volatilizes fairly rapidly. This is expected to be a relatively minor route of exposure since most of these products have probably been used up or discarded from the majority of households.

1,2-Dichloroethane has been detected in several food products as discussed in Section 6.4.4, but consumption of these products should not disproportionately affect children. No data are available regarding the weight-adjusted intake of 1,2-dichloroethane. 1,2-Dichloroethane was formerly used as a fumigant, but is not currently registered for use in agricultural products in the United States, Canada, or

the United Kingdom. Therefore, it is expected that exposure to 1,2-dichloroethane through food sources will continue to decrease.

Children are unlikely to be exposed to 1,2-dichloroethane from parents' clothing or other objects removed from the workplace because of its volatility. It is possible that exposure may arise from the exhaled breath of parents who are occupationally exposed to 1,2-dichloroethane, but no quantitative data are available to confirm this. 1,2-Dichloroethane has been detected in humans in a number of studies, following exposure of the test subjects to the compound in ambient air and drinking water (Barkley et al. 1980; EPA 1982a; Wallace et al. 1984).

There have been no documented exposures of children to1,2-dichloroethane from pica. Children are unlikely to be exposed to 1,2-dichloroethane from pica since the majority of 1,2-dichloroethane released to the environment is emitted to the atmosphere. Furthermore, much of the 1,2-dichloroethane released to soil is expected to volatilize to air or leach into subsurface soil and groundwater.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to 1,2-dichloroethane is expected to be highest among certain occupational groups (e.g., chemical and allied products industry workers) (NIOSH 1984a) and members of the general population living in the vicinity of industrial point emission sources (EPA 1985a) and hazardous waste sites. 1,2-Dichloroethane has been detected in both ambient air and water in low concentrations (Fusillo et al. 1985; Isacson et al. 1985; Juttner 1986; McDonald et al. 1988; Singh et al. 1982). No information was found regarding the number of people potentially exposed around hazardous waste sites. It was estimated that .15 million people living in the vicinity of manufacturing and formulation plants were potentially exposed to concentrations ranging from 0.01 to $10 ppb 1,2-dichloroethane in ambient air in the late 1970s (Kellam and Dusetzina 1980).

6.8 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 1,2-dichloroethane 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 1,2-dichloroethane.

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.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,2-dichloroethane are well characterized to permit estimation of its environmental fate (see Chapter 4). No additional studies are needed at this time.

Production, Import/Export, Use, Release, and Disposal. Information on the production and use of 1,2-dichloroethane is available (Anonymous 1998; Archer 1979; Dow Chemical Company 1989b; SRI 1998). Import and export data on 1,2-dichloroethane are also available (Anonymous 1998). More information regarding the amount of 1,2-dichloroethane that is disposed of at hazardous waste sites or abandoned would be useful. No current data are available on the amount of 1,2-dichloroethane disposed of annually.

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 TRI, which contains this information for 1999, became available in 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The partitioning of 1,2-dichloroethane into air, water, and soil is well established (Brüeggemann et al. 1991; Chiou et al. 1980; Dilling 1977; Dilling et al. 1975; EPA 1981, 1985a; Jeng et al. 1992; Jury et al. 1990; Pearson and McConnell 1975; Wilson et al. 1981). 1,2-Dichloroethane is highly mobile in soil and is expected to leach into groundwater. Available laboratory data are sufficient to estimate its atmospheric lifetime, but information on degradation rates in soil and water are limited. Recent data indicates that 1,2-dichloroethane will biodegrade slowly in soil, water, and groundwater under both aerobic and anaerobic conditions. Additional data regarding the

degradation rates of 1,2-dichloroethane in soil and water would be helpful in assessing its environmental fate.

Bioavailability from Environmental Media. 1,2-Dichloroethane has been measured in the breath, blood, urine, and adipose tissue of humans (Barkley et al. 1980; EPA 1980a, 1982a; Wallace et al. 1989). Thus, it can be concluded that 1,2-dichloroethane is bioavailable from the environment. Good quantitative data that correlate varying levels in the environment with levels in the body and associated health effects are lacking. Data are lacking regarding the extent to which 1,2-dichloroethane can be absorbed from various media (e.g., soil).

The health effects observed in humans following exposure to 1,2-dichloroethane are those generally associated with exposure to chlorinated hydrocarbons. Therefore, it may not be possible to correlate the exact levels of 1,2-dichloroethane in the environment with observed health effects in humans. The methodology to predict exposure levels of 1,2-dichloroethane from observed health effects is lacking.

Food Chain Bioaccumulation. The limited experimental data on bioconcentration of 1,2-dichloroethane in aquatic organisms (Banerjee and Baughman 1991; Farrington 1991) and the physical and chemical properties of this compound indicate that bioconcentration and biomagnification are not likely to occur. However, experimental data on food chain biomagnification will aid in determining the potential for human exposure to 1,2-dichloroethane.

Exposure Levels in Environmental Media. 1,2-Dichloroethane has been detected at low levels (ppb) in ambient urban and rural air (Class and Ballschmiter 1986; Cohen et al. 1989; EPA 1988b, 1991c; Juttner 1986; Kelly et al. 1994; Pellizzari et al. 1986; Singh et al. 1982, 1992), in outdoor and indoor air samples of residences located near hazardous waste disposal sites (Andelman 1985; Barkley et al. 1980; Heavner et al. 1996; LaRegina et al. 1986), and in surface water (Brown et al. 1984; EPA 1977a; Yamamoto et al. 1997), groundwater (Barbee 1994; Brown et al. 1984; Lesage et al. 1990; Plumb 1987; Westrick et al. 1984), drinking water (Barkley et al. 1980; Clark et al. 1986; Kelley 1985; Krill and Sonzogni 1986; Lam et al. 1994b; Steichen et al. 1988; Suffet et al. 1980), sediment (Bianchi et al. 1991; Oliver and Pugsley 1986), and food stuffs (Draft 1988, 1989, 1991; Gold 1980; Heikes and Hopper 1986, Heikes 1987; Miyahara et al. 1995; Rembold et al. 1989). Data on estimated human intake from all media have not been located.

Reliable monitoring data for the levels of 1,2-dichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on environmental levels of 1,2-dichloroethane can be used in combination with the known body burden of 1,2-dichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Recent estimates of the size of the population occupationally exposed to 1,2-dichloroethane are not available, and monitoring data on workplace exposure levels (NIOSH 1984a) are generally inadequate. General population exposure estimates have been prepared by the EPA (1985a) for inhalation of the compound in ambient air, which is believed to be the most important route of exposure. However, the general population may also be exposed to low concentrations of 1,2-dichloroethane through ingestion of contaminated water and/or food. The use of old consumer products that contained 1,2-dichloroethane represents a possible, but most likely inconsequential potential exposure route. Quantitative information about the size of the exposed populations and the levels of exposure are generally incomplete. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. There is no information available on the exposure of children to 1,2-dichloroethane. Children are most likely to be exposed to 1,2-dichloroethane via inhalation of ambient air. Ingestion of drinking water and food may also yield childhood exposures. Contact with older household products that contained 1,2-dichloroethane is possible, but is unlikely to be a major source of exposure since 1,2-dichloroethane is no longer used in most consumer products. Children are unlikely to be exposed to 1,2-dichloroethane from pica. Accurate data on the levels of 1,2-dichloroethane in children are needed to identify ways to reduce the potential exposure risks.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for 1,2-dichloroethane 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.

6.8.2 Ongoing Studies

A spectroscopic investigation of the factors that affect the mobility of 1,2-dichloroethane in soil and clay surfaces is being conducted by Dr. Farmer of the University of California, Riverside (FEDRIP 1999). This project, which is sponsored by the U.S. Department of Agriculture, should provide additional information regarding the movement and leaching potential of 1,2-dichloroethane in soil surfaces. No long-term research projects or other ongoing studies of occupational or general population exposures were identified.

As part of the Third National Health and Nutrition Evaluation Survey, the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for 1,2-dichloroethane and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,2-dichloroethane, its metabolites, and other biomarkers of exposure and effect to 1,2-dichloroethane. 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.

7.1 BIOLOGICAL MATERIALS

Table 7-1 lists the analytical methods used for determining 1,2-dichloroethane in biological fluids and tissues. Gas chromatography/mass spectrophotometry (GC/MS) is the most commonly used analytical method for measuring 1,2-dichloroethane in breath, blood, and urine samples (Ashley et al. 1992; Barkley et al. 1980; Wallace et al. 1984, 1986). Sensitivity is in the low- to sub-ppb range. For blood samples, recovery is >74% (Ashley et al. 1992). Precision is adequate (<30% relative standard deviation [RSD]) (Ashley et al 1992). Recovery data were not reported for breath or urine samples.

Glutathione-*S*-transferase (GST) was suggested as a biological marker to detect 1,2-dichloroethane in human erythrocytes (Ansari et al. 1987). 1,2-Dichloroethane inactivates GST in human erythrocytes. A dose-dependent reduction in GST with levels of 1,2-dichloroethane in human erythrocytes *in situ* was reported. However, because a similar response is also reported for acrolein, propylene oxide, styrene oxide, and ethylene dibromide, it is not possible to use measurement of GST activity in human erythrocytes to monitor exposure to 1,2-dichloroethane alone (Ansari et al. 1987).

The presence of metabolites of 1,2-dichloroethane, such as 2-chloroethanol and monochloroacetic acid, in blood and urine could be used as an indicator of exposure to 1,2-dichloroethane (Monster 1986). However, similar metabolites may be found following exposure to other volatile organic compounds. This method is not presently used to determine exposure to 1,2-dichloroethane. Levels of thioethers could be determined analytically in the urine. No analytical measurement for these metabolites are given.

Table 7-1. Analytical Methods for Determining 1,2-Dichloroethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Collect exhaled air in Tenax cartridge	GC/MS-thermal desorption in a fused silica capillary column	1 µg/m^3	No data	Wallace et al. 1984, 1986
Breath	Collect exhaled air in Tenax cartridge	GC/MS-thermal desorption	0.12 µg/m^3	No data	Wallace et al. 1984
Human erythrocytes	Separate erythrocytes from blood; wash and hemolyze; collect GST enzyme	GST activity; not specified	No data	No data	Ansari et al. 1987
Blood/urine	Heat at 50 EC; purge with helium; trap on Tenax GC sorbent	GC/MS	No data	No data	Barkley et al. 1980
Blood	Purge-and-trap blood sample	GC/MS	0.012 ppb	74–116	Ashley et al. 1992

GC = gas chromatography; GST = glutathione-S-transferase; MS = mass spectrophotometry

A pilot study attempted to show a correlation between the levels of halogenated compounds found in the environment and levels measured in blood and urine. The results, however, were not statistically significant (Barkley et al. 1980). The lack of correlation was attributed to differences in body metabolism between the individuals and small sample size. However, the applicability of GC/MS towards correlating environmental levels with body burden levels, given a large enough sample size, was demonstrated.

More information on methods for the analysis of 1,2-dichloroethane in biological materials, including sample preparation techniques can be found in the references cited in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for analyzing 1,2-dichloroethane in environmental samples. GC/MS and GC combined with electron capture detection (ECD) are the most commonly used analytical methods for detecting 1,2-dichloroethane in air (Class and Ballschmiter 1986; Driss and Bouguerra 1991; EPA 1999d; Grimsrud and Rasmussen 1975; Hoyt and Smith 1991; Hsu et al. 1991; Jonsson and Berg 1980; Kessels et al. 1992; Kirshen and Almasi 1992; McClenny et al. 1991; NIOSH 1994; Pleil et al. 1988; Wallace et al. 1984), water, including drinking water, waste water, and tap water (EPA 1982b, 1984c, 1997; Garcia et al. 1992; Otson and Williams 1982; Wallace et al. 1984), sediment (Hiatt 1981), fish (Easley et al. 1981; Hiatt 1981), and food (Daft 1987, 1988, 1989, 1991; Heikes 1987; Heikes and Hopper 1986). Air samples are generally collected on filters and desorbed or collected in canisters. For measuring 1,2-dichloroethane in air samples, sensitivity is in the sub-ppb to low-ppt range for both GC/MS and GC/ECD. Recovery (>90%) and precision (3% RSD) are good (Hsu et al. 1991; Jonsson and Berg 1980).

Purge-and-trap extraction methods are generally used when measuring volatile compounds such as 1,2-dichloroethane in water samples. Sensitivity is in the low-to-sub-ppb and low-ppt range for GC/MS and GC/ECD. High performance gas chromatography (HRGC)/MS has also been used to measure the compound in water with similar sensitivity. Recovery and precision data were not reported. HRGC, with dual detection by ECD and flame ionization detectors (FID) or GC/FID can also be used to measure 1,2-dichloroethane in drinking water and tap water (Driss and Bouguerra 1991; Kessels et al. 1992). Sensitivity for HRGC/ECD-FID is in the sub-ppb range with excellent recovery (100%) (Kessels et al. 1992). Sensitivity data were not reported for GC/FID; however, recoveries were adequate (77.5%) (Driss and Bouguerra 1991). For both methods, precision was good (3.1-21% RSD) (Driss and Bouguerra 1991; Kessels et al. 1992).

Table 7-2. Analytical Methods for Determining 1,2-Dichloroethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect whole air sample in canister; preconcentrate volatile organics from air; treatment of water vapor	GC/MS	0.3 ppb	No data	McClenny et al. 1991
Air	Draw ambient air through a cartridge containing approximately 1–2 g of Tenax. Certain volatile organic compounds are trapped on the Tenax while highly volatile organic compounds and most inorganic atmospheric constituents pass through the cartridge	GC/MS	In general the detection limit should be 20 ng or less	No data	EPA 1999d (Method TO-1)
Air	Draw ambient air through a cartridge containing approximately 0.4 g of a carbon molecular sieve (CMS) adsorbant. Volatile organic compounds are captured on the adsorbant while major inorganic atmospheric constituents pass through (or are only partially retained)	GC/MS	No data	85	EPA 1999d (Method TO-2)
Air	Purge-and-trap	GC/ECD/FID	For many compounds detection limits of 1–5 ng are found using FID	100	EPA 1999d (Method TO-3)

Table 7-2. Analytical Methods for Determining 1,2-Dichloroethane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Draw a sample of ambient air through a sampling train comprised of components that regulate the rate and duration of sampling into a pre-evacuated SUMMA passivated canister	GC/MS	>1 ppb	90–110	EPA 1999d (Method TO-14A)
Workplace air	Place the front and back sorbent sections of the sampler tube in separate vials. Discard the glass wool and foam plugs. Add 1 mL carbon disulfide to each vial	GC/FID	0.2 mg/m^3	No data	NIOSH 1994 (Method 1003)
Air and soil gas	Collect air or soil gas sample in evacuated canister or Tedlar bag through a cryogenically cooled trap to freeze out and preconcentrate volatile compounds; heat trap and transfer volatile analyte to cryogenically cooled column	HRGC/PID-ECD or ELCD	0.05 ppb (ELCD); 0.19 ppb (ECD)	No data	Kirshen and Almasi 1992
Drinking water	Purge-and-trap	GC/MS	5 ng/L	No data	Wallace et al. 1984
Drinking water	Liquid-liquid extraction using *n*-pentane	HRGC/ECD	2.6 µg/L	No data	Garcia et al. 1992
Water and waste water	Purge-and-trap	GC	0.03 µg/L	1.04–1.06C 97.8	EPA 1982b, 1984c (Method 601)
Water and waste water	Purge-and-trap	GC/PID	0.03 µg/L	No data	EPA 1997 (Method 8021B)

Table 7-2. Analytical Methods for Determining 1,2-Dichloroethane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water and waste water	Purge-and-trap	GC/MS	0.06 µg/L	No data	EPA 1997 (Method 8260B)
Water and waste water	Grab sample	GC/MS	4.7 µg/L	1.02+0.45C 99	EPA 1982b, 1984c (Method 624)
Water and waste water	Purge-and-trap	GC/MS	10 µg/L	7.7 µg/L	EPA 1984c (Method 1624B)
Water and waste water	Modified purge-and-trap	GC/HECD and FID simultaneous	0.1 µg/L (FID); <0.1 µg/L (HECD)	78 (FID); 79 (HECD)	Otson and Williams 1982
Water, waste water, and solid waste	Purge-and-trap	GC/MS	5 µg/kg (soil/sediment); 0.5 µg/kg (wastes); 5 µg/L (water)	No data	EPA 1997 (Method 8240B)
Water and waste water	Purge-and-trap	GC	0.002µg/L	No data	EPA 1997 (Method 8010B)
Drinking water	Purge-and-trap extraction technique	HRGC/ECD-FID	0.03 µg/L (ECD); 0.07 µg/L (FID)	100 (ECD); 104–116 (FID)	Kessels et al. 1992
Tap Water	Purge-and-trap extraction technique	GC/FID	No data	77.5	Driss and Bouguerra 1991
Water, solid waste, and tissue	Vacuum distillation extraction technique	GC/MS	No data	No data	EPA 1997 (Method 5032)

Table 7-2. Analytical Methods for Determining 1,2-Dichloroethane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish	Add fish tissue to reagent grade water; disrupt cells ultrasonically; analyze sample by a purge-and -trap method	GC/MS	10 µg/kg	85±11	Easley et al. 1981
Fish	Spiked samples of ground fish tissue; vaporize VOCs from fish under vacuum and condense in purge-and-trap	GC/MS	No data	85±11[a]	Hiatt 1981
Fish	Homogenize fish sample; remove residual moisture by vacuum distillation	GC/MS-fused silica capillary column	No data	No data	Hiatt 1983
Sediment	Spiked samples; vaporize VOCs under vacuum and condense in purge-and-trap	GC/MS	No data	96±17[a]	Hiatt 1981
Grains, legumes, spices, citrus fruits, beverages, dairy products, meat	Acidified acetone-water extraction; isooctane back extraction	GC/ECD	No data	14–75	Daft 1987, 1988, 1989, 1991
Table ready foods	Stirred with water; purge-and-trap on Tenax GC; hexane desorption	GC/ECD	6 ppb	85–104	Heikes 1987; Heikes and Hopper 1986

[a]Reported as percent spike recoveries for 25 ppb spikes

ECD = electron capture detector; ELCD = electrolytic conductivity detector; FID = flame ionization detector; GC = gas chromatography; HECD = Hall electron capture detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; PID = photoionization detector; VOCs = volatile organic carbon compounds

The EPA recommends GC/MS for the determination of 1,2-dichloroethane in water and waste water; this method can detect 1,2-dichloroethane levels of $0.03 µg/L (EPA 1997). Under EPA's Contract Laboratory Program, all contract laboratories are required to maintain certain levels of performance to meet specific quantitation levels (EPA 1988c). For volatiles such as 1,2-dichloroethane, the Contract Required Quantitation Level (CRQL) for water and low soil/sediment is 5 µg/L (EPA 1986a). Complete descriptions of these techniques can be found in the references cited in Table 7-2.

GC/MS is adequate for measuring 1,2-dichloroethane in fish samples with sensitivities in the low-ppb range. Good recoveries (>85%) were achieved (Easley et al. 1981; Hiatt 1981). Sensitivity data were not reported for measuring 1,2-dichloroethane in sediment; however, good recovery (96%) was obtained (Hiatt 1981).

GC/ECD is generally used to measure 1,2-dichloroethane in foodstuffs (Daft 1987, 1988, 1989, 1991; Heikes 1987; Heikes and Hopper 1986). For table-ready foods, sensitivity is in the low-ppb range with good recoveries achieved (>85%) (Heikes 1987; Heikes and Hopper 1986). Precision data were not reported.

7.3 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 1,2-dichloroethane 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 1,2-dichloroethane.

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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The activity of the biomarker GST in blood (Ansari et al. 1987) cannot be used reliably as an indication of exposure to 1,2-dichloroethane because similar effects have been noted following exposure to other organic compounds. No method is routinely used to monitor 1,2-dichloroethane metabolites in human urine. Although it has been suggested that measurement of 2-chloroethanol and monochloroacetic acid in urine may provide evidence of exposure to chlorinated hydrocarbons (Monster 1986), these metabolites are not specific to 1,2-dichloroethane. Methods are available to detect and quantify 1,2-dichloroethane in human breath, blood, and urine (Ashley et al. 1992; Barkley et al. 1980; Wallace et al. 1984). There are no quantitative techniques available to correlate the concentration of 1,2-dichloroethane measured in expired air, blood, or urine to levels of environmental exposure or health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available to detect 1,2-dichloroethane in air (Class and Ballschmiter 1986; Driss and Bouguerra 1991; EPA 1999d; Grimsrud and Rasmussen 1975; Hoyt and Smith 1991; Hsu et al. 1991; Jonsson and Berg 1980; Kessels et al. 1992; Kirshen and Almasi 1992; McClenny et al. 1991; NIOSH 1994; Pleil et al. 1988; Wallace et al. 1984), water, including drinking water, waste water, and tap water (EPA 1997; Garcia et al. 1992; Otson and Williams 1982; Wallace et al. 1984), sediment (Hiatt 1981), fish (Easley et al. 1984; Hiatt 1981), and food (Daft 1987, 1988, 1989, 1991; Heikes 1987; Heikes and Hopper 1986). The standardized methods can detect 1,2-dichloroethane levels of $5 ppt in air and of $2 ng/L in water. In addition, numerous techniques for the analysis of 1,2-dichloroethane are reported in the open literature.

The known degradation products of 1,2-dichloroethane that contain chlorine are volatile organic compounds and are often detected and quantified along with 1,2-dichloroethane in monitoring experiments (although they probably arose from anthropogenic sources). Thus, experimental methods used to detect 1,2-dichloroethane are sufficient to quantify its chlorinated degradation products.

7.3.2 Ongoing Studies

No ongoing studies were located regarding techniques for measuring or detecting 1,2-dichloroethane in biological materials or environmental samples.

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 1,2-dichloroethane and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry that permit detection limits in the low parts per trillion (ppt) range.

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines pertaining to 1,2-dichloroethane in air, water, and food are summarized in Table 8-1.

MRLs for inhalation and oral exposure to 1,2-dichloroethane were derived by ATSDR (see Section 2.5 of this toxicological profile). An MRL of 0.6 ppm for chronic-duration inhalation exposure (15–364 days) is based on a NOAEL for liver histopathology in rats (Cheever et al. 1990). An MRL of 0.2 mg/kg/day for intermediate-duration oral exposure (15–364 days) to 1,2-dichloroethane is based on a LOAEL for increased absolute and relative kidney weights in rats (NTP 1991a).

No oral RfD or inhalation RfC toxicity values have been derived for 1,2-dichloroethane by the EPA (IRIS 1999). EPA has determined that 1,2-dichloroethane is a probable human carcinogen (B2 classification) and derived a slope factor (q_1*) of 0.091 $(mg/kg/day)^{-1}$ for cancer risk associated with exposure to 1,2-dichloroethane (IRIS 1999). Similarly, the International Agency for Research on Cancer (IARC) has classified 1,2-dichloroethane as a Group 2B carcinogen (possibly carcinogenic to humans) (IARC 1987).

1,2-Dichloroethane is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987a).

Table 8-1. Regulations and Guidelines Applicable to 1,2-Dichloroethane

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2001
WHO	Inhalation carcinogenic potency (50,000-fold less than the estimated carcinogenic potential)	0.36–2.0 µg/m^3	WHO 2001a
	Drinking water (lifetime cancer risk of 10^{-5})	30 µg/L	WHO 2001b
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV–TWA	10 ppm	ACGIH 2000
NIOSH	REL (10-hour TWA)	1 ppm	NIOSH 2001
	STEL	2 ppm	
	IDLH	50 ppm	
	Potential occupational carcinogen		
OSHA	PEL (8-hour TWA)	50 ppm	OSHA 2001b
	PEL (ceiling)	100 ppm	
	PEL (maximum peak above ceiling concentration for an 8-hour shift for a maximum duration of 5 minutes in any 3-hours)	200 ppm	
	PEL (8-hour TWA) for construction industry	50 ppm	OSHA 2001c 29CFR1926.55
	PEL (8-hour TWA) for shipyard industry	50 ppm	OSHA 2001a 29CFR1915.1000
USC	HAP		USC 2001 42USC7412
b. Water			
EPA	Drinking water standard	$5x10^{-3}$ mg/L	EPA 2001g 40CFR141.32

Table 8-1. Regulations and Guidelines Applicable to 1,2-Dichloroethane *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	Groundwater monitoring		EPA 2001f
	Suggest method	8010 8240	40CFR264
	PQL	0.5 µgL 5 µgL	Appendix IX
	MCLG	0 mg/L	EPA 2001h 40CFR141.50
	MCL	$5x10^{-3}$ mg/L	EPA 2001i 40CFR141.61
	Water pollution—hazardous substance designation		EPA 2001m 40CFR116.4
	Water programs—determination of reportable quantity	100 pounds	EPA 2001n 40CFR117.3
	Water quality criteria for human health for consumption of:		EPA 2001a
	Water and organism	0.38 µg/L[b]	
	Organism only	99 µg/L[b]	
c. Food			
FDA	Bottled water—concentration limit	$5x10^{-3}$ mg/L	FDA 2000d 21CFR165.110
	Chemicals used to wash or to assist in the peeling of fruits and vegetables	not to exceed 0.2 ppm	FDA 2000f 21CFR173.315 (a)(3)
	Food additives permitted for direct addition—adjuvants for pesticide use dilutions		FDA 2000b 21CFR172.710
	Food additives permitted in feed and drinking water of animals:		FDA 2000e 21CFR573.440
	Used as a solvent in the extraction processing of animal byproducts for use in animal feeds		
	Maximum quantity of the additive permitted to remain on the extracted byproducts	not to exceed 300 ppm	
	Extracted animal byproduct added as a source of protein to all rations consistent with good feeding practices	not to exceed 13% of the total ration	

Table 8-1. Regulations and Guidelines Applicable to 1,2-Dichloroethane *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
FDA	Indirect food additives —adhesives and components of coatings		FDA 2000g 21CFR175.105 (c)(5)
	Indirect food additives —polycarbonate resins		FDA 2000c 21CFR177.1580(b)
	Secondary direct food additive for human consumption	30 ppm	FDA 2000a 21CFR173.230
d. Other			
ACGIH	Carcinogenicity classification	A4[c]	ACGIH 2000
DOT	Reportable quantity	100 pounds	DOT 2001 49CFR172.101 Appendix A
EPA	Carcinogenicity classification	Group B2[d]	EPA 2001b
	Cancer slope factor (oral)	9.1×10^{-2}	IRIS 2001
	Carcinogenic drinking water unit risk	6.7×10^{-3} $(\mu g/L)^{-1}$	
	Carcinogenic inhalation unit risk	2.6×10^{-5} $(\mu g/m^3)^{-1}$	
	Chemical information rules —chemical lists and reporting periods		EPA 2001c 40CFR712.30
	Effective date	08/04/95	
	Reporting date	10/03/95	
	Community Right-to-Know; toxic chemical release reporting —effective date	01/01/87	EPA 2001d 40CFR372.65
	Health and environmental protection standards at uranium and thorium mill tailings—listed constituent		EPA 2001e 40CFR192 Appendix I
	Identification and listing of hazardous waste	U077	EPA 2000 40CFR261.33(f)
	Reportable quantity	100 pounds	EPA 2001j 40CFR302.4
	RfC	not established	IRIS 2001
	RfD	not established	

Table 8-1. Regulations and Guidelines Applicable to 1,2-Dichloroethane *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	Risk specific doses		EPA 2001k
	Unit risk	$2.6x10^{-5}$ µg/L	40CFR266
	RsD	$3.8x10^{-1}$ µg/L	Appendix V
	TSCA—health and safety data reporting		EPA 2001l 40CFR716.120
	Effective date	06/01/87	
	Sunset date	06/01/87	
STATE			
Regulations and Guidelines:			
a. Air			
California	Toxic air contaminant		California 2001
California	REL	95 µg/m^3	
Colorado	Fence line air quality criteria for remediation:		Colorado 2000
	Cancer	0.10 µg/m^3	
	Noncancer	4.9 µg/m^3	
Kansas	Ambient air quality standard	0.8 tons/year	CDC 1999b
New Jersey	Required use of a MSHA/NIOSH approved supplied-air respirator	$1 ppm	New Jersey Department of Health 1994
b. Water			
Alabama	MCL	0.5 mg/L	ADEM 2000
Alaska	MCL	0.005 mg/L	ADEC 2000
	Groundwater clean-up level	0.005 mg/L	
Arizona	Drinking water guideline	0.38 µg/L	HSDB 2001
Arkansas	MCL	0.5 mg/L	APCEC 2000
California	Drinking water standard	0.5 µg/L	HSDB 2001
Connecticut	Notification threshold concentration:		CDEP 2000b
	Drinking water well	1 µg/L	
	Groundwater	1 µg/L	
Florida	Drinking water standard	3 µg/L	HSDB 2001

Table 8-1. Regulations and Guidelines Applicable to 1,2-Dichloroethane *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Georgia	Instream concentration	98.6 µg/L	GDNR 2000
Hawaii	MCL	0.005 mg/L	Hawaii Department of Health 1997
Maine	Drinking water guideline	5 µg/L	HSDB 2001
Massachusetts	MCL	0.05 mg/L	FSTRAC 1999a
Minnesota	Drinking water guideline	4 µg/L	HSDB 2001
New Jersey	Drinking water standard	2 µg/L	HSDB 2001
South Dakota	Human health standards contaminant level	$5x10^{-3}$ mg/L	FSTRAC 1999b
c. Other			
California	Carcinogenicity classification		California 2001
	Cancer potency factor (oral)	$7.0x10^{-2}$ mg/kg/day	
	Cancer potency factor (inhalation)	$2.2x10^{-5}$ $(µg/m^3)^{-1}$	
Colorado	Chronic fence line criteria Cancer Noncancer	 0.1 µg/m^3 4.9 µg/m^3	Colorado 2000
	Hazardous air pollutant (HAP) list	1.000 fm305[e]	Colorado 2001
Connecticut	Hazardous waste contaminant level	0.5 mg/L	CDEP 1996

[a]Group 2B: possible human carcinogen
[b]This criterion is based on carcinogenicity of 10^{-6} risk. Alternate risk levels may be obtained by moving the decimal point (e.g., for a risk level of 10^{-5}, move the decimal point in the recommended criterion one place to the right).
[c]A4: not classifiable as a human carcinogen
[d]Group B2: not classifiable as a human carcinogen
[e]fm305: method 305 fraction measure factor

ACGIH = American Conference of Governmental Industrial Hygienists; ADEC = Alaska Department of Environmental Conservation; ADEM = Alabama Department of Environmental Management; APCEC = Arkansas Pollution Control and Ecology Commission; CDC = Center for Disease Control; CDEP = Connecticut Department of Environmental Protection; CFR = Code of Federal Regulations; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal–State Toxicology Risk Analysis Committee; GDNR = Georgia Department of Natural Resources; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MSHA = Mining Safety and Health Administration; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantity limit; REL = recommended exposure limit; RfC = oral reference concentration; RfD = oral reference dose; RsD = risk specific dose; STEL = short-term exposure limit; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

9. REFERENCES

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH. 252-253.

ACGIH. 1998. Documentation of the threshold limit values and biological exposure indices. 6th Ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 2000. Documentation of the threshold limit values and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ADEC. 2000. Environmental conservation: Drinking water. Alaska Department of Environmental Conservation. Http://www.state.ak.us/local/akpages/ENV.CONSERV/title18/aac80ndx.htm. December 12, 2000.

*ADEM. 2000. Hazardous waste program: Identification and listing of hazardous waste. Alabama Department of Environmental Management. Http://www.adem.state.al.us/RegsPermit/ADEMRegs/rules.html. December 20, 2000.

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

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect 101:103-112.

Adolph EF. 1949. Quantitative relations in the physiological constitutions of mammals. Science 109:579-585.

Agranovich BYA. 1948. Clinical treatment and pathology of toxicologic-chemical injuries of the liver in the case of industrial poisoning. Academies of Medical Science, 132-143.

Albaiges J, Casado F, Ventura F. 1986. Organic indicators of groundwater pollution by a sanitary landfill. Water Res 20:1153-1159.

*Albano E, Poli G, Tomasi A, et al. 1984. Toxicity of 1,2-dibromoethane in isolated hepatocytes: Role of lipid peroxidation. Chem Biol Interact 50:255-265.

*Altman PK, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III, 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

*Alumot E, Nachtomi E, Mandel E, et al. 1976. Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet Toxicol 14:105-110.

*Andelman JB. 1985. Inhalation exposure in the home to volatile organic contaminants of drinking water. Sci Total Environ 47:443-460.

---

*Cited in text

9. REFERENCES

*Anders MW, Livesey JC. 1980. Metabolism of 1,2-dihaloethanes. In: Ames B, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 331-341.

*Andersen ME, Kirshnan 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: Refinement, reduction, replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ 3rd, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

*Anonymous. 1998. Chemical profile: Ethylene dichloride. Chem Mark Rep. February 16, 1998.

*Ansari AS, Singh SV, Gan JC, et al. 1987. Human erythrocyte glutathione S-transferase: A possible marker of chemical exposure. Toxicol Lett 37:57-62.

*Ansari GAS, Gan JC, Barton BK. 1988a. *In-vitro* inactivation of plasma alpha-1 proteinase inhibitor by epoxides and 1,2 dihaloethanes. Arch Environ Contam Toxicol 17:537-542.

*Ansari GAS, Gan JC, Barton BK. 1988b. Synergistic inactivation of plasma alpha inhibitor by aldehydes of cigarette smoke with styrene oxide and 1,2- dichloroethane. Arch Environ Contam Toxicol 17:533-536.

*Aragno M, Tamagno E, Danni O, et al. 1992. *In vivo* studies on halogen compound interactions: III. Effects of carbon tetrachloride plus 1,2-dichloroethane on liver necrosis and fatty accumulation. Res Commun Chem Pathol Pharmacol 76:341-354.

* Archer, WL. 1979. Chlorocarbons,-hydrocarbons(other). In: Grayson M, Eckroth D, ed. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, Inc., 724-725.

*APCEC. 2000. Hazardous waste management: Regulation 23. Arkansas Pollution Control and Ecology Commission.

*Armstrong MJ, Galloway SM. 1993. Micronuclei induced in peripheral blood of E mu-PIM-1 transgenic mice by chronic oral treatment with 2-acetylaminofluorene or benzene but not with diethyl-nitrosamine or 1,2-dichloroethane. Mutat Res 302:61-70.

*Arnts RR, Seila RL, Bufalini JJ. 1989. Determination of room temperature OH rate constants for acetylene, ethylene dichloride, ethylene dibromide, p-dichlorobenzene, and carbon disulfide. J Air Pollut Contr Assoc 39:453-460.

*Ashley DL, Bonin MA, Cardinali FL, et al. 1992. Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. Anal Chem 64:1021-1029.

Ashley DL, Bonin MA, Cardinali FL, et al. 1994. Blood concentrations of volatile organic compounds in a nonoccupationally exposed U.S. population and in groups with suspected exposure. Clin Chem 40:1401-1404.

Assmuth T, Kalevi K. 1992. Concentrations and toxicological significance of trace organic compounds in municipal solid waste landfill gas. Chemosphere 24:1207-1216.

9. REFERENCES

*Atkinson R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. Journal of Physical and Chemical Reference Data. Monograph No. 1.

Atlas E, Giam CS. 1981. Global transport of organic pollutants: Ambient concentrations in the remote marine atmosphere. Science 211:163-165.

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

*Austin SG, Schnatter AR. 1983a. A case-control study of chemical exposures and brain tumors in petrochemical workers. J Occup Med 25:313-320.

*Austin SG, Schnatter AR. 1983b. A cohort mortality study of petrochemical workers. J Occup Med 25:304-312.

*Baertsch A, Lutz WK, Schlatter C. 1991. Effect of inhalation exposure regimen on DNA binding potency of 1,2-dichloroethane in the rat. Arch Toxicol 65:169-176.

*Ballering LA, Nivard MJ, Vogel EW. 1993. Characterization of the genotoxic action of three structurally related 1,2-dihaloalkanes in *Drosophila melanogaster*. Mutat Res 285:209-217.

*Ballering LAP, Nivard MJM, Vogel EW. 1994. Mutation spectra of 1,2-dibromoethane, 1,2-dichloroethane and 1-bromo-1-chloroethane in excision repair proficient and repair deficient strains of *Drosophila melanogaster*. Carcinogenesis 15:869-875.

*Banerjee S. 1988. DNA damage in rodent liver by 1,2-dichloroethane, a hepatocarcinogen. Cancer Biochem Biophys 10:165-173.

*Banerjee S, Baughman GL. 1991. Bioconcentration factors and lipid solubility. Environ Sci Technol 25:536-539.

*Banerjee S, Van Duuren BL. 1979. Binding of carcinogenic halogenated hydrocarbons to cell macromolecules. J Natl Cancer Inst 63:707-711.

*Banerjee S, Van Duuren BL, Oruambo FI. 1980. Microsome-mediated covalent binding of 1,2-dichloroethane to lung microsomal protein and salmon sperm DNA. Cancer Res 40:2170-2173.

*Barbash JE, Reinhard M. 1989. Abiotic dehalogenation of 1,2-dichloroethane and 1,2-dibromoethane in aqueous solution containing hydrogen sulfide. Environ Sci Technol 23:1349-1358.

*Barbee GC. 1994. Fate of chlorinated aliphatic hydrocarbons in the vadose zone and ground water. Ground Water Monit Remed 14:129-140.

*Barber ED, Donish WH, Mueller KR. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. Mutat Res 90:31-48.

Barber LB, Thurman EM, Schroeder MP, et al. 1988. Long-term fate of organic micropollutants in sewage-contaminated groundwater. Environ Sci Technol 22:205-211.

9. REFERENCES

*Barkley J, Bunch J, Bursey JT, et al. 1980. Gas chromatography mass spectrometry computer analysis of volatile halogenated hydrocarbons in man and his environment—A multimedia environmental study. Biomed Mass Spectrom 7:139-147.

*Barnes DG, Dourson M. 1988. Reference dose (RfD) description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Bell J, Melcer H, Monteith H, et al. 1993. Stripping of volatile organic compounds at full-scale municipal wastewater treatment plants. Water Environ Res 65:708-716.

*Benson LO, Teta MJ. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br J Ind Med 50:710-716.

*Berger G. 1994. Epidemiology of endometriosis. In: Modern surgical management of endometriosis. New York, NY: Springer-Verlag.

*Bianchi AP, Varney MS, Phillips J. 1991. Analysis of volatile organic compounds in estuarine sediments using dynamic headspace and gas chromatography-mass spectrometry. J Chromatogr 542:413-450.

Bingham E, Lane JM. 1980. Actions and interactions. Vet Hum Toxicol 22:31-33.

Bolla KI, Schwartz BS, Stewart W, et al. 1995. Comparison of neurobehavioral function in workers exposed to a mixture of organic and inorganic lead and in workers exposed to solvents. Am J Ind Med 27:231-246.

Bond GG, Cook RR, Wight PC, et al. 1983. A case-control study of brain tumor mortality at a Texas chemical plant. J Occup Med 25:377-386.

*Borisover MD, Graber ER. 1997. Specific interactions of organic compounds with soil organic carbon. Chemosphere 34:1761-1776.

*Bosma TNP, van Aalst-van Leeuwen M, Geritse J, et al. 1998. Intrinsic dechlorination of 1,2-dichloroethane at an industrial site. In: Wickramanayake GB, Hinchee RE, eds. Natural attenuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 7-11.

*Bove FJ. 1996. Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicol Ind Health 12:255-266.

*Bove FJ, Fulcomer MC, Klotz JB, et al. 1995. Public drinking water contamination and birth outcomes. Am J Epidemiol 141:850-862.

Bowman A, Maibach HI. 1996. Influence of evaporation and repeated exposure on the percutaneous absorption of organic solvents. Curr Probl Dermatol 25:47-56.

Brack W, Rottler H, Frank H. 1998. Volatile fractions of landfill leachates and their effect on *Chalmydomonas reinhardII*: In vivo chlorophyll a fluorescence. Environ Toxicol Chem 17:1982-1991.

*Brem H, Stein AB, Rosenkranz HS. 1974. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res 34:2576-2579.

9. REFERENCES

Brennan RA, Nirmalakhandan N, Speece RE. 1998. Comparison of predictive methods for Henry's law coefficients of organic chemicals. Water Res 32:1901-1911.

*Brittebo EB, Kowalski B, Ghantous H, et al. 1989. Epithelial binding of 1,2-dichloroethane in mice. Toxicology 56:35-46.

*Brondeau GR, Bonnet P, Guenier JP, et al. 1983. Short-term inhalation test for evaluating industrial hepatotoxicants in rats. Toxicol Lett 19:139-146.

*Brosseau J, Heitz M. 1994. Trace gas compound emissions from municipal landfill sanitary sites. Atmos Environ 28:285-293.

*Brown HS, Bishop DR, Rowan CA. 1984. The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am J Public Health 74:479-484.

Brown SK, Sim MR, Abramson MJ, et al. 1994. Concentrations of volatile organic compounds in indoor air—A review. Indoor Air 4:123-134.

Browning E. 1965. Dichloroethane. Toxicity and metabolism of industrial solvents. New York, NY: Elsevier Publishing Company, 251-252.

*Brüeggemann R, Trapp S, Matthies M. 1991. Behavior assessment of a volatile chemical in the Rhine River. Environ Toxicol Chem 10:1097-1104.

Bryzhin FF. 1945. [Pathomorphological changes of internal organs in connection with poisoning.] Farmakol Toksikol 8:43-49. (Russian)

Bucher J. 1992. Written communication (March 1992) from Dr. John Bucher, National Toxicology Program, Research Triangle Park, NC to Patricia Bittner, Clement International Corporation.

Budavari SS, ed. 1989. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway, NJ: Merck and Co., Inc., 598.

*Budavari S, O'Neil MJ, Heckelman PE, et al. 1996. The Merck index. 12th ed. Whitehouse Station, NJ: Merck and Co., Inc., 646.

*Buijs W, van der Gen A, Mohn GR, et al. 1984. The direct mutagenic activity of alpha, omega-dihalogenoalkanes in *Salmonella typhimurium*. Mutat Res 141:11-14.

Bunce NJ, Schneider UA. 1994. Chemical lifetimes of chlorinated aliphatic priority pollutants in the Canadian troposphere. J Photochem Photobiol A 81:93-101.

*Bundschuh I, Herbort C, Fels LM, et al. 1993. Renal fibronectin excretion as a marker for renal environmental toxins. Contrib Nephrol 101:177-184.

Burke DP. 1987. Chemical week buyers' guide issue 1988. Washington, DC: McGraw-Hill.

C & E News. 1983. Aerosols suffer another bad year. C & E News 61:6.

Cabbar C, Dogu G, Dogu T, et al. 1994. Analysis of diffusion and sorption of chlorinated hydrocarbons in soil by single-pellet moment technique. Environ Sci Technol 28:1312-1319.

9. REFERENCES

Caldwell JC, Woodruff TJ, Morello-Frosch R, et al. 1998. Application of health information to hazardous air pollutants modeled in EPA's cumulative exposure project. Toxicol Ind Health 14:429-454.

*California. 2001. Chemical profile for 1,2-Dichloroethane, Health effects. CalEPA Air Resources Board Toxic Air Contaminant Summary. Http://www.scorecard.org/chemical-p...mmary.tcl?edf_substance_id=107-06-2. January 12, 2001.

Campbell DM, Davidson RJL. 1970. Toxic haemolytic anaemia in pregnancy due to a pica for paradichlorobenzene. J Obstet Gynaecol Br Commonw 77:657-659.

*Canter LW, Sabatini DA. 1994. Contamination of public ground water supplies by superfund sites. Int J Environ Stud 46:35-57.

*Capel PD, Larson SJ. 1995. A chemodynamic approach for estimating losses of target organic chemicals from water during sample holding time. Chemosphere 30:1097-1107.

Caprino L, Togna GI. 1998. Potential health effects of gasoline and its constituents: A review of current literature (1990-1997) on toxicological data. Environ Health Perspect 106:115-125.

Carpenter CP, Smyth HFJ, Pozzani VC. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 31:343-346.

*Casciola LAF, Ivanetich KM. 1984. Metabolism of chloroethanes by rat liver nuclear cytochrome P-450. Carcinogenesis (London) 5:543-548.

CDC. 1999a. Hawaii. Center for Disease Control and Prevention. Http://search.cdc.gov/shd/search2.html. May 25, 1999.

*CDC. 1999b. Kansas. Center for Disease Control and Prevention. Http://search.cdc.gov/shd/search2.html. May 25, 1999.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CDEP. 2000a. Hazardous waste determinations. Connecticut Department of Environmental Protection. Http://www.dep.state.ct.us/wst/proddisp/hwd.htm. December 12, 2000.

*CDEP. 2000b. Significant environmental hazard condition notification threshold concentrations, Reference table A. Connecticut Department of Environmental Protection. Http://search.state.ct.us/query.htm...=0&oq=&rq=0&qt=1%2C2-dichloroethane. December 12, 2000.

Cetnarowicz J. 1959. [Experimental and clinical studies on effects of dichloroethane.] Folia Med Cracov 1:169-192. (Polish)

*Chang HL, Alvarez-Cohen L. 1995. Transformation capacities of chlorinated organics by mixed cultures enriched on methane, propane, toluene, or phenol. Biotechnol Bioeng 45:440-449.

Chang HL, Alvarez-Cohen L. 1996. Biodegradation of individual and multiple chlorinated aliphatic hydrocarbons by methane-oxidizing cultures. Appl Environ Microbiol 62:3371-3377.

Chaudhry GR, Chapalamadugu S. 1991. Biodegradation of halogenated organic compounds. Microbiol Rev 55:59-79.

*Cheever KL, Cholakis JM, el-Hawari AM, et al. 1990. Ethylene dichloride: The influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundam Appl Toxicol 14:243-261.

*Cheh AM, Hooper AB, Skochdopole J, et al. 1980. A comparison of the ability of frog and rat S-9 to activate promutagens in the Ames test. Environ Mol Mutagen 2:487-508.

*Chen C, Puhakka JA, Ferguson JF. 1996. Transformations of 1,1,2,2-tetrachloroethane under methanogenic conditions. Environ Sci Technol 30:542-547.

*Cheng T-J, Huang M-L, You N-C, et al. 1999. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. J Occup Environ Med 41(12):1128-1133.

*Chiou CT, Freed VH, Peters LJ. 1980. Evaporation of solutes from water. Environ Inter 3:231-236.

Christensen TH, Kjeldsen P, Albrechtsen HJ, et al. 1994. Attenuation of landfill leachate pollutants in aquifers. Crit Rev Environ Sci 24:119-202.

*Clark RM, Goodrich JH, Deininger RA. 1986. Drinking water and cancer mortality. Sci Total Environ 53:153-172.

*Class TH, Ballschmiter K. 1986. Chemistry of organic traces in air: VI. Distribution of chlorinated C1-C4 hydrocarbons in air over the northern and southern Atlantic Ocean. Chemosphere 15:413-427.

Clegg ED, Cook JC, Chapin RE, et al. 1997. Leydig cell hyperplasia and adenoma formation: Mechanisms and relevance to humans. Reprod Toxicol 11:107-121.

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

*CMA. 1989. Written communication. Public comment on toxicological profile for 1,2-dichloroethane. Chemical Manufacturers Association, Washington, DC. June 1989.

*Cmarik JL, Inskeep PB, Meredith MJ, et al. 1990. Selectivity of rat and human glutathione S-transferase in activation of ethylene dibromide by glutathione conjugation and DNA binding and induction of unscheduled DNA synthesis in human hepatocytes. Cancer Res 50:2747-2752.

*Cohen MA, Ryan PB, Yanagisawa Y, et al. 1989. Indoor-outdoor measurements of volatile organic compounds in the Kanawha Valley of West Virginia USA. J Air Pollut Contr Assoc 39:1086-1093.

*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.

*Colorado. 2000. RMA information for health care providers. Rocky Mountain Arsenal Medical Monitoring Program. Http://www.cdphe.state.co.us/rma/hlthcare.htm. December 12, 2000.

*Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. Arch Environ Health 30:290-295.

9. REFERENCES

*Corapcioglu MY, Hossain MA. 1990. Ground-water contamination by high-density immiscible hydrocarbon slugs in gravity-driven gravel aquifers. Ground Water 28:403-412.

Cottalasso D, Barisione G, Fontana L, et al. 1994. Impairment of lipoglycoprotein metabolism in rat liver cells induced by 1,2-dichloroethane. Occup Environ Med 51:281-285.

Cottalasso D, Bellocchio A, Norese R, et al. 2000. Effects of vitamin E on dolichol content of rats acutely treated with 1,2-dichloroethane. Toxicology 143:283-292.

Cox EE, McMaster M, Major DW, et al. 1998. Natural attenuation of 1,2-dichloroethane and chloroform in groundwater at a superfund site. In: Wickramanayake GB, Hinchee RE, eds. Natural attentuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 309-314.

Crawford DW, Bonnevie NL, Wenning RJ. 1995. Sources of pollution and sediment contamination in Newark Bay, New Jersey. Ecotoxicol Environ Saf 30:85-100.

*Crebelli R, Carere A. 1988. Genotoxic activity of halogenated aliphatic hydrocarbons in *Aspergillus nidulans*. Occup Toxicol 8:437-442.

*Crebelli R, Benigni R, Franekic J, et al. 1988. Induction of chromosome malsegregation by halogenated organic solvents in *Aspergillus-nidulans* unspecific of specific mechanism Mutat Res 201:401-412.

*Crebelli R, Conti G, Conti L, et al. 1984. Induction of somatic segregation by halogenated aliphatic hydrocarbons in *Aspergillus nidulans*. Mutat Res 138:33-38.

*Crespi CL, Seixas GM, Turner TR, et al. 1985. Mutagenicity of 1,2-dichloroethane and 1,2-dibromoethane in two human lymphoblastoid cell lines. Mutat Res 142:133-140.

Crisp TM, Clegg ED, Cooper RL, et al. 1998. Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(Suppl. 1):11-56.

*Croen LA, Shaw GM, Sanbonmatsu L, et al. 1997. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epidemiology 8(4):347-354.

Cronin MTD. 1996. Quantitative structure-activity relationship (QSAR) analysis of the acute sublethal neurotoxicity of solvents. Toxicol in Vitro 10:103-110.

Crume RV. 1991. The comparison of health risks between different environmental media at Superfund hazardous waste sites. Proc Ann Meet Air Waste Manage Assoc 84:91/109.4.

Dacre JC. 1994. Hazard evaluation of army compounds in the environment. Drug Metab Rev 26:649-662.

*Daft J. 1987. Determining multifumigants in whole grains and legumes, milled and low-fat grain products, spices, citrus fruit, and beverages. J Assoc Off Anal Chem 70:734-739.

*Daft JL. 1988. Rapid determination of fumigant and industrial chemical residues in food. J Assoc Off Anal Chem 71:748-760.

9. REFERENCES

*Daft JL. 1989. Determination of fumigants and related chemicals in fatty and nonfatty foods. J Agric Food Chem 37:560-564.

*Daft JL. 1991. Fumigants and related chemicals in foods: Review of residue findings, contamination sources, and analytical methods. Sci Tot Environ 100:501-518.

*Daniel FB, Robinson M, Olson GR, et al. 1994. Ten and ninety-day toxicity studies of 1,2-dichloroethane in Sprague-Dawley rats. Drug Chem Toxicol 17:463-477.

*Danni O, Aragno M, Tamagno E, et al. 1992. *In vivo* studies on halogen compound interactions: IV. Interaction among different halogen derivatives with and without synergistic action on liver toxicity. Res Commun Chem Pathol Pharmacol 76:355-366.

*Daubert TE, Danner RP, Sibul HM, et al. 1989. Physical and thermodynamic properties of pure chemicals: Data compilation. Washington, DC: Taylor & Francis.

Davidson IWF, Sumner DD, Parker JC. 1982. Ethylene dichloride: A review of its metabolism, mutagenic and carcinogenic potential. Drug Chem Toxicol 5(4):319-388.

Davies P, Landy M. 1998. Suxamethonium and mivacurium sensitivity from pregnancy-induced plasma cholinesterase deficiency. Anaesthesia 53:1109-1116.

*Dawes VJ, Waldock MJ. 1994. Measurement of volatile organic compounds at UK national monitoring plan stations. Mar Pollut Bull 28:291-298.

Dawson BV, Johnson PD, Goldberg SJ, et al. 1990. Cardiac teratogenesis of trichloroethylene and dichloroethylene in a mammalian model. J Am Coll Cardiol 16:1304-1309.

*Dawson BV, Johnson PD, Goldberg SJ, et al. 1993. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol 21:1466-1472.

Dayal H, Gupta S, Trieff N, et al. 1995. Symptom clusters in a community with chronic exposure to chemicals in two superfund sites. Arch Environ Health 50:108-111.

DeJongh J, Verhaar HJM, Hermens JLM. 1998. Role of kinetics in acute lethality of nonreactive volatile organic compounds (VOCS). Toxicol Sci 45:26-32.

Dekant W, Vamvakas S. 1993. Glutathione-dependent bioactivation of xenobiotics. Xenobiotica 23:873-887.

DeLeon IR, Byrne CJ, Perler EA, et al. 1986. Trace organic and heavy metal pollutants in the Mississippi River. Chemosphere 15:795-805.

*DeMarini DM, Brooks HG. 1992. Induction of prophage lambda by chlorinated organics: Detection of some single-species/single-site carcinogens. Environ Mol Mutagen 19:98-111.

Dempsey CR. 1993. A comparison of organic emissions from hazardous waste incinerators versus the 1990 toxic release inventory air releases. J Air Waste Manage Assoc 43:1374-1379.

De Rooij BM, Commandeur JNM, Vermeulen NPE. 1998. Mercapturic acids as biomarkers of exposure to electrophilic chemicals: Applications to environmental and industrial chemicals. Biomarkers 3:239-303.

Dewulf J, Van Langenhove H. 1997. Chlorinated C_1- and C_2-hydrocarbons and monocyclic aromatic hydrocarbons in marine waters: An overview on fate processes, sampling, analysis, and measurements. Water Res 31:1825-1838.

*Dilling WL. 1977. Interphase transfer processes: II. Evaporation rates of chloromethanes, ethanes, ethylenes, propanes, and propylenes from dilute aqueous solutions: Comparisons with theoretical predictions. Environ Sci Technol 11:405-409.

*Dilling WL, Tefertiller NB, Kallos GJ. 1975. Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other chlorinated compounds in dilute aqueous solutions. Environ Sci Technol 9:833-838.

*Doherty AT, Ellard S, Parry EM, et al. 1996. An investigation into the activation and deactivation of chlorinated hydrocarbons to genotoxins in metabolically competent human cells. Mutagenesis 11:247-274.

*DOT. 2001. List of hazardous substances and reportable quantities. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101, Appendix A. Http://www.dot.gov/safety.html. May 02, 2001.

Dow Chemical Company. 1989a. Comparison of the acute lethality of selected hydrocarbons via intratracheal and oral routes. Final report. Dow Chemical Company, Midland, MI. OTS0520615.

*Dow Chemical Company. 1989b. Written communication. Public comment on toxicological profile for 1,2-dichloroethane. Dow Chemical Company, Midland, MI. June 1989.

*Driss MR, Bouguerra ML. 1991. Analysis of volatile organic compounds in water by purge-and-trap and gas chromatography techniques. Int J Environ Anal Chem 45:193-204.

*D'Souza RW, Francis WR, Andersen ME. 1988. Physiological model for tissue glutathione depletion and increased resynthesis after ethylene dichloride exposure. J Pharm Exp Therap 245:563-568.

*D'Souza R, Francis WR, Bruce RD, et al. 1987. Physiologically based pharmacokinetic model for ethylene dichloride and its application in risk assessment. In: Pharmacokinetics in risk assessment: Drinking water and health. Washington, DC: National Research Council, 8:286-301.

*Easley DM, Kleopfer RD, Carasea AM. 1981. Gas chromatographic-mass spectrometric determination of volatile organic compounds in fish. J Assoc Off Anal Chem 64:653-656.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

Eitzer BD. 1995. Emissions of volatile organic chemicals from municipal solid waste composting facilities. Environ Sci Technol 29:896-902.

*Ellenhorn MJ. 1997. The hydrocarbon products. In: Ellenhorn MJ, ed. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins, 1437-1438.

9. REFERENCES

*Ellenhorn MJ, Barceloux DG. 1988. Hydrocarbon products. In: Ellenhorn MJ, Barceloux DG, ed. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Science Publishing Company, Inc., 976-977.

EPA. 1975. Report on the problem of halogenated air pollutants and stratospheric ozone. Washington, DC: U.S. Environmental Protection Agency. EPA 600/9-75-008.

*EPA. 1977a. Monitoring to detect previously unrecognized pollutants in surface water. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/6-77-015.

EPA. 1977b. Review of the environmental fate of selected chemicals. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-77-003.

EPA. 1979a. Source assessment: Chlorinated hydrocarbon manufacture. Washington, DC: U.S. Environmental Protection Agency. EPA 66/2-70-019g.

EPA. 1979b. Investigations of selected environmental pollutants: 1,2-Dichloroethane. Washington, DC: U.S. Environmental Protection Agency. EPA 560/2-78-006.

EPA. 1979c. Criteria and standards for the National Pollutant Discharge Elimination System. Environmental Protection Agency. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125.

EPA. 1979d. Assessment of human exposures to ethylene dichloride. Research Triangle Park, NC: Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. EPA contract No. 68-02-2845.

*EPA. 1980a. Acquisition and chemical analysis of mother's milk for selected toxic substances. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. EPA 560/13-80-029.

EPA. 1980b. Ambient water quality criteria for chlorinated ethanes. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards, Criteria and Standards Division. EPA 440/5-80-029.

EPA. 1980c. Fate of toxic and hazardous materials in the air environment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Sciences Research Laboratory. EPA 600/3-80-084.

EPA. 1980d. Guidelines and methodology used in the preparation of health effect assessment chapters of the consent decree water criteria documents. U.S. Environmental Protection Agency. Federal Register 45:79347-79357.

EPA. 1980e. TSCA section 8(e). Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. Status report No. 8EHQ-0979-484.

EPA. 1980f. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33(f).

9. REFERENCES

*EPA. 1981. Aquatic fate process data for organic priority pollutants. Report to Office of Water Regulations and Standards, U.S. Environmental Protection Agency. EPA 440/4-81-014.

*EPA. 1982a. Direct measurement of volatile organic compounds in breathing-zone air, drinking water, breath, blood, and urine. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. NTIS PB82-186545. EPA 600/4-82-015.

*EPA. 1982b. Test methods for organic chemical analysis of municipal and environmental wastewater. Cincinnati, OH: Monitoring and Support Laboratories, U.S. Environmental Protection Agency. EPA 600/4-82-057.

EPA. 1983. General permits. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122.28.

EPA. 1984a. Survey of ethylene dichloride emission sources. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA 450/3-84-018.

EPA. 1984b. Health effects assessment for 1,2-dichloroethane. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA 540/1-86-002.

*EPA. 1984c. Methods of organic chemical analysis of municipal and industrial wastewater. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136—Appendix A.

*EPA. 1985a. Health assessment document for 1,2-dichloroethane. Final report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-84-006F.

EPA. 1985b. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1985c. National primary drinking water regulations: Volatile synthetic organic chemicals. Environmental Protection Agency. Federal Register 50:46880-46901.

EPA. 1985d. Superfund public health evaluation manual. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA 540/1-86-060.

EPA. 1985e. Health advisory for 1,2-dichloroethane. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.

EPA. 1985f. Quantification of toxicological effects of 1,2-dichloroethane. Washington, DC: Office of Drinking Water, U.S. Environmental Protection Agency. PB86-118080/AS.

*EPA. 1985g. Synthetic organic compound sampling survey of public water supplies. Washington, DC: U.S. Environmental Protection Agency. PB 85 214427/AS.

*EPA. 1986a. Contract Laboratory Program—attachment A: Statement of work for organics analysis. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1986b. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 403.

EPA. 1986c. Hazardous constituents. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261—Appendix VIII.

EPA. 1986d. Inventory Reporting Regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 710.

*EPA. 1987a. Toxic chemical release reporting: Community right-to-know. U.S. Environmental Protection Agency. Federal Register 52:21152-21208.

EPA. 1987b. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.

EPA. 1987c. Health advisory for 1,2-dichloroethane. Washington, DC: Office of Drinking Water, U.S. Environmental Protection Agency.

*EPA. 1987d. Atmospheric persistence of eight air toxics: Project summary. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory. EPA-600/83-87/004.

EPA. 1988a. Contract Laboratory Program Database. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1988b. National ambient volatile organic compounds (VOCs) database update. Washington, DC: U.S. Environmental Protection Agency. EPA/600/3-88/010.

*EPA. 1988c. National Priorities Listing Technical Database. National Priorities Listing. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1989a. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1989b. Interaction between water pollutants: Quantitative electron microscopy of hepatic morphological changes induced by 1,2-dichloroethane (DCE) and 1,1,-dichloroethylene (VDC). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory. PB89-214126.

EPA. 1989c. Reportable quantity adjustments: Delisting of ammonium thiosulfate. U.S. Environmental Protection Agency. Federal Register. 40 CFR Parts 116,117, and 302. Vol 54:155.

*EPA. 1989d. Interim methods for development of inhalation reference concentrations. Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency. EPA/600/8-90/066F.

*EPA. 1991c. 1990 Urban air toxics monitoring program. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Office of Air and Radiation. EPA 450/4-91-024.

*EPA. 1992a. Superfund record of decision (EPA region 1). Darling Hill dump, Lyndon, VT. (First remedial action), June 1992. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. PB93-963702.

*EPA. 1992b. Superfund record of decision: Pacific Coast pipeline, CA. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. PB93-964502.

*EPA. 1992c. Superfund record of decision (EPA region 5). Clare water supply site, Clare County, Clare, MI. (Second remedial action), September 1992. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. PB93-964106.

*EPA. 1993. A literature review of atmospheric transformation products of clean air act title III hazardous air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA/600/R-94/088.

*EPA. 1996. Drinking water regulations and health advisories. Washington DC: U.S. Environmental Protection Agency, Office of Water. EPA 822-B-96-002.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. EPA/630/R-96/012.

*EPA. 1998a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1998b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1998c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264.

*EPA. 1998d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*EPA. 1998e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61.

*EPA. 1998f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.

*EPA. 1998g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61.01.

*EPA. 1998h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.

*EPA. 1999a. National Recommended Water Quality Criteria—Correction. U.S. Environmental Protection Agency, Office of Water. EPA 822-Z-99-001.

EPA. 1999b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 15, 2001.

EPA. 1999c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 15, 2001.

EPA. 1999d. Compendium of methods for the determination of toxic organic compounds in ambient air - second edition. U.S. Environmental Protection Agency, Office of Research and Development. EPA/625/R-96/010b.

*EPA. 2000. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 15, 2001.

*EPA. 2001a. Drinking water and health: National primary drinking water regulations. U.S. Environmental Protection Agency. Http://www.epa.gov/OGWDW/dwh/c-voc/12-dichl.html. January 12, 2001.

*EPA. 2001b. 1,2-Dichloroethane (Ethylene Dichloride): Hazard summary. U.S. Environmental Protection Agency. Http://www.epa.gov/ttn/uatw/hlthef/di-ethan.html. January 12, 2001.

*EPA. 2001c. Chemical information rules. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 712.30. Http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...TI&QUERY=74990&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001d. Community right-to-know. Toxic chemical release reporting. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. Http://ecfrback.access.gpo.gov/otcgi/cfr...3&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001e. Health and environmental protection standards at uranium and thorium mill tailings. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Appendix I. Http://ecfrback.access.gpo.gov/otcgi/cfr...2&RGN=BAPPCT&SUBSET =SUBSET& FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001f. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX. Http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...nd&QUERY=51143&&RGN=BAPPCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001g. National primary drinking water regulations. Drinking water standard. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32. Http://ecfrback.access.gpo.gov/otcgi/cfr...8&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001h. National primary drinking water regulations. Maximum contaminant level goals for organic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50. Http://ecfrback.access.gpo.gov/otcgi/cfr...8&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001i. National primary drinking water regulations. Maximum contaminant levels for organic contaminants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61. Http://ecfrback.access.gpo.gov/otcgi/cfr...TI&QUERY=13712&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001j. Superfund. Designation of hazardous substance. Reportable quantity. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. Http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...I&QUERY=439160&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001k. Risk specific doses. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendix V. Http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...and&QUERY=9974&RGN=BAPPCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 02, 2001.

*EPA. 2001l. Toxic Substances Control Act (TSCA). Health and Safety Data Reporting. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 716.120. Http://ecfrback.access.gpo.gov/otcgi/cfr/otfilter.cgi...I&QUERY=173296&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 02, 2001.

*EPA. 2001m. Water pollution. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. Http://ecfrback.access.gpo.gov/otcgi/cf...=BAPPCT&SUBSET =SUBSET& FROM=1&ITEM=1. May 03, 2001.

*EPA. 2001n. Water programs. Determination of reportable quantity. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. Http://ecfrback.access.gpo.gov/otcgi/cfr...8&RGN=BSECCT&SUBSET=SUBSET&FROM=1&ITEM=1. May 03, 2001.

Eriksson L, Sjostrom M, Berglind R, et al. 1993. Multivariate biological profiling of the subacute effects of halogenated aliphatic hydrocarbons. J Environ Sci Health Part A A28:1123-1144.

*Erve JCL, Deinzer ML, Reed DJ. 1996. Reaction of human hemoglobin toward the alkylating agent S-(2-chloroethyl)glutathione. J Toxicol Environ Health 49:127-143.

Evans RT, Wroe JM. 1980. Plasma cholinesterase changes during pregnancy. Anaesthesia 35:651-654.

Evans GF, Lumpkin TA, Smith DL, et al. 1992. Measurements of VOCs from the TAMS network. J Air Waste Manage Assoc 42:1319-1323.

*Fabricant JD, Chalmers Jr JH. 1980. Evidence of the mutagenicity of ethylene dichloride and structurally related compounds. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 309-329.

*Farrington JW. 1991. Biogeochemical processes governing exposure of organic pollutant compounds in aquatic organisms. Environ Health Perspect 90:75-84.

Fattore E, Muller LL, Davoli E, et al. 1998. Industrial pollutants in ground waters from northern Milan. Chemosphere 36:2007-2017.

*FDA. 1998a. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110.

*FDA. 1998b. Food and Drug Administration. Code of Federal Regulations. 21 CFR 573.440.

*FDA. 1999a. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.230.

*FDA. 1999b. Food and Drug Administration. Code of Federal Regulations. 21 CFR 172.710.

*FDA. 1999c. Food and Drug Administration. Code of Federal Regulations. 21 CFR 177.1580.

*FDA. 1999d. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.315.

*FDA. 1999e. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105.

*FDA. 2000a. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.230. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000b. Food and Drug Administration. Code of Federal Regulations. 21 CFR 172.710. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000c. Food and Drug Administration. Code of Federal Regulations. 21 CFR 177.1580. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000d. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000e. Food and Drug Administration. Code of Federal Regulations. 21 CFR 573.440. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000f. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.315. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FDA. 2000g. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 16, 2001.

*FEDRIP. 1999. Federal Research in Progress.

*Ferreri AM, Rocchi P, Capucci A, et al. 1983. Induction of diphtheria toxin-resistant mutants in human cells by halogenated compounds. Cancer Res and Clin Oncol 105:111-112.

Ferreiro JA, Consuegra S, Sierra LM, et al. 1997. Is the *White-ivory* assay of *Drosophila melanogaster* a useful tool in genetic toxicology. Environ Mol Mutagen 29:406-417.

Fishbein L. 1980. Production, uses, and environmental fate of ethylene dichloride and ethylene dibromide. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 227-238.

Flowtow E. 1952. Poisoning due to chlorinated hydrocarbon compounds, particularly 1,2-dichloro-ethane. Chemical Technology 6:253-254.

*Fomon 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.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

*Först C, Stieglitz L, Roth W, et al. 1989. Quantitative analysis of volatile organic compounds in landfill leachates. Int J Environ Anal Chem 37:287-293.

*Fossett NG, Byrne BJ, Tucker AB, et al. 1995. Mutation spectrum of 2-chloroethyl methanesulfonate in *Drosophila melanogaster* premeiotic germ cells. Mutat Res 331:213-224.

Frantik E, Hornychova M, Horvath M. 1994. Relative acute neurotoxicity of solvents: Isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ Res 66:173-185.

Freiria-Gandara MJ, Lorenzo-Ferreira RA, Alvarez-Devesa A, et al. 1992. Occurrence of halogenated hydrocarbons in the water supply of different cities of Calicia (Spain). Environ Technol 13:437-447.

*FSTRAC. 1999a. Summary of state and federal drinking water standards and guidelines. Washington, DC: U.S. Environmental Protection Agency, Federal-State Toxicology and Regulatory Alliance Committee. February 1990. Http://www.epa.gov/ostwater/fstrac/states.html. May 20, 1999.

*FSTRAC. 1999b. Federal-State Toxicology and Risk Analysis Committee. U.S. Environmental Protection Agency, Office of Water. May 20, 1999. Http://www.epa.gov/ostwater/fstrac/states.html. May 20, 1999.

FSTRAC. 1999c. South Dakota. Federal-State Toxicology and Risk Analysis Committee. U.S. Environmental Protection Agency, Office of Water. May 20, 1999. Http://www.epa.gov/ostwater/fstrac/states.html.

*Fusillo TV, Hochreiter Jr HJ, Lord DG. 1985. Distribution of volatile organic compounds in a New Jersey coastal plain aquifer system. U.S. Geological Survey 23:354-360.

*Garcia C, Tiedra PG, Ruano A, et al. 1992. Evaluation of the liquid-liquid extraction technique and application to the determination of volatile halo-organic compounds in chlorinated water. J Chromatogr 605:251-255.

*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, Medinsky MA, Andersen ME. 1995. Pharmacokinetic modeling approaches for describing the uptake, systemic distribution, and disposition of inhaled chemicals. Crit Rev Toxicol 25:237-254.

*Garrison SC, Leadingham RS. 1954. A fatal case of ethylene dichloride poisoning in an occupational therapy department of a neuropsychiatric hospital. Am J Phys Med 33:230-237.

*GDNR. 2000. Georgia instream water quality standards for all waters: Toxic substances. Georgia Department of Natural Resources. Http://www.ganet.org/dnr/environ/plans/chatt-Pdf/chatt-b.pdf. December 12, 2000.

*Giri AK, Hee SSQ. 1988. *In-vivo* sister chromatid exchange induced by 1,2-dichloroethane on bone marrow cells of mice. Environ Mol Mutagen 12:331-334.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101:65-71.

*Gocke E, Wild D, Eckhardt K, et al. 1983. Mutagenicity studies with the mouse spot test. Mutat Res 117:201-212.

*Gold LS. 1980. Human exposures to ethylene dichloride. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 209-225.

*Goldberg MS, Al-Homsi N, Goulet L, et al. 1995. Incidence of cancer among persons living near a municipal solid waste landfill site in Montreal, Quebec. Arch Environ Health 50:416-424.

*Goldberg SJ, Lebowitz MD, Graver EJ, et al. 1990. An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol 16:155-164.

Goldstein JA, Faletto MB. 1993. Advances in mechanisms of activation and deactivation of environmental chemicals. Environ Health Perspect 100:169-176.

Gonzalez FJ, Gelboin HV. 1994. Role of human cytochromes P450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev 26:165-183.

Goss KU. 1997. Conceptual model for the adsorption of organic compounds from the gas phase to liquid and solid surfaces. Environ Sci Technol 31:3600-3605.

Grayson M, ed. 1985. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, 724-725.

Greenwald P, Friedlander BR, Lawrence CE, et al. 1981. Diagnostic sensitivity bias: An epidemiologic explanation for an apparent brain tumor excess. J Occup Med 23:690-694.

Griesemer RA, Eustis SL. 1994. Gender differences in animal bioassays for carcinogenicity. J Occup Med 36:855-859.

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

Guengerich FP. 1994. Metabolism and genotoxicity of dihaloalkanes. Adv Pharmacol 27:211-236.

Guengerich FP. 1997. Mechanism of mutagenicity of DNA adducts derived from alkyl and vinyl halides. Japanese Journal of Toxicology and Environmental Health 43:69-82.

*Guengerich FP, Kim DH, Iwasaki M. 1991. Role of human cytochrome P-450 IIEI in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4:168-179.

*Guengerich FP, Crawford WM, Domoradzki JY, et al. 1980. *In vitro* activation of 1,2-dichloroethane by microsomal and cytosolic enzyme. Toxicol Appl Pharmacol 55:303-317.

Guyton AC. 1947. Measurement of the respiratory volumes of laboratory animals. Am J Physiol 150:70-77.

*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, Harcourt Brace Jovanovich, Inc.

Hallowell M. 1959. Acute haemolytic anaemia following the ingestion of para-dichlorobenzene. Arch Dis Child 34(173):74-75.

Hansch C, Leo A. 1979. Substituent constants for correlation analysis in chemistry and biology. New York, NY: John Wiley & Sons.

*Hansch C, Leo A, Hoekman D, et al. 1995. Exploring QSAR: Hydrophobic, electronic, and steric constants. Washington, DC: American Chemical Society 4.

*Hansen J. 2000. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am J Ind Med 37:349-352.

*Hawaii Department of Health. 1997. Hawaii administrative rules: Rules relating to potable water systems. Http://mano.icsd.hawaii.gov/doh/rules/ei1120.html. December 12, 2000.

*Hayes FD, Short RD, Gibson JE. 1973. Differential toxicity of monochloroacetate, monofluoroacetate and monoiodoacetate in rats. Toxicol Appl Pharmacol 26:93-102.

HazDat. 1999. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HazDat. 2000. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*Heavner DL, Morgan WT, Ogden MW. 1995. Determination of volatile organic compounds and its apportionment in 49 homes. Environ Int 21:3-21.

*Heavner DL, Morgan WT, Ogden MW. 1996. Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. Environ Int 22:159-183.

Heavner DL, Ogden MW, Nelson PR. 1992. Multisorbent thermal desorption/gas chromatography/mass selective detection method for the determination of target volatile organic compounds in indoor air. Environ Sci Technol 26:1737-1746.

*Heikes DL. 1987. Purge and trap method for determination of volatile hydrocarbons and carbon disulfide in table-ready foods. J Assoc Off Anal Chem 70:215-277.

*Heikes DL, Hopper HL. 1986. Purge and trap method for determination of fumigants in whole grains, milled grain products, and intermediate grain-based foods. J Assoc Off Anal Chem 69:990-998.

*Heikes DL, Jensen SR, Fleming-Jones ME. 1995. Purge and trap extraction with GC-MS determination of volatile organic compounds in table-ready foods. J Agric Food Chem 43:2869-2875.

Heindel JJ, Chapin RE, George J, et al. 1995. Assessment of reproductive toxicity of a complex mixture of 25 groundwater contaminants in mice and rats. Fundam Appl Toxicol 25:9-19.

*Hellman B, Brandt I. 1986. Effects of carcinogenic halogenated aliphatic hydrocarbons on [3H]thymidine incorporation into various organs of the mouse: A comparison between 1,2-dibromoethane and 1,2-dichloroethane. Mutat Res 163:193-199.

*Hemminki K, Falck K, Vainio H. 1980. Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals: Epoxides, glycidyl ethers, methylating and ethylating agents, halogenated hydrocarbons, hydrazine derivatives, aldehydes, thiouram and dithiocarbamate derivatives. Arch Toxicol 46:277-285.

*Henson JM, Yates MV, Cochran JW, et al. 1988. Microbial removal of halogenated methanes, ethanes, and ethylenes in an aerobic soil exposed to methane. FEMS Microbiol Ecol 53:193-20.

*Heppel LA, Neal PA, Perrin TL, et al. 1945. The toxicology of 1,2 dichloroethane (ethylene): III. Its acute toxicity and the effect of protective agents. J Pharmacol Exp Ther 84:53-63.

*Heppel LA, Neal PA, Perrin TL, et al. 1946. The toxicology of 1,2-dichloroethane (ethylene dichloride): V. The effects of daily inhalations. J Ind Hyg Toxicol 28:113-120.

*Heppel LA, Porterfield VT, Sharpless NE. 1947. Toxicology of 1,2-dichloroethane (ethylene dichloride): IV. Its detoxication by L-cystine, DL-methionine and certain other sulphur containing compounds. J Pharmacol Exp Ther 91:385-394.

Hertz CD, Hudson CW, Bardsley AR, et al. 1992. Verification of method detection limits for organic compounds in drinking water. Proc Water Qual Technol Conf 1:647-665.

Hertzberg RC, Rice G, Teuschler LK. 1999. Methods for health risk assessment of combustion mixtures. In: Roberts S, Teaf C, Bean J, eds. Hazardous waste incineration: Evaluating the human health and environmental risks. Boca Raton, FL: CRC Press LLC, 105-148.

*Hiatt MH. 1981. Analysis of fish and sediment for volatile priority pollutants. Anal Chem 53:1541-1543.

Hiatt MH. 1983. Determination of volatile organic compounds in fish samples by vacuum distillation and fused silica capillary gas chromatography/mass spectrometry. Anal Chem 55:506-516.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84:313-320.

Hofmann HT, Birnsteil H, Jobst P. 1971. [The inhalation toxicities of von 1,1- and 1,2-dichloroethane.] Arch Toxikol 27:248-265. (German)

*Hogstedt C, Rohlen O, Berndtsson BS, et al. 1979. A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36:276-280.

Hogue C Jr, Brewster MA. 1991. The potential of exposure biomarkers in epidemiologic studies of reproductive health. Environ Health Perspect 90:261-270.

*Holliger C, Schraa G, Stams AJM, et al. 1990. Reductive dechlorination of 1,2-dichloroethane and chloroethane by cell suspensions of methanogenic bacterial. Biodegradation 1:253-261.

Hooper K, Gold LS, Ames BN. 1980. The carcinogenic potency of ethylene dichloride in two animal bioassays: A comparison of inhalation and gavage studies. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 65-80.

Hotz P. 1994. Occupational hydrocarbon exposure and chronic nephropathy. Toxicology 90:163-283.

Hovorka S, Dohnal V. 1997. Determination of air-water partitioning of volatile halogenated hydrocarbons by the inert gas stripping method. J Chem Eng Data 42:924-933.

9. REFERENCES

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.

*Hoyt SD, Smith VL. 1991. Measurement of toxic organic compounds in ambient air using EPA method TO-14. Capillary Chromatogr 83-94.

HSDB. 1993. Hazardous Substances Data Bank. National Library of Medicine, Toxicology Information Program, Bethesda, MD. May 1993.

HSDB. 1999. 1,2-Dichloroethane. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. June 24, 1999.

*HSDB. 2001. 1,2-Dichloroethane. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Hsu JP, Miller G, Moran VI. 1991. Analytical method for determination of trace organics in gas samples collected by canister. J Chromatogr Sci 29:83-88.

Huang J, Onal I, Senkan SM. 1997. Formation of trace byproducts in the premixed flames of CH_3Cl/C_2H_4. Environ Sci Technol 31:1372-1381.

*Hubbs RS, Prusmack JJ. 1955. Ethylene dichloride poisoning. JAMA 159(7):673-675.

*Hueper WC, Smith C. 1935. Fatal ethylene dichloride [sic] poisoning. Am J Med Sci 189:778-784.

*Humphreys WG, Kim DH, Cmarik JL, et al. 1990. Comparison of the DNA-alkylating properties and mutagenic responses of a series of *S*-(2-haloethyl)-substituted cysteine and glutathione derivatives. Biochemistry 29:10342-10350.

*IARC. 1979. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 20: 1,2-Dichloroethane. Lyon, France: World Health Organization, International Agency for Research on Cancer, 249-448.

IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An upgrading of IARC monographs, volumes 1-42. Lyon, France: World Health Organization, International Agency for Research on Cancer, Suppl. 7, 62.

*IARC. 2001. Overall evaluations of carcinogenicity to humans (as evaluated in IARC monographs 1-77). Lyon, France: World Health Organization, International Agency for Research on Cancer. Http://193.51.164.11/monoeval/crthall.html. (Last updated 9 August 2000).

*Igwe OJ, Que Hee SS, Wagner WD. 1986a. Interaction between 1,2-dichloroethane and disulfiram: I. Toxicological effects. Fund Appl Toxicol 6:733-746.

*Igwe OJ, Que Hee SS, Wagner WD. 1986b. Interaction between 1,2-dichloroethane and tetraethylthiuram disulfide (disulphiram): II. Hepatotoxic manifestations with possible mechanisms of action. Toxicol Appl Pharmacol 86:286-297.

*Igwe OJ, Que Hee SS, Wagner WD. 1988. Urinary thioether biological monitoring in the interaction between 1,2-dichloroethane and disulfiram in Sprague-Dawley rats. Am Ind Hyg Assoc J 49:10-16.

*Inskeep PB, Koga N, Cmarik JL, et al. 1986. Covalent binding of 1,2-dihaloalkanes to DNA and stability of the major DNA adduct, S-[2-(N7-guanyl)ethyl]glutathione. Cancer Res 46:2839-2844.

IRIS. 1992. Integrated Risk Information System. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. Cincinnati, OH.

IRIS. 1999. 1,2-Dichloroethane. Integrated Risk Information System, U.S. Environmental Protection Agency. April 19, 1999.

*IRIS. 2001. 1,2-Dichloroethane. Integrated Risk Information System, U.S. Environmental Protection Agency.

*Isacson P, Bean JA, Splinter R, et al. 1985. Drinking water and cancer incidence in Iowa: III. Association of cancer with indices of contamination. Am J Epidemiol 121:856-869.

Jacobziner H, Raybin HW. 1961. Ethylene dichloride poisoning. Arch Pediatr 78:490-495.

Jaeger RJ. 1979. Time-related variation of non-protein sulfhydryl concentrations in rat tissues and human blood. Int Arch Occup Environ Health 42:141-148.

*Jaeger RJ, Conolly RB, Murphy SD. 1974. Effect of 18 hour fast and glutathione depletion on 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats. Exp Mol Pathol 20:187-198.

*Jafvert CT, Wolfe NL. 1987. Degradation of selected halogenated ethanes in anoxic sediment-water systems. Environ Toxicol Chem 6:827-837.

*Jakobson I, Wahlberg JE, Holmberg B, et al. 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol Appl Pharmacol 63:181-187.

*Janssen DB, Scheper A, Witholt B. 1984. Biodegradation of 2-chloroethanol and 1,2-dichloroethane by pure bacterial cultures. In: Houwink EH, van der Meer RR, eds. Innovations in biotechnology. Amsterdam, The Netherlands: Elsevier Science Publishers, 169-178.

Jay K, Stieglitz L. 1995. Identification and quantification of volatile organic components in emissions of waste incineration plants. Chemosphere 30:1249-1260.

*Jean PA, Reed DJ. 1989. *In vitro* dipeptide, nucleoside, and glutathione alkylation by S-(2-chloroethyl) glutathione and S-(2-chloroethyl)-L-cysteine. Chem Res Toxicol 2:455-460.

Jean PA, Reed DJ. 1992. Utilization of glutathione during 1,2-dichloroethane metabolism in rat hepatocytes. Chem Res Toxicol 5:286-391.

*Jeffers PM, Ward LM, Woytowitch LM, et al. 1989. Homogenous hydrolysis rate constants for selected chlorinated methanes, ethanes, ethenes, and propanes. Environ Sci Technol 23:965-969.

*Jeng CY, Chen DH, Yaws CL. 1992. Data compilation for soil sorption coefficient. Pollut Eng 24:54-60.

*Jenssen D, Ramel C. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat Res 75:191-202.

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

*Johansson I, Ekstrom G, Scholte B, et al. 1988. Ethanol-fasting- and acetone-inducible cytochromes P-450 in rat liver: Regulation and characteristics of enzymes belonging to the IIB and IIE gene subfamilies. Biochemistry 27:1925-1934.

Johnson BL. 1995. Nature, extent, and impact of superfund hazardous waste sites. Chemosphere 31:2415-2428.

Johnson MK. 1966. Studies on glutathione S-alkyltransferase of the rat. Biochem J 98:44-56.

*Johnson MK. 1967. Metabolism of chloroethanol in the rat. Biochem Pharmacol 16:185-199.

Jones TD. 1995. Toxicological potency of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin relative to 100 other compounds: A relative potency analysis of *in vitro* and *in vivo* test data. Arch Environ Contam Toxicol 29:77-85.

*Jonsson A, Berg S. 1980. Determination of 1,2-dibromoethane, 1,2- dichloroethane, and benzene in ambient air using porous polymer traps and gas chromatographic-mass spectrometric analysis with selected ion monitoring. J Chromatogr 190:97-106.

*Jury WA, Russo D, Streile G, et al. 1990. Evaluation of volatilization by organic chemicals residing below the soil surface. Water Res 26:13-20.

Jury WA, Russo D, Streile G, et al. 1992. Evaluation of volatilization by organic chemicals residing below the soil surface. Water Resour Res 28:607-608.

*Juttner F. 1986. Analysis of organic compounds (VOC) in the forest air of the southern Black Forest. Chemosphere 15:985-992.

Kadry AM, Skowronski GA, Abdel-Rahman MS. 1995. Evaluation of the use of uncertainty factors in deriving RfDs for some chlorinated compounds. J Toxicol Environ Health 45:83-95.

Kaira FM. 1966. [Alimentary oral dichloroethane poisoning.] Klin Med Mosk 44:143-146. (Russian)

*Kanada M, Miyagawa M, Sato M, et al. 1994. Neurochemical profile of effects of 28 neurotoxic chemicals on the central nervous system in rats (1): Effects of oral administration on brain contents of biogenic amines and metabolites. Ind Health 32:145-164.

*Kanada T, Uyeta M. 1978. Mutagenicity screening of organic solvents in microbial systems. Mutat Res 54:215.

*Kavlock R, Chernoff N, Carver B, et al. 1979. Teratology studies in mice exposed to municipal drinking-water concentrates during organogenesis. Food Cosmet Toxicol 17:343-347.

Kawata K, Tanabe A, Saito S, et al. 1997. Screening of volatile organic compounds in river sediment. Bull Environ Contam Toxicol 58:893-900.

Keith LH, Garrison AW, Allen FR, et al. 1976. Identification of organic compounds in drinking water from thirteen U.S. cities. In: Keith LH, ed. Identification and analysis of organic pollutants in water. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 329-373.

*Kellam RG, Dusetzina MG. 1980. Human exposure to ethylene dichloride: Potential for regulation via EPA's proposed airborne carcinogen policy. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 265-274.

*Kelley M, Magar VS, Hoeppel R, et al. 1998. Intrinsic remediation of chlorinated hydrocarbons in co-contaminated groundwater plumes at the naval air station Fallon, Nevada. In: Wickramanayake GB, Hinchee RE, ed. Natural attenuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 315-320.

*Kelly TJ, Mukund R, Spicer CW, et al. 1994. Concentrations and transformations of hazardous air pollutants. Environ Sci Technol 28:378A-387A.

Kern H, Kirshen NA. 1992. The automatic analysis of volatile organic compounds in air. Spec Publ Royal Soc Chem 108:210-212.

Kernan GJ, Ji B-T, Dosemeci M, et al. 1999. Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. Am J Ind Med 36:260-270.

Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Safety 4:26-38.

*Kessels H, Hoogerwerf W, Lips J. 1992. The determination of volatile organic compounds from EPA method 524.2 using purge and trap capillary gas chromatography, ECD, and FID detection. Analysis 20:M55-M60.

Kilburn KH, Warshaw RH. 1995. Neurotoxic effects from residential exposure to chemicals from an oil reprocessing facility and superfund site. Neurotoxicol Teratol 17:89-102.

*Kim DH, Guengerich FP. 1989. Excretion of the mercapturic acid S-[2-N^7-guanyl) ethyl]-N-acetyl cysteine in urine following administration of ethylene dibromide to rats. Cancer Res 49:5843-5847.

Kim DH, Guengerich FP. 1990. Formation of the DNA adduct S-[2-(N^7-guanyl)ethyl]glutathione from ethylene dibromide: Effects of modulation for glutathione and glutathione S-transferase levels and lack of role for sulfation. Carcinogenesis 11:419-424.

*King MT, Beikirch H, Eckhardt K, et al. 1979. Mutagenicity studies with X-ray-contrast media, analgesics, antipyretics, antirheumatics and some other pharmaceutical drugs in bacterial, *Drosophila* and mammalian test systems. Mutat Res 66:33-43.

*Kirshen N, Almasi E. 1992. The automated determination of volatile organic contaminant in ambient air and/or soil gas by gas chromatography with selected detectors. ASTM Spec Tech Publ 1075:39-55

*Kitchin KT, Brown JL. 1994. Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. Toxicology 88:31-49.

*Klaunig JE, Ruch RJ, Pereira MA. 1986. Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. Environ Health Perspect 69:89-95.

*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.

Kookana RS, Rogers SL. 1995. Effects of pulp mill effluent disposal on soil. Rev Environ Contam Toxicol 142:13-64.

Kozik I. 1957. [Problems of occupational hygiene in the use of dichloroethane in the aviation industry.] Gig Tr Prof Zabol 1:31-38. (Russian)

*Kramers PGN, Mout HCA, Bissumbhar B, et al. 1991. Inhalation exposure in drosophila mutagenesis assays: Experiments with aliphatic halogenated hydrocarbons, with emphasis on the genetic activity profile of 1,2-dichloroethane. Mutat Res 252:17-33.

*Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc (September):70-75.

*Krishnan K, Andersen ME, Clewell H 3rd, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York, NY: Academic Press, 399-437.

*Kronevi T, Wahlberg JE, Holmberg B. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. Int J Tissue React 3:21-30.

*Kuhn EP, Sulfita JM. 1989. Dehalogenation of pesticides by anaerobic microorganisms in soils and groundwater: A review. In: Reactions and movement of organic chemicals in soils. SSSA Special Publ 22:111-180.

Kuhne R, Ebert RU, Kleint F, et al. 1995. Group contribution methods to estimate water solubility of organic chemicals. Chemosphere 30:2061-2077.

Kuo HW, Chiang TF, Lo II, et al. 1997a. Exposure assessment of volatile organic compounds from water in Taiwan metropolitan and petrochemical areas. Bull Environ Contam Toxicol 59:708-714.

Kuo HW, Chiang TF, Lo II, et al. 1997b. VOC concentration in Taiwan's household drinking water. Sci Total Environ 208:41-47.

Kurashov OV, Trotsevich VA. 1991. Hemosorption in the combined treatment of acute 1,2-dichloro-ethane poisonings. Vrach Delo 5:38-40.

Kurashow OV, Trotsevich VA. 1992. [Acetylcystene in the complex treatment of patients with acute 1,2-dichloroethane poisoning.] Vrach Delo 10:109-111.

Kuwabara T, Quevedo AR, Cogan DG. 1968. An experimental study of dichloroethane poisoning. Arch Ophthalmol 79:321-330.

Lam RHF, Brown JP, Fan AM, et al. 1994a. Chemicals in California drinking water: Source contaminants, risk assessment, risk management, and regulatory standards. J Hazard Mater 39:173-192.

*Lam RHF, Brown JP, Fan AM. 1994b. Chemicals in California drinking water: Source of contamination, risk assessment, and drinking water standards. In: Wang RGM, ed. Water contamination and health: Integration of exposure assessment, toxicology, and risk assessment. New York, NY: Marcel Dekker, Inc., 15-44.

*Lane RW, Riddle BL, Borzelleca JF. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicol Appl Pharmacol 63:409-421.

*Lanzarone NA, McCarty PL. 1990. Column studies of methanotrophic degradation of trichloroethene and 1,2-dichloroethane. Ground Water 28:910-919.

*LaRegina J, Bozzelli JW, Harbov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. Environmental Progress 5(1):18-27.

*Lee MD, Mazierski PF, Buchanan RJ, et al. 1995. Intrinsic in situ anaerobic biodegradation of chlorinated solvents at an industrial landfill. In: Hinchee RE, ed. Intrinsic bioremediation. Columbus, OH: Battelle Press, 205-222.

*Leeder JS, Kearns GL. 1997. Pharmcogenetics in pediatrics: Implications for practice. Pediatr Clin North Amer 44:55-77.

Leisinger T. 1996. Biodegradation of chlorinated aliphatic compounds. Curr Opin Biotechnol 7:295-300.

*Lesage S, Jackson RE, Priddle MW, et al. 1990. Occurrence and fate of organic solvent residues in anoxic groundwater at the Gloucester Landfill, Canada. Environ Sci Technol 24:559-566.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. New York, NY: Stockton Press, 153-164.

Levaggi DA, Siu W. 1991. Gaseous toxics monitoring in the San Francisco Bay area: A review and assessment of four years of data. Proc Annu Meet Air Waste Manage Assoc 84:91/78.12.

*Lewis RJ. 1993. Ethylene dichloride. In: Lewis RJ, ed. Hawley's condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company, 487.

Li KM, Cheng WT. 1991. The occupational exposure level of 1,2-dichloroethane in an EM preparation laboratory. J R Soc Health 111:169.

*Lide DR. 1998. CRC handbook of chemistry and physics: A ready-reference book of chemical and physical data. 79th ed. Boca Raton, FL: CRC Press.

Lindgaard-Jorgensen P, Bender K. 1994. Review of environmental accidents and incidents. Water Sci Technol 29:165-172.

*Livesey JC, Anders MW. 1979. *In vitro* metabolism of 1,2-dihaloethanes to ethylene. Drug Metab Dispos 7:199-203.

*Livingston, AL. 1978. Forage Plant Estrogens. J Toxicol Environ Health 4:301-324.

*Lochhead HB, Close HP. 1951. Ethylene dichloride plastic cement: A case of fatal poisoning. J Am Med Assoc 146:1323.

*Lock EA. 1989. Mechanism of nephrotoxic action due to organohalogenated compounds. Toxicol Lett 46:93-106.

Loew GH, Rebagliati M, Poulsen M. 1984. Metabolism and relative carcinogenic potency of chloroethanes: A quantum chemical structure-activity study. Cancer Biochem Biophys 7:109-132.

*Loffler FE, Champine JE, Ritalahti KM, et al. 1997. Complete reductive dechlorination of 1,2-dichloropropane by anaerobic bacteria. Appl Environ Microbiol 63:2870-2875.

*Lorah MM, Olsen LD. 1999. Degradation of 1,1,2,2-tetrachloroethane in a freshwater tidal wetland: Field and laboratory evidence. Environ Sci Technol 33:227-234.

Luster MI, Rosenthal GJ. 1993. Chemical agents and the immune response. Environ Health Perspect 100:219-236.

*Luster MI, Munson AE, Thomas PT, et al. 1988. Methods evaluation: Development of a testing battery to assess chemical-induced immunotoxicity: National toxicology program's guidelines for immunotoxicity evaluation in mice. Fundam Appl Toxicol 10:2-19.

*Maltoni C, Valgimigli L, Scarnato C. 1980. Long-term carcinogenic bioassays on ethylene dichloride administered by inhalation to rats and mice. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 3-33.

*Martin G, Knorpp K, Huth K, et al. 1969. Clinical features, pathogenesis and management of dichloro-ethane poisoning. Germ Med Mon 14:62-67.

Mathison BH, Harman AE, Bogdanffy MS. 1997. DNA damage in the nasal passageway: A literature review. Mutat Res 380:77-96.

*Matsushima T, Nagano K, Nishizawa T, et al. 1998. Long term inhalation toxicity studies of five chlorinated hydrocarbons in F344 rats and BDF1 mice. J Toxicol Sci 23(Suppl. II):296.

Mayer GJ, Cheng IS, Pau P, et al. 1994. Emissions of air toxics from wastewater treatment plants. Water Environ Res 66:140-144.

*Mayr U, Butsch A and Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

*McCarty LP, Flannagan DC, Randall SA, et al. 1992. Acute toxicity in rats of chlorinated hydrocarbons given via the intratracheal route. Hum Exp Toxicol 11:173-177.

*McClenny WA, Pleil JD, Evans GF, et al. 1991. Canister-based method for monitoring toxic VOCs in ambient air. J Air Waste Manage Assoc 41:1308-1318.

*McCollister DD, Hollingsworth RL, Oyen F, et al. 1956. Comparative inhalation toxicity of fumigant mixtures: Individual and joint effect of ethylene dichloride, carbon tetrachloride, and ethylene dibromide. Arch Ind Health 13:1-7.

*McDonald TJ, Kennicutt MC, Brooks JM, et al. 1988. Volatile organic compounds at a coastal Gulf of Mexico site. Chemosphere 17:123-136.

McGeorge LJ, Krietzman SJ, Dupuy CJ, et al. 1992. National survey of drinking water standards and guidelines for chemical contaminants. Am Water Works Assoc J 84:72-76.

*McNally WD, Fostvedt G. 1941. Ethylene dichloride: Poisoning. Ind Med 10(9):373-374.

Michael LC, Pellizzari ED, Norwood DL. 1991. Application of the master analytical scheme to the determination of volatile organics in wastewater influents and effluents. Environ Sci Technol 25:150-155.

*Milman HA, 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. In: Maltoni C, Selikoff IJ, eds. Annals of the New York Academy of Sciences. Living in a chemical world: Occupational and Environmental Significance of Industrial Carcinogens International Conference, Bologna, Italy, October 6-10, 1985. U.S. Environmental Protection Agency 534:521-530.

*Mitoma C, Steeger T, Jackson SE, et al. 1985. Metabolic disposition study of chlorinated hydrocarbons in rats and mice. Drug Chem Toxicol 8:183-194.

*Miyahara M, Toyoda M, Ushijima K, et al. 1995. Volatile halogenated hydrocarbons in foods. J Agric Food Chem 43:320-326.

*Miyamoto K, Urano K. 1996. Reaction rates and intermediates of chlorinated organic compounds in water and soil. Chemosphere 32:2399-2408.

Mizutani T, Nakahori Y, Yamamoto K. 1994. *p*-Dichlorobenzene-induced hepatotoxicity in mice depleted of glutathione by treatment with buthionine sulfoximine. Toxicology 94:57-67.

Monks TJ, Lau SS. 1988. Reactive intermediates and their toxicological significance. Toxicology 52:1-54.

*Monster AC. 1986. Biological monitoring of chlorinated hydrocarbon solvents. J Occup Med 28:583-588.

Morgan D. 1991. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) in F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (drinking water and gavage studies). Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. NTP TOX 4, NIH Publication No. 91-3123.

*Morgan DL, Cooper SW, Carlock DL, et al. 1991. Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environ Res 55:51-63.

Morita T, Asano N, Awogi T, et al. 1997. Erratum to `Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (Groups 1, 2A and 2B). The summary report of the 6th collaborative study by CSGMT/JEMS MMS' [Mutation Research 389(1997) 3-122]. Mutat Res 391:259-267.

*Moriya M, Ohta T, Watanabe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216.

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

*Munson AE, Sanders VM, Douglas KA, et al. 1982. *In vivo* assessment of immunotoxicity. Environ Health Perspect 43:41-52.

Murray JS, Rao KS, Young JT, et al. 1980. Ethylene dichloride: Single-generation inhalation reproduction study in rats. OTS 0515986.

Nachtomi E. 1970. The metabolism of ethylene dibromide in the rat: The enzymic reaction with glutathione *in vitro* and *in vivo*. Biochem Pharmacol 19:2853-2860.

*Nachtomi E, Alumot E, Bondi A. 1966. The metabolism of ethylene dibromide in the rat: I. Identification of detoxification of products in urine. Isr J Chem 4:239-246.

*Nakajima T, Sato A. 1979. Enhanced activity of liver drug-metabolizing enzymes for aromatic and chlorinated hydrocarbons following food deprivation. Toxicol Appl Pharmacol 50:549-556.

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

NATICH. 1993. National Air Toxics Information Clearinghouse. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. May 1993.

*NCI. 1978. Bioassay of technical grade 1,2-dichloroethane for possible carcinogenicity. Bethesda, MD: National Cancer Institute, Division of Cancer Cause and Prevention, Carcinogenesis Testing Program. NCI-CG-TR 55.

Neeper-Bradley TL, Tyl RW, Fisher LC, et al. 1989. Reproductive toxicity study of inhaled paradichlorobenzene vapor in CD rats [Abstract]. Teratology 39(5):470-471.

*Nestmann ER, Lee EGH, Matula TI, et al. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the *Salmonella*/mammalian-microsome assay. Mutat Res 79:203-212.

NIEHS. 1991. Sixth annual report on carcinogens. Summary 1991. U.S. Department of Health and Human Services, Public Health Service. National Institute of Environmental Health Sciences, Research Triangle Park, NC.

*NIOSH. 1976a. National occupational hazard survey (1972-74). Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1976b. Criteria for a recommended standard—occupational exposure to ethylene dichloride. USDHEW. Cincinnati, OH: National Institute for Occupational Safety and Health. NIOSH publication No. 76-139.

*NIOSH. 1978a. Revised recommended standard: Occupational exposure to ethylene dichloride (1,2-dichloroethane). Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, Division of Criteria Documents and Standards Development. PB80-176092, NIOSH-78-211.

NIOSH. 1978b. Special hazard review—ethylene dichloride. National Institute for Occupational Safety and Health.

*NIOSH. 1984a. National occupational exposure survey (1980-83). Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1984b. NIOSH manual of analytical methods. Method 1003. Vol. 2, 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1990. 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.

NIOSH. 1992. NIOSH recommendations for occupational safety and health: Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. PB92-162536.

*NIOSH. 1994. NIOSH manual of analytical methods. Method 1003. Vol 2, 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1999. Ethylene Dichloride. Pocket guide to chemical hazards. Washington DC: National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services.

*NIOSH. 2001. Ethylene Dichloride. National Institute for Occupational Safety and Health. Http://www.cdc.gov/niosh/idlh/107062.html. January 11, 2001.

*NJ. 1994. 1,2-Dichloroethane, Hazardous substance fact sheet. U.S. Environmental Protection Agency, Envirofacts Warehouse. Http://www.epa.gov/enviro/html/emci/chemref/107062.html. January 12, 2001.

NJDH. 1986. Hazardous substance fact sheet. Trenton, NJ: New Jersey Department of Health, Right to Know Program.

NJDH. 1992a. Report on phase IV-A: Public drinking water contamination and birthweight, fetal deaths, and birth defects; A cross-sectional study. Trenton, NJ: New Jersey Department of Health. April 1992.

NJDH. 1992b. Report on phase IV-B: Public drinking water contamination and birthweight, fetal deaths, and birth defects; A cross-sectional study. Trenton, NJ: New Jersey Department of Health. April 1992.

NJDEH. 1987. STAL for 1,2-dichloroethane. Trenton, NJ: New Jersey Department of Environmental Health.

Noetzel O. 1944. Lethal poisoning with ethylene chloride. Chem Z 68:146-147.

*Nouchi T, Miura H, Kanayama M, et al. 1984. Fatal intoxication by 1,2-dichloroethane—a case report. Int Arch Occup Environ Health 54:111-113.

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

NTP. 1986. Toxicology and carcinogenesis studies of isophorone in F344/N rats and B6C3F1 mice. Gavage studies. National Toxicology Program, Research Triangle Park, NC. NIH/86-2547.

NTP. 1989. Draft NTP technical report on the toxicity studies of 1,2-dichloroethane in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (drinking water and gavage studies). National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC.

*NTP. 1991a. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats and B6C3F1 mice (drinking water and gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program. NIH Publication No. 91-3123.

NTP. 1991b. Sixth annual report on carcinogens: Summary 1991. Research Triangle Park, NC: U.S. Department of Health and Humans Services, Public Health Service, National Toxicology Program, 162-165.

*NTP. 2000. Ninth report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. National Institute of Environmental Health Sciences, Research Triangle Park, NC.

*Nylander P-O, Olofsson H, Rasmuson B, et al. 1978. Mutagenic effects of petrol in *Drosophila melanogaster:* I. Effects of benzene and 1,2-dichloroethane. Mutat Res 57:163-167.

Oda Y, Yamazaki H, Thier R, et al. 1996. A new *Salmonella typhimurium* NM5004 strain expressing rat glutathione S-transferase 5-5: Use in detection of genotoxicity of dihaloalkanes using an SOS/*umu* test system. Carcinogenesis 17:297-302.

*Oldenhuis R, Vink RLJM, Janssen D, et al. 1989. Degradation of chlorinated aliphatic hydrocarbons by methylosinus-trichosporium OB3B expressing soluble methane monooxygenase. Appl Environ Microbiol 55:2819-2826.

*Oliver BG, Pugsley CW. 1986. Chlorinated contaminants in St. Clair river sediments. Water Pollut Res J Can 21:368-379.

OSHA. 1982. Access to employee exposure and medical records; proposed modification; request for comments and notice of public hearing. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 47:30420-30438.

OSHA. 1989. Limits for air contaminants. Occupational Safety and Health Administration. U.S. Department of Labor. Federal Register. 12(12)2937.

*OSHA. 1998a. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55.

*OSHA. 1998b. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

*OSHA. 1998c. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

9. REFERENCES

*OSHA. 2001a. Air contaminants. Shipyards. Occupational Safety and Health Administration. U.S. Department of Labor. Code of Federal Regulations. 29 CFR 1915.1000, Table Z. Http://www.osha-slc.gov/OshStd_data/1915_1000.html. March 26, 2001.

*OSHA. 2001b. Chemical sampling information: Ethylene dichloride. Occupational Safety and Health Administration. Http://www.osha-slc.gov/dts/chemicalsampling/data/CH_240397.html. January 12, 2001.

*OSHA. 2001c. Threshold limit values of airborne contaminants for construction. Occupational Safety and Health Administration. U.S. Department of Labor. Code of Federal Regulations. 29 CFR 1926.55, Appendix A. Http://www.osha-slc.gov/OshStd_data/1926_0055_APP_A.html. March 26, 2001.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-436. April 1990.

Otson R. 1996. Vapor-phase organic compounds in Canadian residences. In: Wang W, Schnoor J, Doi J, eds. Volatile organic compounds in the environment. American Society for Testing and Materials, 66-76.

*Otson R, Williams DT. 1982. Headspace chromatographic determination of water pollutants. Anal Chem 54:942-946.

*Ott MG, Teta J, Greenberg HL. 1989. Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am J Ind Med 16:631-644.

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

*Ozonoff D, Colten ME, Cupples A, et al. 1987. Health problems reported by residents of a neighborhood contaminated by a hazardous waste facility. Am J Ind Med 11:581-597.

Park JH, Lee HJ. 1993. Estimation of bioconcentration factor in fish, adsorption coefficient for soils and sediments and interfacial tension with water for organic nonelectrolytes based on the linear solvation energy relationships. Chemosphere 26:1905-1916.

*Parkinson A. 1996. Biotransformation of xenobiotics. In: Klaassen CD, Amdur MO, Doull J, eds. Casarett and Doull's toxicology: The basic science of poisons. New York, NY: McGraw-Hill Companies, Inc., 113-114,172-175.

*Payan JP, Beydon D, Fabry JP, et al. 1993. Urinary thiodiglycolic acid and thioether excretion in male rats dosed with 1,2-dichloroethane. J Appl Toxicol 13:417-422.

*Payan JP, Saillenfait AM, Bonnet P, et al. 1995. Assessment of the developmental toxicity and placental transfer of 1,2-dichloroethane in rats. Fundam Appl Toxicol 28:187-198.

PCOC. 1966. Pesticide chemicals official compendium. Association of American Pesticide Control Officials, Inc., Topeka, KS.

*Pearson CR, McConnell G. 1975. Chlorinated C1 and C2 hydrocarbons in the marine environment. Proc R Soc London [Biol] 189:305-322.

*Peijnenburg W, Eriksson L, de Groot A, et al. 1998. The kinetics of reductive dehalogenation of a set of halogenated aliphatic hydrocarbons in anaerobic sediment slurries. Environ Sci Pollut Res Int 5:12-16.

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, Hartwell TD, Perritt RL, et al. 1986. Comparison of indoor and outdoor residential levels of volatile organic chemicals in five U.S. geographical areas. Environ Int 12:619-623.

*Perocco P, Prodi G. 1981. DNA damage by haloalkanes in human lymphocytes cultured *in vitro*. Cancer Lett 13:213-218.

*Peterson LA, Harris TM, Guengerich FP. 1988. Evidence for an episulfonium ion intermediate in the formation of S-[2-(N^7-guanyl)ethyl] glutathione in DNA. J Am Chem Soc 110:3284-3291.

Pleil JD, Lindstrom AB. 1997. Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. Clin Chem 43:723-730.

*Pleil JD, Oliver KD, McClenny WA. 1988. Ambient air analyses using nonspecific flame ionization and electron capture detection compared by mass spectroscopy. J Air Pollut Contr Assoc 38:1006-1010.

*Plumb RH Jr. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. Ground Water Monitoring Review, 94-100.

*Pott WA, Benjamin SA, Yang RS. 1998. Antagonistic interactions of an arsenic-containing mixture in a multiple organ carcinogenicity bioassay. Cancer Lett 133:185-190.

Poulin P, Krishnan K. 1996. A tissue composition-based algorithm for predicting tissue: Air partition coefficients for organic chemicals. Toxicol Appl Pharmacol 136:126-130.

*Prodi G, Arfellini G, Colacci A, et al. 1986. Interaction of halocompounds with nucleic acids. Toxicol Pathol 14:438-444.

*Przezdziak J, Bakula S. 1975. [Acute poisoning with 1,2-dichloroethane.] Wiad Lek 28:983-987. (Polish)

*Raisbeck MF, Brown EM, Kanchanapangka S, et al. 1990. Ketonic potentiation of haloalkane-induced nephrotoxicity. In: Goldstein RS, Hewitt WR, Hook JB, eds. Toxic interactions. San Diego, CA: Academic Press, Inc., 321-366.

Rannug U. 1980. The use of different metabolizing systems in the elucidation of the mutagenic effects of ethylene dichloride in *Salmonella*. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 83-95.

*Rannug U, Beije B. 1979. The mutagenic effect of 1,2-dichloroethane on *Salmonella typhimurium:* II. Activation by the isolated perfused rat liver. Chem Biol Interact 24:265-285.

*Rannug U, Sundvall A, Ramel C. 1978. The mutagenic effect of 1,2-dichloroethane on *Salmonella typhimurium*: I. Activation through conjugation with glutathione *in vitro*. Chem Biol Interact 20:1-16.

*Rao KS, Murray JS, Deacon MM, et al. 1980. Teratogenicity and reproduction studies in animals inhaling ethylene dichloride. In: Ames B, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 149-166.

*Rao KS, Murray JS, Deacon MM, et al. 1987. Teratogenicity and reproduction studies in animals inhaling ethylene dichloride. Dow Chemical Company, Toxicology Research Laboratory, Health and Environmental Sciences, Midland MI. OPTS Public Files 86-870002338, OTS 0515862.

*Reeve GR, Bond GG, Lloyd JW, et al. 1983. An investigation of brain tumors among chemical plant employees using a sample-based cohort method. J Occup Med 25:387-393.

*Regno V, Arulgnanendran J, Nirmalakhandan N. 1998. Microbial toxicity in soil medium. Ecotoxicol Environ Saf 39:48-56.

*Reitz RH, Fox TR, Domoradzki JY, et al. 1980. Pharmacokinetics and macromolecular interactions of ethylene dichloride: Comparison of oral and inhalation exposures. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 135-148.

*Reitz RH, Fox TR, Ramsey JC, et al. 1982. Pharmacokinetics and macromolecular interactions of ethylene dichloride in rats after inhalation or gavage. Toxicol Appl Pharmacol 62:190-204.

*Rembold H, Wallner P, Nitz S. 1989. Volatile components of chickpea (*Cicer arietinum* L.) seed. J Agric Food Chem 37:659-662.

*Rhode Island Department of Health. 1989. Report of chemicals detected in private wells. Office of Private Well Water Contamination. February 28, 1989.

*Rodriguez-Arnaiz R. 1998. Biotransformation of several structurally related 2B compounds to reactive metabolites in the somatic w/w+ assay of *Drosophila melanogaster*. Environ Mol Mutagen 31:390-401.

Rogan WJ. 1995. Environmental poisoning of children—lessons from the past. Environ Health Perspect 103(Suppl. 6):19-23.

*Roldan-Arjona T, Garcia-Pedrajas MD, Luque-Romero FL, et al. 1991. An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagenesis 6:199-205.

*Romert L, Magnusson J, Ramel C. 1990. The importance of glutathione and glutathione transferase for somatic mutations in *Drosophila melanogaster* induced by *in vivo* by 1,2-dichloroethane. Carcinogenesis 11:1399-1402.

Rosenkranz HS, Klopman G. 1996. A study of the structural basis of the ability of chlorinated alkanes and alkenes to induce aneuploidy and toxicity in the mold *Aspergillus nidulans*. Mutat Res 354:183-193.

Rosenkranz M, Rosenkranz HS, Klopman G. 1997. Intercellular communication, tumor promotion and non-genotoxic carcinogenesis: Relationships based upon structural considerations. Mutat Res 381:171-188.

Roubal J. 1947. [Two fatal cases of intoxication with symmetric dichloroethane ingestion.] Cas Lek Cesk 86:203-206. (Czech)

RTECS. 1999. 1,2-Dichloroethane. Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health. April 19, 1999.

Ruddick JA, Black WD, Villeneuve DC, et al. 1983. A teratological evaluation following oral administration of trichloro- and dichlorobenzene isomers to the rat [Abstract]. Teratology 27(2):73A-74A.

Ruelle P, Kesselring UW. 1997. Aqueous solubility prediction of environmentally important chemicals from the mobile order thermodynamics. Chemosphere 34:275-298.

Rush GF, Smith JH, Newton JF, et al. 1984. Chemically-induced nephrotoxicity: Role of metabolic activation. CRC Crit Rev Toxicol 13:99-160.

Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am Ind Hyg Assoc J 47:142-151.

*Sablijic A, Gusten H, Verhaar H, et al. 1995. QSAR modeling of soil sorption. Improvements and systematics of log K_{oc} vs. K_{ow} correlations. Chemosphere 95:4489-4515.

*Saint-Fort R. 1991. Ground water contamination by anthropogenic organic compounds from waste disposal sites: Transformations and behavior. J Environ Sci Health A26:13-62.

Salkinoja-Salonen M, Uotila J, Jokela J, et al. 1995. Organic halogens in the environment: Studies of environmental biodegradability and human exposure. Environ Health Perspect 103(Suppl. 5):63-69.

Samet JM. 1995. What can we expect from epidemiologic studies of chemical mixtures. Toxicology 105:307-314.

Sample BE, Arenal CA. 1999. Allometric models for interspecies extrapolation of wildlife toxicity data. Bull Environ Contam Toxicol 62(6):653-663.

*Sano M, Tappel AL. 1990. Halogenated hydrocarbon and hydroperoxide induced lipid peroxidation in rat tissue slices. J Agric Food Chem 38:437-441.

*Sasaki YF, Saga A, Akasaka M, et al. 1998. Detection of in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Mutat Res 419:13-20.

*Sasaki YF, Sakaguchi M, Yamada H, et al. 1994. Evaluation of micronucleus induction in mice by four organochlorine pesticides: 1,2-dibromo-3-chloropropane, 1,3-dichloropropene, 1,2-dichloroethane, and nitrofen. MMS Com 2:87-93.

Sato A, Nakajima T. 1985. Enhanced metabolism of volatile hydrocarbons in rat liver following food deprivation, restricted carbohydrate intake, and administration of ethanol, phenobarbital, polychlorinated biphenyl and 3-methylcholanthrene: a comparative study. Xenobiotica 15(1):67-75.

*Sato A, Nakajima T, Koyama Y. 1981. Dose-related effects of a single dose of ethanol on the metabolism in rat liver of some aromatic and chlorinated hydrocarbons. Toxicol Appl Pharmacol 60:8-15.

Sawhney BL, Kozloski RP. 1984. Organic pollutants in leachates from landfill sites. J Environmental Quality 13:349-352.

Sax NI, ed. 1992. 1,2-Dichloroethane. Dangerous properties of industrial materials report 12(1). New York, NY: Van Nostrand Reinhold Co., 61-82.

Sax NI, Lewis RJ Jr. 1987. Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Co., 486-487.

Schanstra JP, Kingma J, Janssen DB. 1996. Specificity and kinetics of haloalkane dehalogenase. J Biol Chem 271:14747-14753.

*Schlacter MM, Crawford AA, John JA, et al. 1979. Effects of inhaled ethylene dichloride on embryonal and fetal development in rats and rabbits. Dow Chemical Co. Midland, MI. OTS0515988.

*Schönborn H, Prellwitz W, Baum P. 1970. [Consumption coagulation pathology of 1,2-dichloroethane poisoning.] Klin Wochenschr 48:822-824. (German)

Schumann AM, Quast JF, Watanabe PG. 1980. The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. Toxicol Appl Pharmacol 55:207-219.

Secchi GC, Chiappino G, Lotto A, et al. 1968. [Actual chemical composition of the "commercial trieline" and their hepatotoxic effect: Clinical and enzymological studies.] Med Lav 59:486-497. (Italian)

Semprini L. 1997. Strategies for the aerobic co-metabolism of chlorinated solvents. Environmental Biotechnology 8:296-308.

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

Shehepotin BM, Bondarenko UD. 1978. [Chemical syndromes and pathogenic treatment principles of dichloroethane intoxication.] Vrach Delo 7:134-139. (Russian)

Shen TT. 1982. Estimation of organic compound emissions from waste lagoons. J Air Pollut Control Assoc 32:79-82.

*Sherwood RL, O'Shea W, Thomas PT, et al. 1987. Effects of inhalation of ethylene dichloride on pulmonary defenses of mice and rats. Toxicol Appl Pharmacol 91:491-496.

Sidhu KS. 1991. Standard setting processes and regulations for environmental contaminants in drinking water: State versus federal needs and viewpoints. Regul Toxicol Pharmacol 13:293-308.

*Simula TP, Glancey MJ, Wolf CR. 1993. Human glutathione S-transferase-expressing *Salmonella typhimurium* tester strains to study the activation/detoxification of mutagenic compounds: Studies with halogenated compounds, aromatic amines and aflatoxin B1. Carcinogenesis 14:1371-1376.

Singh HB, Salas LJ, Smith AJ, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 15:601-612.

*Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 16:872-880.

*Singh HB, Salas LJ, Viezee W. 1992. Measurement of volatile organic chemicals at selected sites in California. Atmos Environ 26:2929-2946.

*Sipes IG, Gandolfi AJ. 1980. *In vitro* comparative bioactivation of aliphatic halogenated hydrocarbons. In: Holmstedt B, Lauwerys R, Mercier M, et al., eds. Developments in toxicology and environmental science. Vol. 8: Mechanisms of toxicity and hazard evaluation. Proceedings of the Second Congress on Toxicology held in Brussels, Belgium, July 6-11, 1980. Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press, 501-506.

Sopikov NF, Gorshunova AK. 1979. [Investigation of the uptake, distribution, and excretion of ethylene dichloride in rats.] Gig Tr Prof Zabol 4:36-40. (Russian)

*Speitel GE, Closmann FB. 1991. Chlorinated solvent biodegradation by methanotrophs in unsaturated soils. J Environmental Engineering-American Society Civil Engineers 117:541-548.

*Spencer HC, Rowe VK, Adams EM, et al. 1951. Vapor toxicity of ethylene dichloride determined by experiments on laboratory animals. Arch Ind Hyg Occup Med 4:482-493.

Spreafico F, Zuccato E, Murcurei F, et al. 1978. Metabolism of 1,2-dichloride in experimental animals. Reports 1 and 2 to Chemical Manufacturers Association by Ist Ricerche Farmacol, Milan, Italy.

Spreafico F, Zuccato E, Murcurei F, et al. 1979. Distribution and metabolism of 1,2-dichloroethane (EDC) in experimental animals. Reports 3 and 4 to Chemical Manufacturers Association by Ist Ricerche Farmacol, Milan, Italy.

*Spreafico F, Zuccato E, Marcucci F, et al. 1980. Pharmacokinetics of ethylene dichloride in rats treated by different routes and its long-term inhalatory toxicity. In: Ames BN, Infante P, Reitz R, eds. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, New York, NY: Cold Spring Harbor Laboratory, 107-133.

SRI. 1988. 1988 Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

SRI. 1991. 1991 Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 620.

SRI. 1993. 1993 Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

*SRI. 1998. 1998 Directory of chemical producers: United States of America. Menlo Park, CA: SRI International.

*Stangroom SJ, Collins CD, Lester JN. 1998. Sources of organic micropollutants to lowland rivers. Environ Technol 19:643-666.

*Staudinger J, Roberts PV. 1996. A critical review of Henry's law constants for environmental applications. Crit Rev Environ Sci 26:205-297.

*Steichen J, Koelliker J, Grosh D, et al. 1988. Contamination of farmstead wells by pesticides, volatile organics and inorganic chemicals in Kansas, USA. Ground Water Monit Rev 8:153-160.

*Stoner GD. 1991. Lung tumors in strain a mice as a bioassay for carcinogenicity of environmental chemicals. Exp Lung Res 17:405-424.

*Storer RD, Conolly RB. 1983. Comparative *in vivo* genotoxicity and acute hepatotoxicity of three 1,2-dihaloethanes. Carcinogenesis 4:1491-1494.

*Storer RD, Conolly RB. 1985. An investigation of the role of microsomal oxidative metabolism in the *in vivo* genotoxicity of 1,2-dichloroethane. Toxicol Appl Pharmacol 77:36-46.

*Storer RD, Cartwright ME, Cook WO, et al. 1995. Short-term carcinogenesis bioassay of genotoxic procarcinogens in PIM transgenic mice. Carcinogenesis 16:285-293.

*Storer RD, Jackson NM, Conolly RB. 1984. *In vivo* genotoxicity and acute hepatotoxicity of 1,2-dichloroethane in mice: Comparison of oral, intraperitoneal, and inhalation routes of exposure. Cancer Res 44:4267-4271.

Storey CL, Kirk LD, Mustakas GC. 1972. Fate of EDC-CC14 (75:25) residues during milling and oil extraction of soybeans. J Econ Entomol 65:1126-1129.

Storm DL. 1994. Chemical monitoring of California's public drinking water sources: Public exposures and health impacts. In: Wang RGM, ed. Water contamination and health: Integration of exposure assessment, toxicology, and risk assessment. New York, NY: Marcel Dekker, Inc., 67-124.

Story DL, Meierhenry EF, Tyson CA, et al. 1986. Differences in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol Ind Health 2:351-362.

Stover EL, Kincannon DF. 1983. Biological treatability of specific organic compounds found in chemical industry wastewaters. J Water Poll Cont Fed 55:97-109.

Streete PJ, Ruprah M, Ramsey JD, et al. 1992. Detection and identification of volatile substances by headspace capillary gas chromatography to aid the diagnosis of acute poisoning. Analyst 117:1111-1127.

*Stucki G, Thuer M. 1994. Increased removal capacity for 1,2-dichloroethane by biological modification of the granular activated carbon process. Appl Microbiol Biotechnol 42:167-172.

*Stucki G, Krebsen V, Leisinger T. 1983. Bacterial growth on 1,2-dichloroethane. Experientia 39:1271-1273.

*Suffet IH, Brenner L, Cairo PR. 1980. GC/MS identification of trace organics in Philadelphia drinking waters during a 2-year period. Water Res 14:853-867.

*Sundaram KM, Shreehan MM, Olszewski EF. 1994. Ethylene. In: Kroschwitz JI, Howe-Grant M, ed. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, Inc., 881.

*Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.

*Tafazoli M, Baeten A, Geerlings P, et al. 1998. *In vitro* mutagenicity and genotoxicity study of a number of short-chain chlorinated hydrocarbons using the micronucleus test and the alkaline single cell gel electrophoresis technique (Comet assay) in human lymphocytes: A structure-activity relationship (QSAR) analysis of the genotoxic and cytotoxic potential. Mutagenesis 13:115-126.

*Tan EL, Hsie AW. 1981. Mutagenicity and cytotoxicity of haloethanes as studied in the CHO/HGPRT system. Mutat Res 90:183-191.

Tanigawa T, Araki S, Abo T, et al. 1996. Increase in CD57 + CD16-lymphocytes in workers exposed to benzidine and beta-naphthylamine: Assessment of natural killer cell subpopulations. Int Arch Occup Environ Health 69:69-72.

*Taningher M, Parodi S, Grilli S, et al. 1991. Lack of correlation between alkaline DNA fragmentation and DNA covalent binding induced by polychloroethanes after *in vivo* administration: Problems related to the assessment of a carcinogenic hazard. Cancer Detect Prevent 15:35-39.

Tase N. 1992. Groundwater contamination in Japan. Environ Geol Water Sci 20:15-20.

*Teta MJ, Ott MG, Schnatter AR. 1989. An update of mortality due to brain neoplasms and other causes among employees of petrochemical facility. Union Carbide Corporation, Danbury, CT: OTS 0000743.

*Theiss JC, Stoner GD, Shimkin MB, et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res 37:2717-2720.

*Thier R, Taylor JB, Pemble SE, et al. 1993. Expression of mammalian glutathione S-transferase 5-5 in *Salmonella typhimurium* TA1535 leads to base-pair mutations upon exposure to dihalomethanes. Proc Natl Acad Sci U S A 90:8576-8580.

*Torkelson TR. 1994. Halogenated aliphatic hydrocarbons. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. New York, NY: John Wiley and Sons, Inc., 4098-4099.

*Torkelson TR, Rowe VK. 1981. Halogenated aliphatic hydrocarbons. Patty's industrial hygiene and toxicology. Vol. 2B: Toxicology. New York, NY: John Wiley & Sons, 3491-3497.

TRI96. 1999. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

TRI98. 2000. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Offices of Environmental Information. U.S. Environmental Protection Agency. Toxic Release Inventory. Http://www.epa.gov/triexplorer/. April 16, 2000.

*TRI99. 2001. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Offices of Environmental Information. U.S. Environmental Protection Agency. Toxic Release Inventory. Http://www.epa.gov/triexplorer/. April 27, 2001.

*Tse SYH, Mak IT, Weglicki WB, et al. 1990. Chlorinated aliphatic hydrocarbons promote lipid peroxidation in vascular cells. J Toxicol Environ Health 31:217-226.

*Tsuruta H. 1975. Percutaneous absorption of organic solvents: 1. Comparative study of the *in vivo* percutaneous absorption of chlorinated solvents in mice. Ind Health 13:227-236.

Tsuruta H. 1977. Percutaneous absorption of organic solvents: 2. A method for measuring the penetration rate of chlorinated solvents through excised rat skin. Ind Health 15:131-139.

*UATW. 1999. Unified Air Toxics Website. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. May 6, 1999. Http://www.epa.gov/ttnuatw1/uatwn.html. May 26, 1999.

*Urusova TP. 1953. [The possible presence of dichloroethane in human milk with exposure in industrial conditions.] Gig Sanit 18:36-37. (Russian)

*USC. 2001. Hazardous air pollutants. U.S. Code. 42 USC 4712. Http://www4.law.cornell.edu/uscode/ 42/7412.text.html. May 02, 2001.

US DOC. 1986a. U.S. imports for consumption and general imports, 1985. Washington, DC: U.S. Department of Commerce. USDOC publication number FT246/Annual 1985.

US DOC. 1986b. U.S. imports for consumption and general imports: TS USA commodity by country of origin. Washington, D.C: U.S. Department of Commerce, Bureau of the Census. FT246/Annual 1985.

USITC. 1984. Synthetic organic chemicals: United States production and sales, 1983. Washington, DC: U.S. International Trade Commission. USTIC publication number 1588.

*USITC. 1985. Synthetic organic chemicals: United States production and sales, 1984. Washington, DC: U.S. International Trade Commission. USITC publication number 1745:258, 292.

*USITC. 1986. Synthetic organic chemicals: United States production and sales, 1985. Washington, DC: U.S. International Trade Commission. USITC publication number 1892:268, 300.

*USITC. 1987. Synthetic organic chemicals. United States production and sales, 1986. Washington, D.C: U.S. International Trade Commission. USITC publication number 2009:183, 212, 233.

*USITC. 1991. Synthetic organic chemicals. United States production and sales, 1990. Washington, DC: U.S. International Trade Commission. USITC publication number 2470:15-8.

*USTIC. 1993. Synthetic organic chemicals. United States production and sales, 1992. Washington, DC: U.S. International Trade Commission. USTIC publication number 2720:3-18.

*USITC. 1994. Synthetic organic chemicals. United States production and sales, 1993. Washington, DC: U.S. International Trade Commission. USITC publication number 2810:3-18.

*USITC. 1995. Synthetic organic chemicals. United States production and sales, 1994. Washington, DC: U.S. International Trade Commission.

*Vamvakas S, Dekant W, Henschler D. 1989. Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine-S-conjugates of haloalkenes and haloalkanes. Mutat Res 222:329-335.

*Vamvakas S, Dekant W, Schiffmann D, et al. 1988. Induction of unscheduled DNA synthesis and micronucleus formation in Syrian hamster embryo fibroblasts treated with cysteine S-conjugates of chlorinated hydrocarbons. Cell Biol Toxicol 4:393-404.

*Van Bladeren PJ. 1983. Metabolic activation of xenobiotics: Ethylene dibromide and structural analogs. J Am Coll Toxicol 2:73-83.

*Van Bladeren PJ, Breimer DD, Rotteveel-Smijs GMT, et al. 1981. The relation between the structure of vicinal dihalogen compounds and their mutagenic activation via conjugation to glutathione. Carcinogenesis 2:499-505.

*Vandenbergh PA, Kunka BS. 1988. Metabolism of volatile chlorinated aliphatic hydrocarbons by *Pseudomonas fluorescens*. Appl Environ Microbiol 54:2578-2579.

Vandenwijngaard AJ, Vanderkamp K, Vanderploeg J, et al. 1992. Degradation of 1,2-dichloroethane by ancylobacter aquaticus and other facultative methylotrophs. Appl Environ Microbiol 58:976-983.

*Van Duuren BL, Goldschmidt BM, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst 63:1433-1439.

*van Esch GJ, Kroes R, van Logtenen MJ, et al. 1977. Ninety-day toxicity study with 1,2-dichloroethane (DCE) in rats. Utrecht: Rijks Instituut voor de Volksgezondheid.

*Ventura F, Romero J, Pares J. 1997. Determination of dicyclopentadiene and its derivatives as compounds causing odors in groundwater supplies. Environ Sci Technol 31:2368-2374.

Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold, Company, 643-645.

*Veschueren K. 1996. Handbook of environmental data on organic chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Company, 963-965.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vogel EW, Nivard MJM. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8:57-81.

Voskoboinik I, Drew R, Ahokas JT. 1996. Effect of peroxisome proliferator nafenopin on the cytotoxicity of dihaloalkanes in isolated rat hepatocytes. Toxicol in Vitro 10:577-584.

*Vozovaya MA. 1974. [Development of posterity of two generations obtained from females subjected to the action of dichloroethane.] Gig Sanit 39:25-28. (Russian)

Vozovaya MA. 1975. [The effect of low concentrations of benzene, dichloroethane alone and their combination on the reproductive function animals and on the development of progeny.] Gig Tr Prof Zabol 7:20. (Russian).

Vozovaya MA. 1976. [Effect of low concentrations of benzene, and dichloroethane separately and combined on the reproductive function animals.] Gig Sanit 6:100-102. (Russian)

*Vozovaya MA. 1977. [The effect of dichloroethane on the sexual cycle and embryogenesis of experimental animals.] Akusk Ginekol (Moscow) 2:57-59.

*Vulcan Materials Company. 1989. Written communication. Public comment on toxicological profile for 1,2-dichloroethane. Vulcan Materials Company, Birmingham, AL.

Wahlberg JE, Bowman A. 1996. Prevention of contact dermatitis from solvents. Curr Probl Dermatol 25:57-66.

*Wallace LA. 1991. Comparison of risks from outdoor and indoor exposure to toxic chemicals. Environ Health Perspect 95:7-13.

Wallace LA. 1997. Human exposure and body burden for chloroform and other trihalomethanes. Crit Rev Environ Sci 27:113-194.

Wallace L, Nelson W, Ziegenfus R, et al. 1991. The Los Angeles team study: Personal exposures, indoor-outdoor air concentrations, and breath concentrations of 25 volatile organic compounds. J Exposure Anal Environ Epidemiol 1:157-192.

*Wallace L, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds: I. Direct measurements in breathing-zone air, drinking water, food and exhaled breath. Environ Res 35:293-319.

*Wallace L, Pellizzari E, Hartwell T, et al. 1986. Concentrations of 20 volatile organic compounds in the air and drinking water of 350 residents of New Jersey compared with concentrations in their exhaled breath. J Occup Med 28:603-608.

*Wallace LA, Pellizzari ED, Hartwell TD, et al. 1989. The influence of personal activities on exposure to volatile organic compounds. Environ Res 50:37-55.

*Wallace L, Pellizzari E, Leaderer B, et al. 1987. Emissions of volatile organic compounds from building materials and consumer products. Atmos Environ 21:385-393.

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

Wallington TJ, Bilde M, Mogelberg TE, et al. 1996. Atmospheric chemistry of 1,2-dichloroethane: UV spectra of $CH_2ClCHCl$ and $CH_2ClCHCClO_2$ radicals, kinetics of the reactions of $CH_2ClCHCl$ radicals with O_2 and $CH_2ClCHClO_2$ radicals with NO and NO_2, and fate of alkoxy radical $CH_2ClCHClO$. J Phys Chem 100:5751-5760.

Ware JH, Spengler JD, Neas LM, et al. 1993. Respiratory and irritant health effects of ambient volatile organic compounds. Am J Epidemiol 137:1287-1301.

Warren DL, Reed DJ. 1991. Modification of hepatic vitamin E stores *in vivo*: III. Vitamin E depletion by 1,2-dibromomethane may be related to initial conjugation with glutathione. Arch Biochem Biophys 288:449-455.

*Watwood ME, White CS, Dahm CN. 1991. Methodological modifications for accurate and efficient determination of contaminant biodegradation in unsaturated calcareous soils. Appl Environ Microbiol 57:717-720.

*Waxweiler RJ, Alexander V, Leffingwell SS, et al. 1983. Mortality from brain tumor and other causes in a cohort of petrochemical workers. J Natl Cancer Inst 70:75-81.

Weisburger EK. 1993. Comparison of results from carcinogenicity tests of two halogenated compounds by oral, dermal, and inhalation routes. In: Wang RGM, Knaak JB, Maibach HI, ed. Health risk assessment. Boca Raton, FL: CRC Press, 275-281.

*Weiss G, ed. 1980. Hazardous chemicals data book. Vol. 4. Park Ridge, NJ: Noyes Data Corporation, 433.

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

*Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Am Water Works Assoc 52-59.

WHO. 1987. Environmental health criteria: 1,2 Dichloroethane. 62:1-90. World Health Organization, Geneva.

*WHO. 1995. International program on chemical safety. Environmental health criteria 176. World Health Organization, Geneva.

*WHO. 2001a. Chemical toxicology, carcinogenicity. World Health Organization, Geneva.

*WHO. 2001b. Drinking water quality. World Health Organization, Geneva.

*Widdowson EM, Dickerson JWT. 1964. Chapter 17: 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.

*Williams GM, Mori H, McQueen CA. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221:263-286.

*Wilson JT, Enfield CG, Dunlap WJ, et al. 1981. Transport and fate of selected organic pollutants in a sandy soil. J Environ Qual 10:501-506.

*Wilson JT, McNabb JF, Balkwill DL, et al. 1983. Enumeration and characterization of bacteria indigenous to a shallow water-table aquifer. Groundwater 21:134-142.

Wilson SC, Burnett V, Waterhouse KS, et al. 1994. Volatile organic compounds in digested United Kingdom sewage sludges. Environ Sci Technol 28:259-266.

Windholz. 1983. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 10th ed. Rahway, NJ: Merck & Co, Inc, 550, 3743.

*Wirtschafter ZT, Schwartz ED. 1939. Acute ethylene dichloride poisoning. J Ind Hyg Toxicol 21(4):126-131.

*Withey JR, Collins BT. 1980. Chlorinated aliphatic hydrocarbons used in the foods industry: The comparative pharmacokinetics of methylene chloride, 1,2-dichloroethane, chloroform and trichloroethylene after i.v. administration in the rat. J Environ Pathol Toxicol 3:313-332.

*Withey JR, Karpinski K. 1985. The fetal distribution of some aliphatic chlorinated hydrocarbons in the rat after vapor phase exposure. Biol Res Pregnancy Perinatol 6:79-88.

*Withey JR, Collins BT, Collins PG. 1983. Effect of vehicle on the pharmacokinetics and uptake of four halogenated hydrocarbons from the gastrointestinal tract of the rat. J Appl Toxicol 3:249-253.

Wolff MS, Collman GW, Barrett JC, et al. 1996. Breast cancer and environmental risk factors: Epidemiogical and experimental findings. Annu Rev Pharmacol Toxicol 36:573-596.

Wolska L, Olszewska C, Turska M, et al. 1998. Volatile and semicolatile organo-halogen trace analysis in surface water by direct aqueous injection GC-ECD. Chemosphere 37:2645-2651.

Woodruff TJ, Axelrad DA, Caldwell J, et al. 1998a. Public health implications of 1990 Air Toxics concentrations across the United States. Environ Health Perspect 106(Suppl. 5):245-251.

Woodruff TJ, Axelrad DA, Caldwell J, et al. 1998b. Public health implications of 1990 air toxics concentrations across the United States. Environ Health Perspect 106(Suppl. 5):245-251.

*Yamamoto K, Fukushima M, Kakutani N, et al. 1997. Volatile organic compounds in urban rivers and their estuaries in Osaka, Japan. Environ Pollut 95:135-143.

Yllner S. 1971a. Metabolism of chloroacetate-1-14C in the mouse. Acta Pharmacol Toxicol 30:69-80.

*Yllner S. 1971b. Metabolism of 1,2-dichloroethane-14C in the mouse. Acta Pharmacol Toxicol 30:257-265.

*Yodaiken RE, Babcock JR. 1973. 1,2-Dichloroethane poisoning. Arch Environ Health 26:281-284.

*Zhang LH, Jenssen D. 1994. Studies on intrachromosomal recombination in SP5/V79 Chinese hamster cells upon exposure to different agents related to carcinogenesis. Carcinogenesis 15:2303-2310.

*Zhao SF, Zhang XC, Bao YS. 1984. The study on the effects of 1,2-dichloroethane on the development of mice. Chinese J Ind Hyg Occup Dis 2:343-346.

*Zhao SF, Zhang XC, Bao YS. 1989. The study on the effects of 1,2-dichloroethane on reproductive function. Chinese J Prevent Med 23:199-202.

*Zhao SF, Zhang XC, Zhang LF, et al. 1997. The evaluation of developmental toxicity of chemicals exposed occupationally using whole embryo culture. Int J Dev Biol 41:275-282.

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

Zuccato E, Marcucci F, Mussini E. 1980. GLC determination of ethylene dichloride (EDC) in biological samples. Anal Lett 13:363-370.

10. GLOSSARY

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

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

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

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

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

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

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

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

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

In Vivo—Occurring within the living organism.

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

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

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

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

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

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

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

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

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

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

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

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

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

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

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

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

APPENDIX A

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) WORKSHEETS

Chemical name: 1,2-Dichloroethane
CAS number(s): 107-06-2
Date: May 11, 2001
Profile status: Draft 3
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 48
Species: Rat

MRL: 0.6 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Cheever KL, Cholakis JM, el-Hawari AM, et al. 1990. Ethylene dichloride: The influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundam Appl Toxicol 14: 243-261.

Experimental design: Groups of 50 male and 50 female Sprague-Dawley rats were exposed to 50 ppm 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years. Additional rats were similarly exposed to 50 ppm with either 0.05% disulfiram in the diet or 5% ethanol in the drinking water. Signs of toxicity, body weight and food consumption were evaluated during the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Effects noted in study and corresponding doses: The only effect associated with exposure to 1,2-dichloroethane alone was a slight increase in the incidence of unspecified basophilic focal cellular changes in the pancreas in female rats. The significance of the pancreatic changes is unclear because the incidence was not reported, dose-response cannot be assessed because only one exposure level was tested, the effect was induced in only one sex, and the study was designed to evaluate carcinogenicity.

Effects due to combined exposure to 1,2-dichloroethane and disulfuram included increased kidney lesions (chronic nephropathy, calculi of the renal pelvis, and hyperplasia of the pelvic epithelium) in males, increased liver lesions (mostly bile duct cysts) in both sexes, and increased tumor incidences in both sexes (intrahepatic bile duct cholangiomas in males and females, mammary neoplasms in females, testicular interstitial cell tumors in males). No significant increases in tumor incidences were found after exposure to either 1,2-dichloroethane alone or in combination with ethanol. Congestion of the mesenteric lymph node was reported in both disulfuram-only and disulfuram/1,2-dichloroethane combined treatment groups to a similar extent and appears to be related to disulfuram exposure. Disulfuram, a known inhibitor of the microsomal aldehyde dehyderogenase system, apparently produced an overall decrease in the rate of biotransformation, leading to increased blood levels of 1,2-dichloroethane which may have contributed to the carcinogenic effect of combined exposure.

Dose and end point used for MRL derivation:

The 50 ppm exposure concentration is a NOAEL for histopathology in the liver and other tissues.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for interspecies extrapolation since a dosimetric adjustment was applied to the exposure concentration
[X] 10 for human variability
[X] 3 used as a modifying factor to account for database deficiencies

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No conversion from intermittent to continuous exposure was used since blood levels of 1,2-dichloroethane reach equilibrium within 2 to 3 hours of the onset of inhalation exposure (see Section 2.3.1.1).

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

The human equivalent concentration ($NOAEL_{[HEC]}$) was determined following U.S. EPA (1994; *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*), Section 4.3.6.2 (Remote (Extrarespiratory) Effects) for exposure to Category 3 gases. The equation used for obtaining the $NOAEL_{[HEC]}$ from the NOAEL (50 ppm) is as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times [(H_{b/g})_A/(H_{b/g})_H)]$$

where,

$NOAEL_{[HEC]}$	= human equivalent NOAEL (ppm)
$NOAEL_{[ADJ]}$	= exposure-adjusted NOAEL (ppm) [no adjustment was used]
$(H_{b/g})_A$ and $(H_{b/g})_H$	= blood/gas partition coefficient for animals (A) and humans (H) (unitless)

The following default value was used:

$(H_{b/g})_A / (H_{b/g})_H = 1$ (unitless).

Empirical blood/gas partition coefficients were available for rats and humans (Gargas et al. 1989). However, the default value of 1 was used for both rat and human blood/gas partition coefficients, since $(H_{b/g})_A > (H_{b/g})_H$ (U.S. EPA 1994).

The $NOAEL_{[HEC]}$ was calculated as follows:

$NOAEL_{[HEC]} = 50$ ppm x (1) = 50 ppm

Application of an uncertainty factor of 90 (3 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies) results in a chronic duration inhalation MRL of 0.6 ppm.

Other additional studies or pertinent information that lend support to this MRL:

The MRL is based on a free-standing NOAEL for liver histopathology. Although other concentrations of 1,2-dichloroethane were not tested, there is confidence in the NOAEL due to the number of animals (50/sex) and scope of histological examinations. Additionally, the liver is a documented target of 1,2-dichloroethane toxicity in several acute and intermediate-duration inhalation studies (Heppel et al. 1946; Spencer et al. 1951), as well as in a number of studies of orally-exposed animals. Limitations in the acute and intermediate inhalation studies preclude considering them as the basis for derivation of an MRL for intermediate-duration inhalation exposure, but the weight-of-evidence indicates that NOAELs for hepatotoxicity in the intermediate-duration studies are higher than the chronic liver NOAEL. Consequently, the chronic-duration inhalation MRL of 0.6 ppm is also expected to be protective of toxic effects after intermediate duration inhalation exposures to 1,2-dichloroethane.

Agency Contact (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name: 1,2-Dichloroethane
CAS number(s): 107-06-2
Date: May 11, 2001
Profile status: Draft 3
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 25
Species: Rat

MRL: 0.2 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: NTP. 1991a. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats and B6C3F1 mice (drinking water and gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program. NIH Publication No. 91-3123.

Experimental design: Groups of F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (10 animals/sex/strain) were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm of 1,2-dichloroethane for 13 weeks. The high concentration was close to the solubility limit for 1,2-dichloroethane in water. Reported estimates of intake from the water were 0, 49-60, 86-99, 146-165, 259-276, and 492-518 mg/kg/day in the male rats and 0, 58-82, 102-126, 172-213, 311-428, and 531-727 mg/kg/day in the female rats. Intake estimates in the mice were 0, 249, 448, 781, 2,710, and 4,207 mg/kg/day in males and 0, 244, 647, 1,182, 2,478, and 4,926 mg/kg/day in females. Additional groups of F344/N rats (10/sex) were administered 1,2-dichloroethane by gavage on 5 days/week for 13 weeks to compare toxicity resulting from bolus administration with that of the continuous exposure in drinking water. Gavage doses were 0, 30, 60, 120, 240, and 480 mg/kg in the male rats and 0, 18, 37, 75, 150, and 300 mg/kg in the female rats. Signs of toxicity, body weight, food and water consumption, hematology, and serum chemistry were evaluated throughout the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Effects noted in study and corresponding doses: Rat drinking water studies: Dose-related decreased water consumption occurred in all strains and both sexes. There was >10% reduction in body weight gain at $259 mg/kg in male F344/N rats, 518 mg/kg in male Sprague-Dawley rats, and 492 mg/kg in male Osborne-Mendel rats. There were no significant reductions in body weight gain in female rats of any strain. Liver weight and/or liver:body weight ratio significantly increased at $147 mg/kg in F344/N males and 102, 320, and 601 mg/kg in females; at $60 mg/kg in Sprague-Dawley males and 531 mg/kg in females; and at $88 mg/kg in Osborne-Mendel males. Kidney weight and/or kidney:body weight ratio significantly increased at $58 and $86 mg/kg in F344/N females and males, respectively; at $60 and $76 mg/kg in Sprague-Dawley males and females, respectively; and at $82 and $88 mg/kg in Osborne-Mendel females and males, respectively. There was a dose-related increase in the incidence of renal tubular regeneration (minimal to mild) in F344/N females at $58 mg/kg/day; incidences progressively increased from 1/10 at 102 mg/kg/day to 9/10 at 601 mg/kg/day.

Mouse drinking water study: No mortality except in 90% of high-dose females. Body weight gain significantly reduced in high-dose males. Increased liver weight/liver:body weight ratio, significant at $249 mg/kg/day in males and $647 mg/kg/day in females. Increased kidney weight and kidney:body weight ratio, significant at $448 mg/kg/day in males and $244 mg/kg/day in females. Increased tubular

regeneration (minimal to moderate) in males, increasing in incidence from 1/10 at 249 mg/kg/day to 9/10 at $4,207 mg/kg/day. Karyomegaly, dilatation, protein casts, and mineralization in kidneys also occurred in males at 4,207 mg/kg/day.

Rat gavage study: Deaths occurred in all males at $240 mg/kg and 90% of females at 300 mg/kg; clinical signs preceding death included tremors, salivation, and emaciation. Pathology in moribund/dead animals included necrosis in the thymus and cerebellum. Small but significant changes in various hematological parameters occurred in higher dose groups and were considered to be indicative of dehydration and attributed to significantly reduced in water consumption (60% compared to controls). No effects on growth at sublethal doses. Other effects included minimal to mild hyperplasia and inflammation of the forestomach epithelium (sometimes with foci of necrosis and mineralization) in 5/10 males at 240 mg/kg, 3/10 males at 480 mg/kg, and 3/10 females at 300 mg/kg. Liver weight and liver:body weight ratio significantly increased in males at 120 mg/kg (no data from higher doses due to mortality) and females at all doses (appears dose-related). Kidney weight and/or kidney:body weight ratio significantly increased in males at $30 mg/kg and $75 mg/kg in females. Kidney weight changes appeared to be dose-related, but no renal histopathological changes were observed.

Dose and end point used for MRL derivation:

The lowest dose in female rats, 58 mg/kg/day, is a LOAEL for kidney effects. The increased kidney weight is considered to be an early-stage adverse effect because dose-related renal histopathology (tubular regeneration, indicative of previous tubular injury with subsequent repair) developed at higher doses in the same strain of rats.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for interspecies extrapolation
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Estimated daily doses were reported by the investigators.

Was a conversion used from intermittent to continuous exposure?

Not applicable.

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

Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion; renal effects observed in people who died following acute high-level exposure included diffuse necrosis, tubular necrosis, and kidney failure (Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984; Yodaiken and Babcock 1973). Renal effects (e.g., increased kidney weight and tubular epithelial degeneration) were also found in animals following high-level acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; NTP 1991a; Spencer et al. 1951). Reports of increased relative kidney weight in rats that were treated with $75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977) are supportive of the 58 mg/kg/day LOAEL used to derive the MRL.

Agency Contact (Chemical Manager): Malcolm Williams

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

Relevance to Public Health

This chapter 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 chapter 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 chapter. 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 Chapter 3 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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. 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.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(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 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

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

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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 end point 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 9 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 3-1

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

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

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

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

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

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

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

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

SAMPLE

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

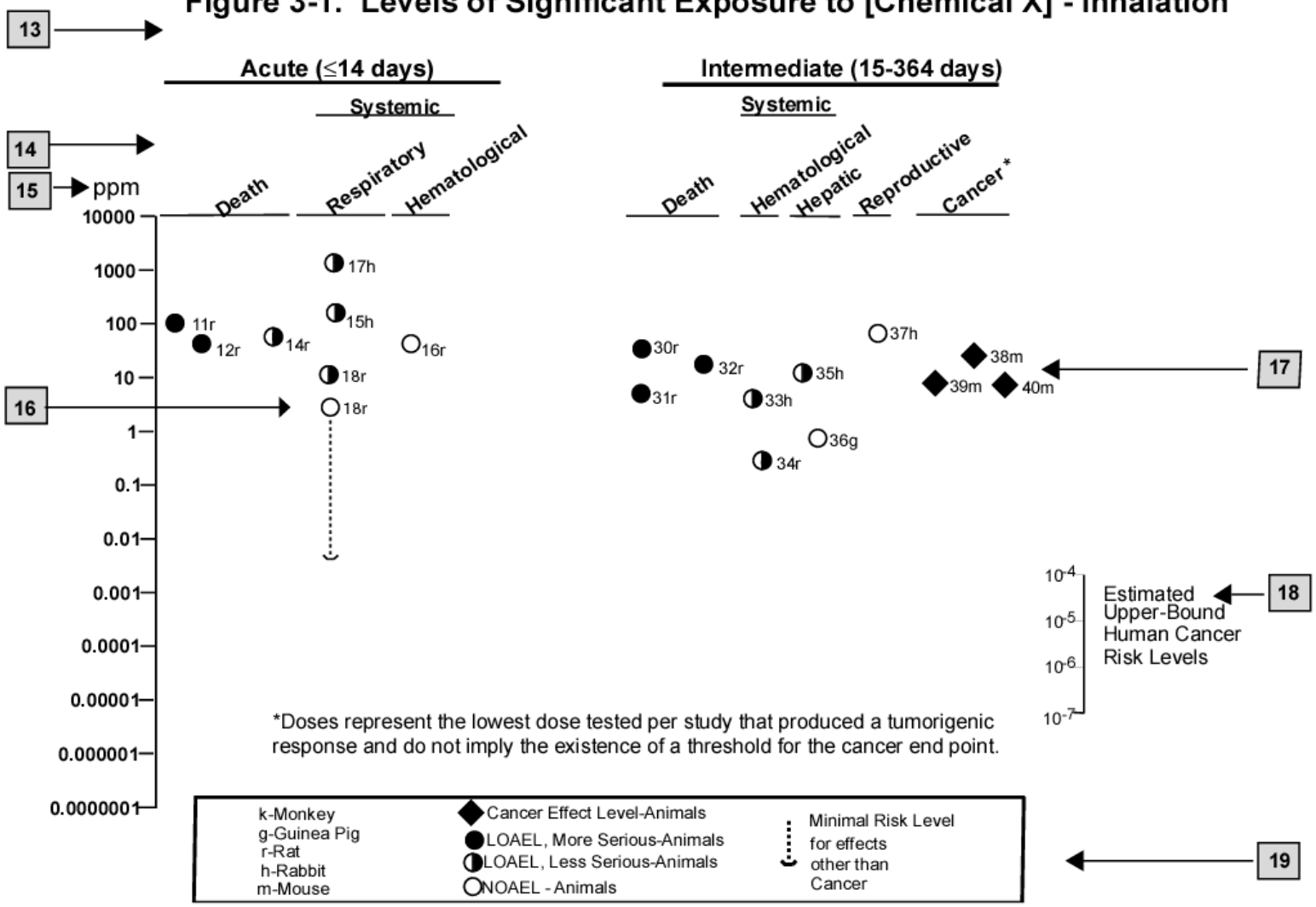
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
5	6	7	8	9			10
3 Systemic	9	9	9	9	9		9
4 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE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

[a] The number corresponds to entries in Figure 3-1.

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

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

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

µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX

APPENDIX D

APPENDIX D