TOXICOLOGICAL PROFILE FOR 1,1-DICHLOROETHENE

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

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DISCLAIMER

UPDATE STATEMENT

A Toxicological Profile for 1,1-dichloroethene was released on December 1990. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances 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 Environmental Protection Agency (EPA). The revised list of the 275 most hazardous substances was published in the Federal Register on October 28, 1992 (57 FR 48801). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166).

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

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

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

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

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

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

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 protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

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

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. 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 endpoints.

3. 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.

4. Quality Assurance Reviews. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been fcllowed.

PEER REVIEW

A peer review panel was assembled for 1,1-dichloroethene. The panel consisted of the following members:

1. Dr. C. Clifford Conaway, Research Scientist, American Health Foundation, Valhalla, New York

2. Dr. Arthur Gregory, Private Consultant, Techto Enterprises, Sterling, Virginia

3. Dr. Nancy Tooney, Associate Professor of Biochemistry, Department of Chemistry, Polytechnic University, Brooklyn, New York.

These experts collectively have knowledge of 1,1-dichloroethene'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.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,1-dichloroethene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,350 hazardous waste sites as the most serious in the nation. These sites comprise the "National Priorities List" (NPL): Those sites which are targeted for long-term federal cleanup activities. 1,1-dichloroethene has been found in at least 492 of the sites on the NPL. However, the number of NPL sites evaluated for 1,1-dichloroethene is not known. As EPA evaluates more sites, the number of sites at which 1,1-dichloroethene is found may increase. This information is important because exposure to 1,1-dichloroethene may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,1-dichloroethene.

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 can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as 1,1-dichloroethene, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS 1,1-DICHLOROETHENE?

1,1-dichloroethene, also known as vinylidene chloride, is a chemical used to make certain plastics (such as packaging materials, flexible films like SARAN wrap) and flameretardant coatings for fiber and carpet backing. It is a colorless liquid that evaporates quickly at room temperature. It has a mild sweet smell and burns quickly.

1,1-dichloroethene is a man-made chemical and is not found naturally in the environment. Although 1,1-dichloroethene is manufactured in large quantities, most of it is used to make other substances or products such as polyvinylidene chloride. For information on the chemical and physical properties and use of 1,1-dichloroethene, see Chapters 3 and 4.

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

1,1-dichloroethene can enter the environment when it is released to the air during its production or released to surface water or soil as a result of waste disposal. Most 1,1-dichloroethene evaporates quickly and mainly enters the environment through the air, although some enters into rivers or lakes. 1,1-dichloroethene can enter soil, water, and air in large amounts during an accidental spill. 1,1-dichloroethene can also enter the environment as a breakdown product of other chemicals in the environment.

1,1-dichloroethene behaves differently in air, water, and soil. 1,1-dichloroethene evaporates to the air very quickly from soil and water. In the air, 1,1-dichloroethene is broken down by reactive compounds formed by sunlight. 1,1-dichloroethene remains in the air for about 4 days.

From water, 1,1-dichloroethene evaporates into the air; it breaks down very slowly in water. We do not know exactly how long 1,1-dichloroethene stays in water. It is not readily transferred to fish or birds, and only very small amounts enter the food chain.

In soil, 1,1-dichloroethene either evaporates to the air or percolates down through soil with rainwater and enters underground water. Small living organisms in soil and groundwater may transform it into other less harmful substances, although this happens slowly.

More information on what happens to 1,1-dichloroethene in the environment can be found in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO 1,1-DICHLOROETHENE?

You may be exposed to 1,1-dichloroethene by breathing it when it is in the air or eating food or water that contains it. You may also be exposed to 1,1-dichloroethene if it touches your skin. 1,1-dichloroethene is found at very low levels in indoor and outdoor air (estimated as less than 1 part per trillion parts of air [ppt]). Therefore, the potential for exposure in the environment is extremely low. The amounts are somewhat higher near some factories that make or use 1,1-dichloroethene (those that make foodpackaging films, adhesives, flame-retardant coatings for fiber and carpet backing, piping, and coating for steel pipes), hazardous waste sites, and areas near accidental spills. The exact amount of 1,1-dichloroethene in the air near these factories is not known. In air around waste sites where it has been identified, the amount of 1,1-dichloroethene ranges from 0.39 to 97 parts 1,1-dichloroethene per billion parts of air (ppb, 1 ppb is 1,000 times more than 1 ppt). The levels of 1,1-dichloroethene in air around waste sites are usually much lower than those that have caused health effects in animals. We estimate that 1,1-dichloroethene contaminates the air around 97 chemical factories in the United States. Factories that make 1,1-dichloroethene are mainly located in Texas and Louisiana. Measured air levels inside manufacturing plants range from less than 5 to 1900 parts 1,1-dichloroethene per million parts of air (ppm, 1 ppm is 1,000 times more than 1 ppb).

A small percentage (3%) of the drinking water sources in the United States contain low amounts of 1,1-dichloroethene (0.2-0.5 ppb with an estimated average of 0.3 ppb). The amounts are very low compared with levels that are expected to affect human health. The concentration of 1,1-dichloroethene in groundwater samples from hazardous waste sites ranged from 0.001 to 0.09 ppm.

Since 1,1-dichloroethene is used to make some ccmsumer products, exposure might occur while these products are made or used. For example, the estimated average amount of 1,1-dichloroethene in plastic food-packaging films ranged from <0.02 to 1.26 ppm. The measured average amount in food wrapped in these films was less than 0.01 ppm. Not every tested food sample contained 1,1-dichloroethene, so these numbers only reflect the levels found in food samples tested that did contain 1,1-dichloroethene. The Food and Drug Administration (FDA) regulates the use of plastic packaging films. The FDA has determined that the films can contain no more than 10 ppm 1,1-dichloroethene and that the low levels of 1,1-dichloroethene found in food wrapped in these films present no health risk to the consumer. Besides environmental exposures, occupational exposure can occur for workers who are involved in the manufacture and use of 1,1-dichloroethene. These workers include primarily carpenters, warehouse workers, and machine operators. More information on human exposure can be found in Chapter 5.

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

1,1-dichloroethene can easily enter the body through the lungs as an air pollutant or through the stomach and intestines if you eat or drink contaminated food or water. Based on the physical and chemical properties of 1,1-dichloroethene, we think that 1,1-dichloroethene can also enter the body through the human skin. Harmful effects have occurred in animals after 1,3-dichloroethene was applied to their skin.

Animal studies indicate that following exposure, 1,1-dichloroethene partly leaves the body through the lungs. The remaining 1,1-dichloroethene breaks down into other substances that leave the body in the urine within 1-2 days. Some of the breakdown products of 1, 1-dichloroethene such as dithioglycolic acid, are more harmful than 1, 1-dichloroethene. The way 1,1-dichloroethene and its breakdown products leave the body depends on the amount of 1,1-dichloroethene that enters the body. Low or moderate levels breathed in (25-200 ppm) or taken by mouth (up to 50 milligrams per kilogram of body weight) leave the body mainly as breakdown products in the urine. As the amount of 1,1-dichloroethene that enters the body increases, more and more 1,1-dichloroethene leaves the body in the exhaled breath. Whether 1,1-dichloroethene is inhaled or taken by mouth it leaves the body in about the same way. 1,1-dichloroethene is not stored very much in the body when low-to-moderate amounts enter the body. More information on how 1,1-dichloroethene enters and leaves the body is found in Chapter 2.

1.5 HOW CAN 1,1-DICHLOROETHENE AFFECT MY HEALTH?

How a chemical affects your health depends on how much you are exposed to and for how long. As the level and length of your exposure increase, the effects are likely to become more severe. Information on the health effects in humans after breathing 1,1-dichloroethene is insufficient. People who breathed high amounts of 1,1-dichloroethene in a closed space lost their breath and fainted. Some people who breathed 1,1-dichloroethene at work for several years had abnormal liver function. However, exposure to other chemicals may have also contributed to this effect. Available information indicates that prolonged inhalation of 1,1-dichloroethene can induce adverse neurological effects and is possibly associated with liver and kidney damage in humans. Studies in animals indicate that 1,1-dichloroethene can affect the normal functions of the liver, kidneys, and lungs. However, the amount of 1,1-dichloroethene in the air to which the animals were exposed was much higher than the amounts in the air that the general public usually breathes. Some animals that breathed large amounts of 1,1-dichloroethene died within a few days. The liver and kidneys of animals were affected after breathing air that contained 1,1-dichloroethene for days, months, or years. After pregnant rats breathed 1,1-dichloroethene in air, some of the newborn rats had birth defects.

We have no information on health effects in humans who ate food or drank water that contained 1,1-dichloroethene. Animals fed food that contained 1,1-dichloroethene or that had 1,1-dichloroethene placed experimentally in their stomachs developed liver and kidney disease, and some even died. These amounts, however, were very much higher than those which occur in drinking water supplies. Birth defects did not occur in the newborn of female rats that drank 1,1-dichloroethene.

Spilling 1,1-dichloroethene on your skin or in your eyes can cause irritation. We do not know what other health effects might occur if 1,1-dichloroethene comes into contact with your skin for long periods. However, no serious effects or deaths occurred in mice after small amounts of 1,1-dichloroethene were put on their skin over a period of months. We do not know whether spilling 1,1-dichloroethene on your skin can cause birth defects or affect fertility.

We do not know whether coming into contact with 1,1-dichloroethene increases the risk of cancer in humans. Evidence from epidemiology studies of workers exposed to 1,1-dichloroethene is inconclusive. Several studies examined the possibility that 1,1-dichloroethene may increase the risk of cancer in animals. Only one of these studies indicated that mice breathing 1,1-dichloroethene for 1 year developed kidney cancer, but the particular type of mouse used may be especially sensitive to 1,1-dichloroethene. The U.S. Department of Health and Human Services has not classified 1,1-dichloroethene with respect to carcinogenicity. The International Agency for Research on Cancer (IARC) has determined that 1,1-dichloroethene is not classifiable as to its carcinogenicity in humans. The EPA has determined that 1,1-dichloroethene is a possible human carcinogen. NTP does not include it in its list of substances expected to be human carcinogens.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,1-DICHLOROETHENE?

1,1-dichloroethene can be measured in the breath, blood, urine, and body tissues of individuals who come in contact with the chemical. However, only relatively high levels of 1,1-dichloroethene in body tissues and fluids can be measured. Because breath samples are easily collected, tests of exhaled air are now the most common way to tell whether a person has been exposed to high levels of 1,1-dichloroethene. One of the breakdown products of 1,1-dichloroethene, dithioglycolic acid, can also be measured in urine. None of these tests are regularly available at a doctor's office because they require special equipment, but your doctor can tell you where you can get the tests done. Although these tests can prove that a person has been exposed to 1,1-dichloroethene, they cannot tell if any health effects will occur. Since most of the 1,1-dichloroethene leaves the body within a few days, these methods are best for determining whether exposures have occurred within the last several days. Detection of 1,1-dichloroethene or its breakdown products in the body may not necessarily mean that exposure to 1,1-dichloroethene alone has occurred. People exposed to 1,1-dichloroethene at hazardous waste sites were probably also exposed to other organic compounds, that produce breakdown products similar to those of 1,1-dichloroethene. Other methods for measuring the effects associated with exposure to 1,1-dichloroethene (such as reduced enzyme levels) are not specific enough to detect effects caused by exposure to 1,l -dichloroethene alone. More information on the available tests for detecting 1,1-dichloroethene in the body is found in Chapter 6.

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

The federal government has developed regulatory guidelines and standards to protect people from the possible health effects of 1,1-dichloroethene. The Occupational Safety and Health Administration (OSHA) requires workplace exposure limits of 1 ppm or less for an 9-hour workday to protect workers from noncancer harmful health effects. To guarantee the maximum protection for human health from the possible cancer effects of drinking water or eating seafood (fish or shellfish) that contain over a 1,1-dichloroethene lifetime, the EPA recommends that the level of 1,1-dichloroethene in lakes and streams should not exceed 0.003 ppm. EPA has determined that drinking water containing 3.5 ppm of 1,1-dichloroethene for adults and 1 ppm for children is not expected to cause noncancerous harmful health effects. The National Institute for Occupational Safety and

Health (NIOSH) has recommended that 1,1-dichloroethene is a potential occupational cancer causing chemical.

The EPA limits the amount of 1,1-dichloroethene permitted in publicly owned waste water treatment plants. To minimize human exposure to 1,1-dichloroethene, EPA requires that industry tell the National Response Center when 100 pounds or more of 1,1-dichloroethene have been released in the environment.

For more information on federal and state recommendations, see Chapter 7.

1.8 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, E-29
Atlanta, Georgia 30333
(404) 498-0160

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,1-dichloroethene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure (LSE) 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 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 cffccts (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,l -dichloroethene are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, Figures 2-1 and 2-2 also show 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 1,1-dichloroethene. 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 1990a), 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 A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 1,1-dichloroethene. However, animal studies indicate that 1,1-dichloroethene is lethal following inhalation exposure.

The lethality of 1,1-dichloroethene in animals following inhalation exposure varies considerably and is influenced by such factors as species, strain, sex, and food intake. Differences between strains could account for the range in reported 4-hour LC_{50} values in rats with access to food (nonfasted rats) (≈6,000-8,000 ppm in males and 10,000 ppm in females) (Siegel et al. 1971; Zeller et al. 1979a, 1979b). Higher 4-hour LC_{50} values (10,000-15,000 ppm) have also been reported for nonfasted rats (sex not specified), but the animals were observed for only 24 hours (Jaeger et al. 1973c, 1974).

The LC_{50} values reported for rats that were fasted for 16 hours were generally lower than those reported for nonfasted rats. For instance, the reported 4-hour LC_{50} was 415 ppm in fasted male rats (Zeller et al. 1979b). In fasted female rats, which appear to be more resistant to the detrimental effects of starvation, the 4-hour LC_{50} was 6,545 ppm (Zeller et al. 1979b). A study by Jaeger et al. (1974) compared the effects of food intake on the lethality of male rats exposed to 1,1-dichloroethene for 24 hours. The results of the study revealed that the LC_{50} for fasted animals was almost 30 times lower than that for nonfasted animals. The proposed mechanism by which fasting increases the toxicity of 1,1-dichloroethene is discussed in Sections 2.3 and 2.4.

Identical trends are seen in mice and hamsters (i.e., fasted vs. nonfasted and sex influence the lethality of 1,1-dichloroethene following inhalation exposure). Mice, however, are considerably more susceptible to the lethal effects of 1,1-dichloroethene than are rats. Reported 4-hour LC_{50} values in nonfasted mice range from 40 (males) to 200 ppm (females) (Henschler 1979; Oesch et al. 1983; Short et al. 1977c) and in fasted mice from 40 (males) to 115 ppm (females) (Henschler 1979). Similarly, fasted male Chinese hamsters are more susceptible than fasted females to the lethal effects of inhaled 1,1-dichloroethene (see Table 2-1) (Henschler 1979; Klimisch and Freisberg 1979a, 1979b). Death was also reported in two out of three squirrel monkeys exposed to 25 ppm 1,1-dichloroethene following intermediate exposure (Prendergast et al. 1967).

The LC_{50} values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Limited information is available on the systemic effects of inhaled 1,1-dichloroethene in humans. This information comes primarily from case reports and/or insufficiently detailed mortality studies in which the concentration and duration of exposure to 1,1-dichloroethene were not quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Given these limitations, the information available indicates that inhaled 1,1-dichloroethene can induce neurotoxicity after acute exposure (EPA 1979b) and that 1,l -dichloroethene is possibly associated with hepato- and nephrotoxicity after repeated, low-level exposure in humans (EPA 1976).

Considerable information is available on the systemic effects of 1,1-dichloroethene following both acute, intermediate, and chronic exposure in laboratory animals. The target organs or systems of 1,1-dichloroethene toxicity are reported to be the central nervous system, liver, kidney, and lungs, with adverse effects occasionally being noted in the heart.

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d				8600 (LC50[B]) 7100 (LC50[M]) 10300 (LC50[F])	Zeller et al. 1979a
2	Rat	1 d 4hr/d				500[b] (LC50) 2500[b]	Jaeger et al. 1973c
3	Rat	1 d 4hr/d				2000	Jaeger et al. 1973a
4	Rat	1 d 4hr/d				10000[c] (LC50) 15000[c]	Jaeger et al. 1973c
5	Rat	1 d 4hr/d				2010[b] (LC50[B]) 415[b] (LC50[M]) 6545[b] (LC50[F])	Zeller et al. 1979b
6	Rat	1 d 4hr/d				600[b] (LC50) 15000[c] (LC50)	Jaeger et al. 1974
7	Mouse	1 d 4hr/d				115[c] (LC50[M]) 205[c] (LC50[F])	Henschler 1979
8	Mouse	7 d 23hr/d				98 (LC50[M]) 105 (LC50[F])	Short et al. 1977c
9	Mouse	1-8 d 6hr/d				50 (69% mortality[M])	Oesch et al. 1983
10	Mouse	4 d 22-23 hr/d				40 (70% mortality[M])	Short et al. 1977c
11	Mouse	1 d 4hr/d				40[b] (LC50[M]) 115[b] (LC50[F])	Henschler 1979

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
12	Hamster	1 d 4hr/d				300[b] (LC50[B]) 150[b] (LC50[M]) 455[b] (LC50[F]	Klimisch and Freisbierg 1979b
13	Hamster	1 d 4hr/d				1660 (LC50[M]) 2945 (LC50[F])	Klimisch and Freisbierg 1979a
Systemic							
14	Rat	1 d 4hr/d	Hepatic		250 (decreased mitochondrial glutathione level)		Jaeger 1977a
15	Rat	1 d 4hr/d	Hepatic		2000[c] (increased serum AKT)		Jaeger et al. 1974
			Hepatic		150[b] (increased serum AKT)		
16	Rat	1 d 6hr/d	Hepatic	200[c]		200[b] (necrosis)	McKenna et al. 1978b
			Renal	200[c]		200[b] (hemoglobinurea; tubular degeneration)	
17	Rat	1 d 4hr/d	Resp			5000 (pulmonary hemorrhage and congestion)	Zeller et al. 1979a
18	Rat	1 d 10 min	Cardio			25600 (cardiac arrythmias)	Siletchnik and Carlson 1974
19	Rat	1 d 4hr/d	Hepatic		2000[c] (increased SAKT activity)		Jaeger et al. 1973a
			Other			2000 (bloody ascites)	
20	Rat	1 d 4hr/d	Renal		250[b] (swelling in renal cortex)	300[b] (cortical tubular necrosis)	Jackson and Conolly 1985
21	Rat	1-3 d 23hr/d	Hepatic		60 (centrilobular degeneration)		Short et al. 1977d
			Renal	60			

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
22	Mouse	5 d 23hr/d	Hepatic		15 (cellular degeneration)		Short et al. 1977d
			Renal			15 (tubular nephrosis)	
23	Mouse	10 d 5d/wk 6hr/d	Hepatic		100 ([F]centrilobular swelling and pleomorphism)	200 ([F]hepatocellular degeneration and necrosis)	Henck et al. 1979
			Renal		55 (increased kidney weight)	200 ([M]renal failure)	
24	Mouse	1 d 6hr/d	Hepatic	10	50 (centrilobular swelling)		Reitz et al. 1980
			Renal			10 (nephrosis)	
25	Mouse	1 d 4hr/d	Resp			20[b] ([M]emphysema and congestion of lungs)	Zeller et al. 1979c
Developmental							
26	Rat	11 d Gd6-16 23hr/d				15 (lateral ventrical hydrocephalus)	Short et al. 1977a
27	Rat	10 d Gd6-15 7hr/d		20		80 (wavy ribs and delayed ossification of skull)	Murray et al. 1979
28	Mouse	11 d Gd6-16 23hr/d			15 (unossified incus, incompletely ossified sternebrae)		Short et al. 1977a
29	Mouse	8 d Gd8-15 23hr/d			41 (unossified incus, incompletely ossified supraoccipital)		Short et al. 1977a
30	Rabbit	13 d Gd6-18 7hr/d		80		160 (fetal resorptions)	Murray et al. 1979

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
31	Mouse	4 d Gd12-15 23hr/d				54 (fetal resorption)	Short et al. 1977a
Reproductive							
32	Mouse	5 d 6hr/d		30			Anderson et al. 1977
INTERMEDIATE EXPOSURE							
Death							
33	Gn pig	90 d 24hr/d				15 (3/15 died)	Prendergast et al. 1967
34	Monkey	90 d 24hr/d				25 (2/3 died)	Prendergast et al. 1967
Systemic							
35	Rat	90 d 5d/wk 6hr/d	Hepatic		25 (cytoplasmic vacuolization)		Balmer et al. 1976
36	Rat	6 mo 5d/wk 6hr/d	Resp	75			Quast et al. 1986
			Hemato	75			
			Hepatic		25 (fatty changes in midzonal hepatic lobule)		
			Derm/oc	75			
37	Rat	3 wk 5d/wk 6hr/d	Resp		200 (slight nasal irritation)		Gage 1970
			Hepatic		500 (degeneration of liver cells)		
			Other (body weight)		500 (retarded weight gain)		

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
38	Rat	90 d 24hr/d	Resp	48			Prendergast et al. 1967
			Hepatic	25		48 (focal necrosis)	
			Renal	15	48 (nuclear hypertrophy of tubular epithelium)		
39	Rat	30 d 5d/wk 6hr/d	Hepatic		125 (centrilobular and midzonal cytoplasmic vacuolization)	200 (necrosis)	Quast 1976
40	Rat	6 wk 5d/w 6hr/d	Hemato		100 (increased plasma phosphate levels)		Klimisch et al. 1979
			Hepatic		100 (increased liver weight)		
			Renal		100 (increased kidney weight; desquamation of nephric epithelial cells)		
41	Rat	4 wk 7d/wk 24hr/d	Hepatic		50 (fatty changes and focal necrosis)		Plummer et al. 1990
42	Gn pig	90 d 24hr/d	Resp	48			Prendergast et al. 1967
			Hepatic	5[d]	48 (increased SGPT and AP enzyme activity; decreased lipid content)		
43	Gn pig	6 wk 5d/wk 8hr/d	Resp	100			Prendergast et al. 1967
			Hepatic	100			
44	Dog	90 d 24hr/d	Resp	48			Prendergast et al. 1967
			Hepatic	25		48 (focal necrosis of liver)	

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
45	Dog	6 wk 5d/wk 8hr/d	Resp	100			Prendergast et al. 1967
			Hepatic	100			
46	Monkey	6 wk 5d/wk 8hr/d	Resp	100			Prendergast et al. 1967
			Hepatic	100			
			Other (body weight)		100 (5.9% decrease in body weight)		
47	Monkey	90 d 24hr/d	Resp	48			Prendergast et al. 1967
			Hepatic	25		48 (focal necrosis of liver)	
			Other (body weight)	5		48 (>25% decrease in body weight)	
Reproductive							
48	Rat	11 wk 5d/wk 6hr/d		55			Short et al. 1977b
Cancer							
49	Dog	90 d 24hr/d				48 (adrenal cortical adenoma)	Prendergast et al. 1967
CHRONIC EXPOSURE							
Systemic							
50	Rat	18 mo 5d/wk 6hr/d	Resp	75			Quast et al. 1986
			Hemato	75			
			Hepatic		25 (decreased liver weight; fatty changes in the midzonal region)		
			Renal	75			

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
51	Mouse	1 yr 5d/wk 6hr/d	Hemato	55			Lee et al. 1977
			Hepatic			55 (hepatocellular necrosis)	
			Renal			55 (tubular necrosis)	
52	Mouse	52 wk 5d/wk 4hr/d	Renal	10		25 (tubular nephrosis)	Maltoni et al. 1985
Cancer							
53	Mouse	52 wk 5d/wk 4hr/d				25 (CEL, renal adenocarcinoma)	Maltoni et al. 1985

[a]The number corresponds to entries in Figure 2-1.
[b]Animals were fasted prior to exposure.
[c]Animals were fed prior to exposure (non-fasted).
[d]Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 0.02 ppm; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). A modifying factor of 3 was used to account for the close proximity of serious effects observed at the range of 10-25 ppm.

AKT = alanine alpha-ketoglutarate transaminase; AP = alkaline phosphatase; B = both sexes; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; F = female(s); Gd = gestation day(s); Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; SAKT = serum alanine alpha-ketoglutarate transaminase; SGPT = serum glutamic-pyruvic transaminase; wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation

ACUTE
(≤14 Days)

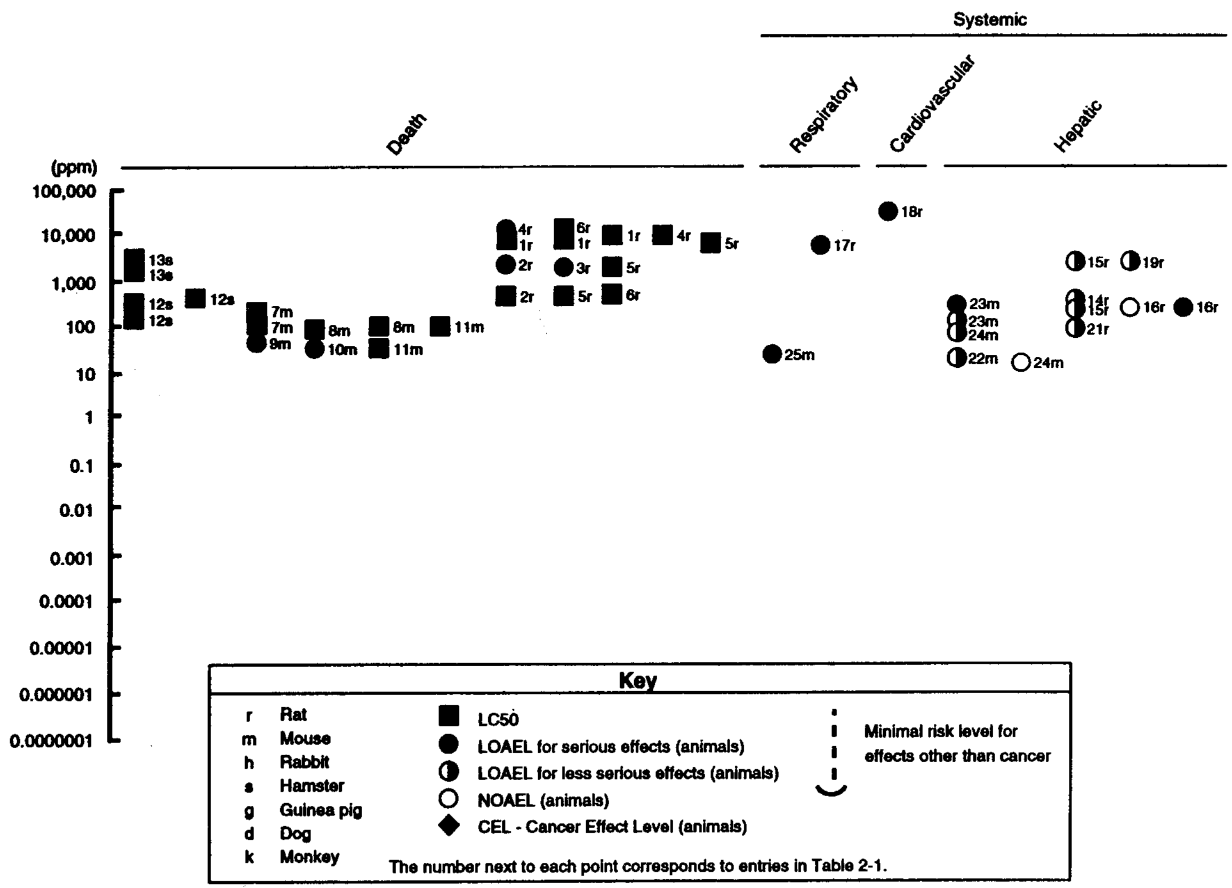


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*

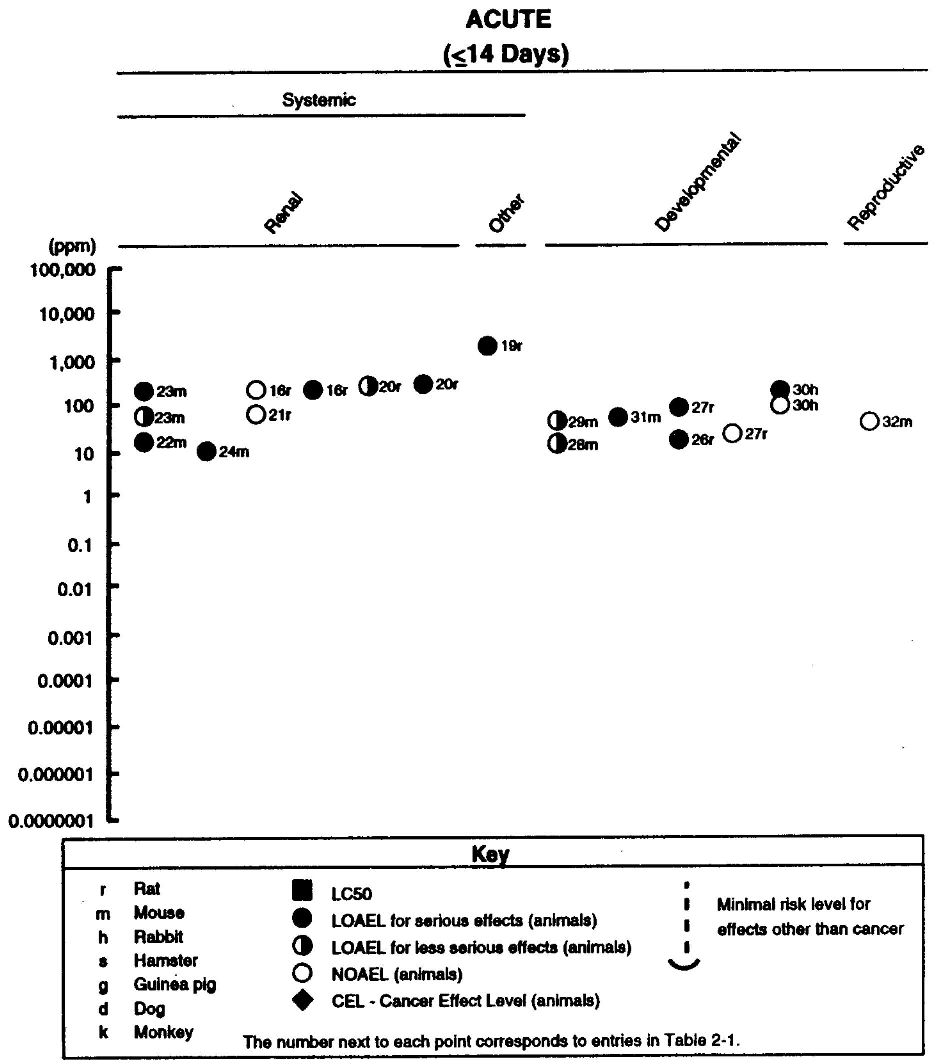


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*

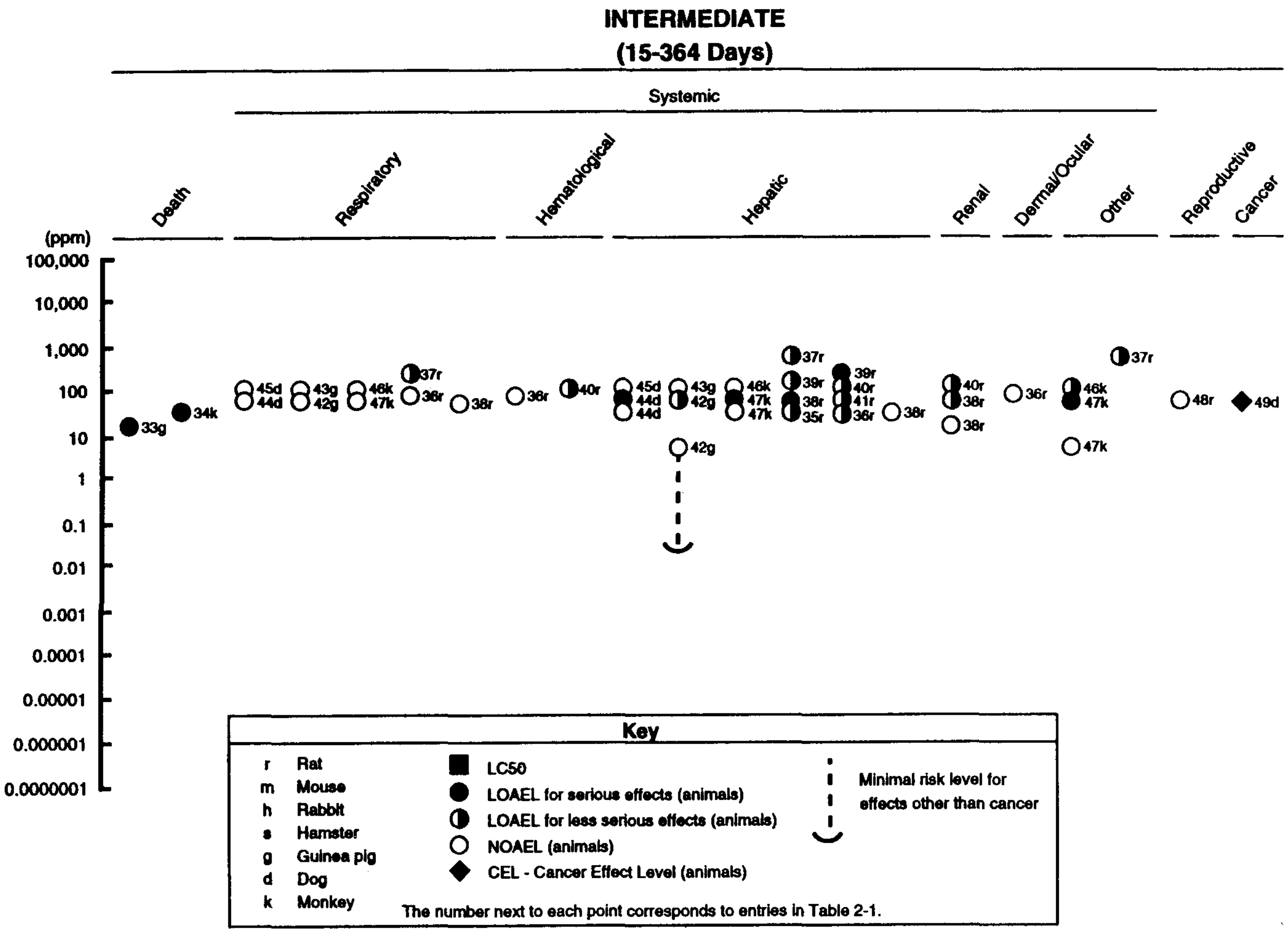
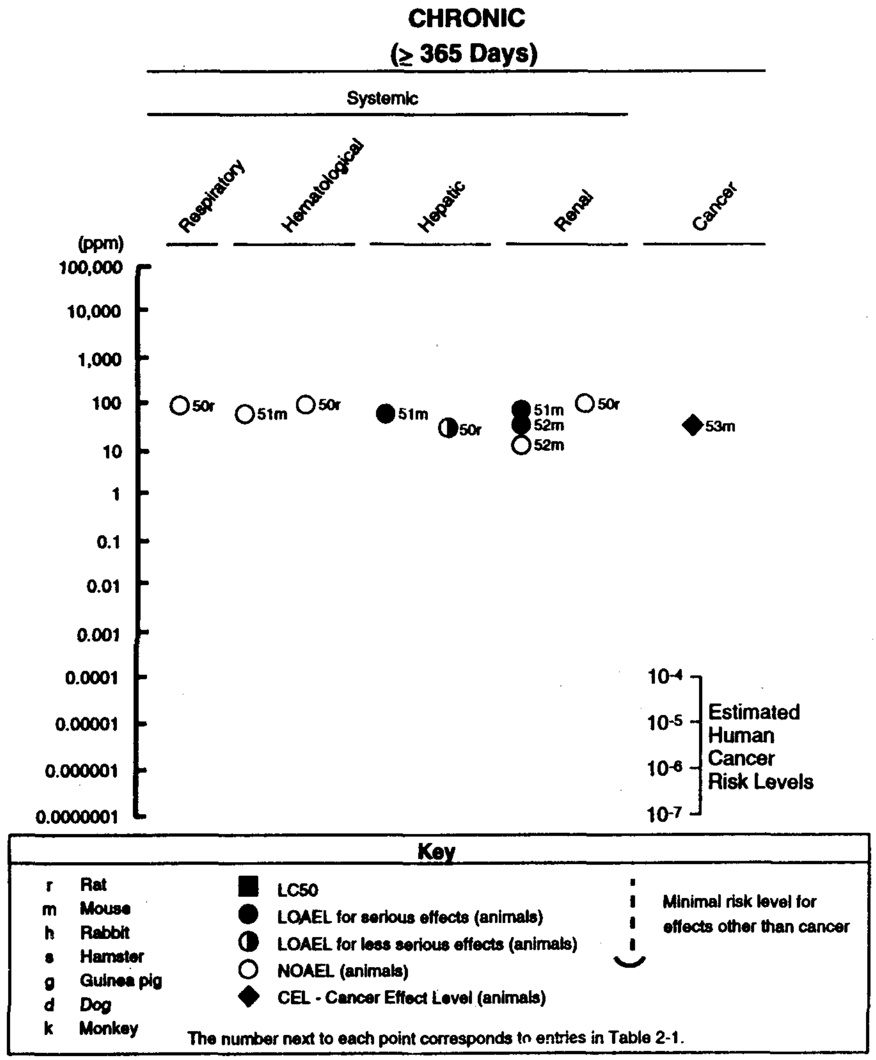


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*



No studies were located regarding gastrointestinal or musculoskeletal effects in humans or animals after inhalation exposure to 1,1-dichloroethene.The systemic effects observed following inhalation exposure are discussed below.

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

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to 1,1 -dichloroethene.

Acute swelling and localized bloody edema and congestion of the lungs are consistently seen at necropsy in rodents acutely exposed to high levels of 1,1-dichloroethene (≈500-15,000 ppm) via inhalation (Klimisch and Freisberg 1979a; Zeller et al. 1979a, 1979b); these effects were seen in hamsters (Klimisch and Freisberg 1979a, 1979b) and along with emphysema in mice (Zeller et al. 1979c) exposed to lower concentrations (150 and 20 ppm, respectively).

Nasal irritation was observed in rats exposed to 200 ppm for 3 weeks (Gage 1970). However, no histopathological effects attributed to treatment were observed in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm 1,1-dichloroethene intermittently for 6 weeks (Prendergast et al. 1967) or in rats similarly exposed to 75 ppm 1,1-dichloroethene for 18 months (Quast et al. 1986).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to 1,1-dichloroethene.

Few studies are available that describe adverse cardiovascular effects of 1,1-dichloroethene following inhalation exposure in laboratory animals. Acute exposure of rats to extremely high concentrations (25,600 ppm for 10 minutes) produced arrhythmias mediated by the sympathetic nervous system (Siletchnik and Carlson 1974). These study authors also found that 1,1-dichloroethene at 25,600 ppm increased the sensitivity of the myocardium to epinephrine, thereby providing a mechanism for the electrocardiographic changes. These effects are best characterized as nonspecific neurological effects.

Cardiac effects such as contraction of the main vessels, and hyperemia were observed following acute, high-level exposure (≈500-15,000 ppm) to 1,1-dichloroethene (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979b). Cardiovascular toxicity was not generally observed after more prolonged, lower-level exposure and is, therefore, most likely not a concern for prolonged lowlevel exposure in humans.

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to 1,1-dichloroethene.

The available studies did not evaluate the hematological parameters following acute and intermediate exposure to 1,1-dichloroethene.No hematological alterations were observed in male rats (Quast et al. 1986) or in mice (Lee et al. 1977) exposed to 75 ppm 1,1-dichloroethene for 18 months or to 55 ppm 1,1-dichloroethene for 12 months, respectively.

Hepatic Effects. Hepatotoxicity has been observed in humans after repeated exposure to 1,1-dichloroethene, presumably by the inhalation route. Preliminary clinical findings of workers exposed to 1,1-dichloroethene for 6 years or less in a 1,1-dichloroethene polymerization plant revealed a high incidence of hepatotoxicity. Liver scans and measurements of liver enzymes revealed 50% or greater loss in liver function in 27 (59%) of the 46 exposed workers (EPA 1976). These findings must be considered only qualitative in nature since the study provided few details and no follow-up study has been reported.

In laboratory animals, the liver is a major target organ of 1,1-dichloroethene toxicity following acute and chronic inhalation exposure. Hepatotoxicity is evident by the appearance of both biochemical changes (alterations in serum enzyme levels indicative of liver injury and induction of hepatic enzymes) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration, and necrosis of hepatocytes). These effects appear to follow a dose-response relationship and may also be influenced by duration of exposure. Mice exposed to 50 ppm 1,1-dichloroethene for 6 hours exhibited only slight centrilobular swelling (Reitz et al. 1980; Watanabe et al. 1980), whereas continuous inhalation exposure of mice to 15 ppm 1,1-dichloroethene for 23 hours/day for 5 days caused cellular degeneration (Short et al. 1977d). Under the same exposure regimen for 2 days, hepatic degeneration was seen at 60 ppm (Short et al. 1977d). Similar results were obtained in four strains of mice that were exposed to 55, 100, or 200 ppm

1,1-dichloroethene for 6 hours/day, 5 days/week, for 10 days. Hepatotoxic effects characterized by hepatocellular degeneration and necrosis with centrilobular hepatocellular swelling and pleomorphism at 100 and 200 ppm were observed in all strains. These effects were more severe in females (Henck et al. 1979). Severe effects were seen at higher doses in rats for even shorter-duration exposures. After inhalation exposure of rats to 200-250 ppm 1,1-dichloroethene for 4 hours the following effects were observed: increased liver weight, increased serum activities of sorbitol dehydrogenase and ornithine carbamoyl transferase (Jackson and Conolly 1985; Jaeger 1977a, 1977b), and frank hemorrhagic centrilobular necrosis (Reynolds et al. 1980).

The food intake of the organism prior to exposure influences the degree of 1,1-dichloroethene-induced hepatotoxicity, with more severe effects displayed by animals fasted overnight prior to exposure. This suggests that a relationship exists between chemical toxicity and depletion of reduced glutathione (GSH) (Reynolds et al. 1980). For example, results from an acute study in male rats demonstrated that inhalation exposures to 150 ppm 1,1-dichloroethene for up to 24 hours induced increases in serum enzyme levels indicative of liver dysfunction-alanine aketoglutarate transaminase (AKT)-in fasted animals to a greater extent compared to nonfasted animals (Jaeger et al. 1974). A significant increase in the serum enzymes (AKT) was observed in nonfasted rats exposed to 2,000 ppm or more 1,1-dichloroethene (Jaeger et al. 1974). Gross and microscopic histopathological and biochemical evidence of hepatotoxicity occurs earlier and is more extensive in fasted rats following short-term inhalation exposure to 1, 1-dichloroethene. Exposing fasted rats to 200 ppm 1,1-dichloroethene for 4 hours or less resulted in aberrations in hepatic GSH levels that preceded and/or accompanied major histological changes (Jaeger et al. 1975b; McKenna et al. 1978b; Reynolds et al. 1980). As mentioned above, the increased hepatotoxic effects of 1,1-dichloroethene following inhalation exposure seen in fasted versus nonfasted animals may be related to depletion of hepatic GSH levels in the fasted animals. GSH is known to be involved in 1,1-dichloroethene metabolism (see Section 2.3). GSH levels in rats fed *ad libitum* exhibited a marked diurnal rhythm; levels were minimal between 7 pm and 1 am and maximal between 7 am and 1 pm (Jaeger et al. 1973a). This increase was prevented in fasted rats, with maximal levels reduced by 50%. Furthermore, the I,l-dichloroethene-induced hepatotoxicity coincided with the reduction in liver GSH levels (Jaeger et al. 1973a). Nonfasted rats exposed to 1,1-dichloroethene via inhalation during the period of maximal GSH levels exhibited no signs of hepatotoxicity, but when they were exposed to similar levels of 1, I-dichloroethene during the diurnal period of minimal GSH levels, 40% died and serum enzyme markers increased markedly.

The hepatotoxic effects of 1,1-dichloroethene following intermediate or chronic exposure in animals are similar to those described above for acute exposure (Gage 1970; Lee et al. 1977; Plummer et al. 1990; Quast et al. 1986). Many of the studies that describe the longer-term effects of 1,1-dichloroethene in animals are limited in that only a few experimental details were provided or only one or two doses were studied. These limitations often prevent an adequate assessment of the quality of the results. Male and female rats exposed for 6 hours/day, 5 days/week, over a day period, to 125 or 200 ppm 1,1-dichloroethene exhibited liver changes. These changes were more severe in females and were characterized by a minimal degree of centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976). Mild dose-related cytoplasmic vacuolation was observed in male and female rats exposed to 25 or 75 ppm 1, 1-dichloroethene 6 hours/day, 5 days/week, for either 30 or 90 days (Balmer et al. 1976). The study authors considered this effect reversible. Fatty infiltration of the liver was reported in rats exposed to 25 ppm of 1,1-dichloroethene 6 hours/day, 5 days/week, for 6 months (Quast et al. 1986).

Animals appear to be much less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. There was no evidence of toxicity in beagle dogs exposed to 100 ppm of 1,1-dichloroethene for 8 hours/day, 5 days/week, for 42 days, but continuous exposure to 48 ppm of 1, 1-dichloroethene for 90 days caused marked liver damage (Prendergast et al. 1967). Similarly, squirrel monkeys continuously exposed to 48 ppm 1, 1-dichloroethene for 90 days exhibited marked evidence of liver damage (i.e., focal necrosis and hemosiderin deposition). However, no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-dichloroethene (Prendergast et al. 1967). It would appear that when animals are exposed to 1,1-dichloroethene on an intermittent basis, they are better able to compensate for the toxic effects induced by this chemical. This observation supports the involvement of depletable stores of liver GSH as a possible mediator of 1,1-dichloroethene-induced hepatotoxicity.

Liver effects in guinea pigs exposed to 5, 15, 25, or 48 ppm of 1,1-dichloroethene for 24 hours per day for 90 days were mottled livers at 15 ppm, and increased SGPT and AP enzyme levels at 45 ppm (Prendergast et al. 1967). Using a NOAEL of 5 ppm based on liver changes, an intermediate inhalation MRL of 0.02 ppm was calculated as described in the footnote in Table 2-1.

Hepatotoxic effects similar to those discussed above are seen following chronic inhalation exposure to 1,1-dichloroethene in laboratory animals (Lee et al. 1977; Quast et al. 1986). Female rats exposed to 1,1-dichloroethene via inhalation at a concentration of 25 ppm for 6 hours/day, 5 days/week, for 18 months, exhibited fatty changes in the liver (Quast et al. 1986). The results of these studies are only suggestive because of the poor presentation of the data.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,1-dichloroethene.

Adverse effects have been observed in the kidneys of laboratory animals following acute, intermediate, and chronic inhalation exposure to 1,1-dichloroethene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978b), gross changes (increase in organ weight) (Henck et al. 1979; Quast et al. 1986), and histological changes (tubular swelling, degeneration, and necrosis) (Henck et al. 1979; Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978b; Prendergast et al. 1967; Reitz et al. 1980; Short et al. 1977d; Watanabe et al. 1980). Following acute exposure, the range of 1,1-dichloroethene concentrations that produced the aforementioned effects in rats was 50-300 ppm, with the severity of the kidney lesions increasing with increasing dose and duration of exposure. Male mice appear to be more susceptible to the acute nephrotoxic effects of inhaled 1,l-dichloroethene than female mice or both sexes of rats. Severe histological lesions of the kidney were observed in mice following acute inhalation exposure to 10-50 ppm of 1,1-dichloroethene (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). Similar results were obtained in four strains of mice exposed to 55, 100, or 200 ppm for 6 hours/day, 5 days/week, for 10 days. Adverse renal effects (characterized by moderate-to-severe nephrosis) were observed in all strains, with the effects observed predominantly in the male mice (Henck et al. 1979).

There is evidence that kidney damage in animals after acute inhalation exposure to 1,1-dichloroethene is reversible, though this may depend on the dose level and duration of exposure. Tubular regeneration was evident in mice after a single 6-hour exposure to 50 ppm 1,l -dichloroethene

(Reitz et al. 1980). However, reversibility of kidney damage at higher exposure concentrations has not been demonstrated.

As was seen with hepatotoxicity, the amount of food intake of the animal appears to be an important determinant of 1,1-dichloroethene-induced nephrotoxicity. Fasted male rats exposed once to 200 ppm 1,1-dichloroethene for 6 hours exhibited delayed hemoglobinuria and marked tubular degeneration, while fed male rats similarly exposed displayed no treatment-related toxic effects (McKenna et al. 1978b). GSH depletion may play an indirect role in the exacerbation of 1,l -dichloroethene-induced nephrotoxicity in the fasted rat.

The bulk of the information on 1,1-dichloroethene-induced nephrotoxicity in animals comes from acute experiments, and evidence of nephrotoxicity after intermediate exposure is limited. Continuous inhalation exposure of rats to 48 ppm 1,1-dichloroethene for 90 days resulted in nuclear hypertrophy of the renal tubular epithelium (Prendergast et al. 1967). Severe nephrotoxicity occurred in male mice exposed to 25 ppm 1, 1-dichloroethene 4 hours/day, 4-5 days/week, for 52 weeks (Maltoni et al. 1985). The reversibility of this effect was not determined. No treatment-related effects were noted in the kidneys of rats chronically exposed to a concentration of 25 or 75 ppm 1,1-dichloroethene for 6 hours/day, 5 days/week, for 18 months (Quast et al. 1986). Strain differences may account for the differential susceptibility to 1,l -dichloroethene exposure.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following inhalation exposure to 1 ,l -dichloroethene.

No eye irritation was observed in rats exposed to an average concentration of 75 ppm 1,1-dichloroethene for 18 months (Quast et al. 1986).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to 1,1-dichloroethene.

A slight decrease in body weight was reported in rabbits exposed to 25 ppm 1,1-dichloroethene continuously for 90 days or to 100 ppm 1,1-dichloroethene intermittently for 6 weeks (Prendergast et al. 1967). Similar results were reported in monkeys exposed to 48 ppm 1,1-dichloroethene continuously for 90 days or intermittently to 100 ppm 1,1-dichloroethene for 6 weeks (Prendergast et al. 1967). Food consumption data were not provided. A decrease in body weight was also reported in rats exposed to 500 ppm 1,1-dichloroethene intermittently for 3 weeks, but the magnitude of the effect was not reported (Gage 1970).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to 1,l -dichloroethene.

2.2.1.4 Neurological Effects

Central nervous system depression and symptoms of inebriation, which may progress to unconsciousness, have been observed in humans after acute exposure to high airborne concentrations (≈4,000 ppm) of 1,1-dichloroethene (EPA 1979b). Complete recovery generally occurs if exposure is not prolonged. However, two cases of persistent cranial nerve disorders were observed following acute inhalation exposure to 1,l -dichloroethene. These cases primarily involved the trigeminal nerve and, to a lesser extent, the hypoglossal, occipital, auricular, and cervical cutaneous nerves, as well as the innervation of muscles of mastication and eye muscles. These two patients were involved in manually cleaning tanks used in the transport of an aqueous dispersion of 1,1-dichloroethene copolymers. The effects were most likely a result of dichloroacetylene formation from 1,1-dichloroethene due to heat and the presence of alkali from the soaps used; chloroacetylenes are highly neurotoxic (Fielder et al. 1985). There is no direct evidence that 1,1-dichloroethene can produce adverse neurological effects by itself, but it is possible that similar conditions could occur (i.e., heat and an alkali environment) and cause neurotoxicity due to chloroacetylenes generated from 1,1-dichloroethene at hazardous waste sites.

Signs of central nervous system toxicity were observed in animals after acute inhalation exposure. The toxic signs are similar across species and consist primarily of central nervous system depression, dyspnea, and narcosis, ultimately resulting in death (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979a, 1979b). These signs can also be accompanied by lethargy, rough coats, and a hunched appearance (Zeller et al. 1979b). Acute exposure of rats to extremely high concentrations (25,600 ppm for 10 minutes) induced increased sympathetic activity, resulting in cardiac arrhythmia (Siletchnik and Carlson 1974).

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to 1,1-dichloroethene.

Premating exposure of male rats to 55 ppm l,1-dichloroethene 6 hours/day, 5 days/week, for 11 weeks did not affect their fertility (Short et al. 1977b); no pre- or post-implantation losses occurred in untreated pregnant females mated to treated males in a dominant-lethal study. Similarly, inhalation exposure of male mice to 10 or 30 ppm 1,1-dichloroethene for 6 hours/day for 5 days appeared to have no adverse effect on fertility (Anderson et al. 1977). Decreased fertility was observed in rats following inhalation exposure to 50 ppm 1,1-dichloroethene for 5 days. The study authors attributed the decrease to infertility in males that ordinarily might not have been used but had to be included in the study in order to establish a sufficient group size. However. this could not be confirmed because of lack of sufficient details.

The highest NOAEL value from a reliable study for reproductive effects in each species and duration category is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to 1,l -dichloroethene.

1,l -Dichloroethene appears to produce both fetotoxic and developmental effects in laboratory animals (Short et al. 1977a). Prenatal exposure resulted in soft tissue anomalies in rats and skeletal defects in rats, mice, and rabbits. Maternal toxicity, as evidenced by decreased body weight and death, was also observed al developmentally toxic doses. Doses of 1,l -dichloroethene used in these studies ranged from 15 to 449 ppm. Increased mortality was observed in both pregnant and nonpregnant mice exposed to 144 ppm or more and rats exposed to 57 ppm or more. Skeletal anomalies in rats and mice and soft tissue anomalies in rats were observed at

15 ppm. Because of the high incidence of fetal resorptions observed in these initial experiments, Short et al. (1977a) conducted additional studies in mice. Pregnant animals were exposed via inhalation to various concentrations of 1,1-dichloroethene ranging from 41 to 112 ppm. The experiments were performed over different exposure durations that covered various phases of fetal development. Statistical analysis by two sample rank tests demonstrated that treatmentinduced increases in resorption frequency were significantly reduced at the shorter exposure periods, although the treatment-related weight loss was still evident in the dams. The viable pups demonstrated a variety of soft tissue anomalies, such as hydrocephalus, microphthalmia, cleft palate, and hydronephrosis. Skeletal anomalies were also observed.

A statistically significant increase in the incidence of skeletal anomalies was observed in the litters of rats exposed to 80 and 160 ppm 1,1-dichloroethene and in the litters of rabbits exposed to 160 ppm 1,l -dichloroethene (Murray et al. 1979). Developmental effects were evidenced by wavy ribs and delayed ossification in rat fetuses and skeletal alterations in rabbit fetuses. Fetotoxicity was indicated by increased resorption. A statistically significant decrease in maternal body weight gain was also noted at these concentrations. In this study, no statistically significant adverse effects were noted in rats exposed to 20 ppm or in rabbits exposed to 80 ppm 7 hours daily during pregnancy. A NOAEL for developmental toxicity following continuous inhalation exposure was not identified.

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

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to 1,l -dichloroethene.

Dominant lethal gene mutations have not been found to occur after inhalation of 1,1-dichloroethene vapors in animals (Anderson et al. 1977; Short et al. 1977b). However, 1, 1-dichloroethene has produced deoxyribonucleic acid (DNA) damage, as indicated by a slight increase in repair rates in mouse kidney cells in which normal replicative DNA synthesis had been inhibited (Reitz et al. 1980). Inhalation of 1,1-dichloroethene has been associated with minimal rates of DNA alkylation in mouse and rat kidney and liver cells (Reitz et al. 1980). These data suggest that inhalation exposure of rats to 55 ppm and mice to 10, 30, and 50 ppm of 1,1-dichloroethene for 6 hours/day for 5 days does not lead to significant levels of unrepaired DNA damage in the germ cells of the testes (as shown by the lack of a dominant lethal effect). However, exposure of mice and rats to 10 and 50 ppm for 6 hours induces a low incidence of DNA damage in the kidney cells of mice and minimal alkylation in the liver and the kidney of mice and rats. 1,l -dichloroethene appears to exert genotoxic effects on somatic cells but not on germ cells.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No relationship between the occurrence of cancer in humans and occupational exposure (primarily chronic inhalation exposure) to 1,1-dichloroethene has been demonstrated. However, only two studies were available for analysis. In addition, neither study was large enough to demonstrate a relationship between cancer and 1,1-dichloroethene unless there was an overt causality.

Chronic occupational exposure to I,l-dichloroethene was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between occupational exposure and cancer mortality in 1,1-dichloroethene production and polymerization plant workers (Ott et al. 1976). The Ott et al. (1976) study is limited in its usefulness in assessing the cancer risk to humans exposed to 1,1-dichloroethene. The cohort size was limited, the observation period was too short, and there was a small number of deaths from specific causes. No allowance was made for a latency period; thus, potential risk was underestimated. The Ott et al. (1976) study described liver enzyme changes in two workers and gave clinical chemistry findings comparing two cohorts. None of the clinical chemistry values were significantly different between the two cohorts.

The carcinogenicity of 1,1-dichloroethene in laboratory animals following inhalation exposure has been evaluated in intermediate and chronic studies with rats, mice, and Chinese hamsters (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). Exposure concentrations of 1,1-dichloroethene in these studies ranged from

10 to 200 ppm. Of the long-term inhalation bioassays conducted in laboratory animals to date, only the results of a study by Maltoni et al. (1985) in mice have provided some suggestive evidence of a carcinogenic effect associated with 1,1-dichloroethene exposure.

In a study reported by Maltoni et al. (1985), male and female Swiss mice were exposed by inhalation to 0, 10, or 25 ppm 1,1-dichloroethene 4 hours/day, 4-5 days/week, for 52 weeks, and then observed until spontaneous death occurred. Increases in both malignant and nonmalignant tumors were observed. In female mice of both treatment groups (10 and 25 ppm), increases in the incidence of carcinomas of the mammary gland occurred; however, no dose-response was evident. Lung tumors (most of which were benign pulmonary adenomas) increased in males at 10 ppm and in males and females at 25 ppm. Although the study authors stated that these increases were statistically significant, no statistical analyses were presented. The study authors concluded that no dose-response relationship could be established for either increased tumor incidence. Of the 150 high-dose males in the 25-ppm group examined, 28 had renal adenocarcinomas, but no such tumors were found in either the 30 males in the low-dose (10 ppm) group or the 186 control males. Renal adenocarcinomas are rare tumors in the Swiss mouse. The kidney tumors were accompanied by severe nephrotoxic effects including nephrosis. Moreover, an increased incidence of renal tumors in the male mice was only observed at doses that induced toxicity and which approximated the acutely lethal concentration. Only one female developed kidney tumorsj but there appeared to be no difference between the sexes with regard to the incidence of regressive changes in the kidney. Thus, it does not appear that the occurrence of nephrosis necessarily predisposes the animal to the development of kidney tumors.

An increased incidence of malignant mammary tumors and leukemia was reported in rats exposed to 100 ppm 1,1-dichloroethene 4-7 hours/day, 5 days/week, for 104 weeks (Cotti et al. 1988; Maltoni et al. 1985). Pregnant female rats were exposed on gestation day 12; the exposures continued in dams and ≈50% of the offspring (in 12-day and older embryos via transplacental exposure, followed by inhalation exposure for all progeny from this group) for 104 weeks. The remaining ≈50% were exposed for 15 weeks only. The highest tumorigenic response was seen in offspring treated for 104 weeks. The study authors concluded that under these exposure conditions (high doses during and after embryonal development), 1,1-dichloroethene is carcinogenic in rats. However. the results of this study are not definitive since the, study authors did not present statistical analyses and used ambiguous terminology (i.e., "total malignant tumors") to present the results.

Results of other inhalation studies with laboratory animals were negative regarding carcinogenicity (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). In studies by Lee et al. (1977, 1978), CD-l mice and CD rats were exposed to 0 or 55 ppm 1,1-dichloroethene for 1 year. Few hepatic hemangiosarcomas, hepatomas, bronchioalveolar adenomas, and skin keratoacanthomas were observed in experimentally treated mice; however, some of the rats exposed to 55 ppm 1,1-dichloroethene developed hemangiosarcomas of the mesenteric lymph nodes and the subcutaneous tissue. The incidence of these lesions, however, was not statistically significant. In a follow-up study, curcinogenicity was examined in rats and mice during a 12-month period (Hong et al. 1981). Except for mammary tumors in female mice, no significant increase in cumulative tumor incidence was observed in either species at 55 ppm 1,1-dichloroethene. The increased tumor incidences observed in the studies by Lee et al. (1977, 1978) and Hong et al. (1981) were not statistically significant.

Male and female Sprague-Dawley rats were exposed to 0, 25, or 75 ppm 1,1-dichloroethene via inhalation for 18 months (Quast et al. 1986). A statistically significant increase ($p<0.05$) in adenocarcinomas of the mammary gland was noted in the low-dose females (25 ppm). The study authors did not consider this increase related to 1,1-dichloroethene exposure because the incidence of mammary gland adenocarcinomas in the treatment groups was within the range of historical control data and was not dose related.

Both female and male rats were exposed to 0, 10, 25, 50, 100, or 150 ppm 1,l-dichloroethene for 52 weeks (Maltoni et al. 1985). The incidence of total mammary tumors (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) increased in females in the 10- and l00-ppm exposure groups. However, evidence for a carcinogenic effect from inhalation exposure to 1,1-dichloroethene in this study was inconclusive because there was no clear dose-related increase in total r mammary tumor incidence, the latency time for mammary tumor incidence was similar in all treated and control groups, the incidence (62%) of spontaneous mammary tumors in controls was high, and the incidence of mammary gland carcinomas in treated groups was lower than that of controls.

The effects of chronic inhalation exposure of CD-1 mice and CD rats to 55 ppm 1,1-dichloroethene for 12 months was studied by Lee et al. (1978, 1979). There was no statistically significant increase in tumors at any of the sites examined compared to the respective control animals. However, 2 of 35 treated male rats and 3 of 35 treated mice exhibited hemangiosarcomas, an uncommon tumor type, while ncme were found in the controls. The study authors claimed that rats were more resistant than mice to the carcinogenic effects of 1,1-dichloroethene, but the data do not support this since there was no significant increase in the incidence of tumors in either species and the incidence of hemangiosarcomas was practically the same for the two species. The short duration of this study may have precluded observing tumors that have a longer latency period.

In a follow-up study, CD-1 mice and CD rats were exposed to 55 ppm 1,1-dichloroethene by inhalation for 1, 3, or 6 months (mice) or 1, 3, 6, or 10 months (rats) followed by a 12-month observation period (Hong et al. 1981). There was no statistically significant increase in the incidence of tumors in any of the treated animals compared to untreated animals. However, the study was limited by the following factors: high mortality occurred; a small number of animals (three to seven per sex per group) was used which decreased the ability of the study to detect a tumorigenic response; and the exposure durations were considerably less than the expected lifetime of the mice.

The negative findings of various inhalation studies may be partially explained by inadequate test conditions. Chronic-duration animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986e). Study limitations for many of these investigations included less than lifetime exposure, use of concentrations well below or above the maximum tolerated dose, small numbers of animals, and/or limited gross or microscopic examinations (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). These limitations impair the sensitivity of a test to detect a carcinogenic response.

EPA has derived an inhalation unit risk of $5x10^{-5}$ μg /m^3 for cancer risk associated with inhalation exposure to 1,1-dichloroethene based on the study by Maltoni et al. (1985) in mice (IRIS 1992). EPA indicates, however, that it may not be appropriate to use this inhalation unit risk if the air concentration exceeds 0.05 ppm. The air concentrations associated with the upper bound for an individual lifetime cancer risk of 10^{-4} to 10^{-7} are $5x10^{-4}$ to $5x10^{-7}$ ppm. This range is plotted in Figure 2-1. The exposure concentration associated with an increased incidence of kidney adenocarcinoma (25 ppm) in male mice is presented in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,1-dichloroethene.

Death has been observed in laboratory animals following oral exposure to 1,1-dichloroethene. The database on the lethality of ingested 1,1-dichloroethene in animals consists primarily of gavage studies in fasted rats. However, there were a few studies located regarding death in mic, or other species.

Reported oral LD_{50} values in rats are ≈1,500 mg/kg (Jenkins et al. 1972; Jones and Hathway 1978a). The threshold for mortality in male rats is 50 mg 1,1-dichloroethene/kg in corn oil (Andersen and Jenkins 1977). The limited data available for mice indicate that this species is considerably more sensitive than rats to the lethal effects of ingested 1,1-dichloroethene. Reported LD_{50} values in mice are ≈200 mg/kg (Jones and Hathway 1978a).

Since all available data are from fasted animals, it is not possible to determine whether the amount of food intake of the animal influenced the lethality of ingested 1,1-dichloroethene, as it does during inhalation exposure. It has been demonstrated by Jenkins et al. (1972) that adrenalectomy in rats exacerbates the lethal effects of ingested 1,1-dichloroethene. These investigators reported an oral LD_{50} of 81 mg/kg for 1,1-dichloroethene in adrenalectomized rats. The mechanism and significance of this effect are unclear but probably involves a compromise in the animal's response to stress.

Oral administration of a single dose of 1,1-dichloroethene to fasted rats revealed that young male rats (100-200 g) appeared to be more susceptible than older rats to its lethal effects (Andersen and Jenkins 1977). This age-dependent difference in toxicity was not seen in females. Male mice fasted before inhalation exposure showed signs of enhanced 1,1-dichloroethene toxicity compared to nonfasted rats.

In summary, ingested 1,1-dichloroethene is very toxic in at least two species of laboratory animals. Young animals and those with compromised stress responses appear to be most susceptible to these effects (Gosselin et al. 1984).

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

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure.

1,1-dichloroethene has been shown to adversely affect several organ systems in laboratory animals. The major target organs of 1,1-dichloroethene toxicity in animals are the liver and kidney. In addition, some studies suggest that 1,1-dichloroethene may induce adverse effects on the respiratory and gastrointestinal systems following oral exposure.

No studies were located regarding cardiovascular, musculoskeletal, or dermal/ocular effects in animals following oral exposure to 1,l -dichloroethene. The systemic effects observed after oral exposure are discussed below.

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

Respiratory Effects. No histopathological changes were observed in the lungs of nonfasted or fasted rats administered a single gavage dose of 200 mg/kg 1,1-dichloroethene in either corn oil, mineral oil, or an aqueous solvent (Chieco et al. 1981).

Pulmonary injury was observed in mice exposed to a single oral dose of 200 mg/kg (Forkert et al. 1985). Histopathological changes were observed in Clara cells within 24 hours, and these were accompanied by pulmonary edema, and hemorrhage. This damage appeared to be reversible;

TABLE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	Once				1550 (LD50)	Jones and Hathway 1978a
2	Rat	(G)	Once				50 (LD_{LO}, 10% died)	Andersen and Jenkins 1977
3	Rat	(G)	Once				1510 (LD50)	Jenkins et al. 1972
4	Mouse	(G)	Once				194 (LD50[F]) 217 (LD50[M])	Jones and Hathway 1978a
Systemic								
5	Rat	(GO)	Once	Hepatic			100 (centrilobular and midzonal necrosis)	Kanz et al. 1991
6	Rat	(G)	Once	Hepatic	100[b]	400[b] (increased plasma levels of LDH, SDH, and transaminases)		Jenkins and Andersen 1978
				Renal	200[b]		400[b] (tubular necrosis; increased plasma creatinin and urea nitrogen)	
7	Rat	(G)	Once	Hepatic		25[b] (morphological changes in bile canaliculi and plasma membranes)		Kanz and Reynolds 1986

TABLE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
8	Rat	(GO)	Once	Hepatic		100[b] (decreased G6Pase and increased SAKT activity)		Jaeger et al. 1973b
9	Rat	(G)	Once	Hepatic		200[b] (decreased bile flow, increased plasma levels of GOT and LDH)		Moslen et al. 1985
10	Rat	(G)	Once	Resp	200			Chieco et al. 1981
				Cardio	200			
				Gastro		200 (edema of forestomach)		
				Hemato		200[b] (increased hemoglobin level)		
				Hepatic			200[b] (hemorrhagic liver and midzonal necrosis)	
				Renal		200[b] (granular "heme" casts in Henle's loop)		
				Other (body weight)	200			
11	Rat	(G)	Once	Hepatic		50[b] (increased SGOT and SGPT activity)		Chieco et al. 1981
12	Mouse	(G)	Once	Resp		200 (reversible damage and disruption of Clara cells)		Forkert et al. 1985
Developmental								
13	Rat	(W)	10 d Gd6-15 ad lib		40			Murray et al. 1979

TABLE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Systemic								
14	Dog	(W)	97 d ad lib	Hemato	25			Quast et al. 1983
				Hepatic	25			
				Renal	25			
CHRONIC EXPOSURE								
Systemic								
15	Rat	(W)	2 yr ad lib	Hemato	19.3			Rampy et al. 1977
				Hepatic	10	19.3 (cytoplasmic vacuolization)		
				Renal	19.3			
16	Rat	(W)	2 yr ad lib	Hepatic		9 (hepatocellular fatty changes, accentuated hepatic lobular pattern)		Nitschke et al. 1983
17	Rat	(W)	2 yr ad lib	Hemato	20			Quast et al. 1983
				Hepatic	10	20 (hepatocellular swelling with midzonal fatty changes)		
18	Rat	(W)	2 yr ad lib	Hemato	30			Quast et al. 1983
				Hepatic		9[c] (hepatocellular swelling with midzonal fatty changes)		

TABLE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
19	Rat	(W)	2 yr ad lib	Hemato	25.6			Rampy et al. 1977
				Hepatic	12.6	25.6 (cytoplasmic vacuolization)		
				Renal	25.6			
Reproductive								
20	Rat	(W)	2 yr ad lib		30			Nitschke et al. 1983

[a]The number corresponds to entries in Figure 2-2.
[b]Animals were fasted prior to exposure.
[c]Used to derive a chronic Minimal Risk Level (MRL) of 0.009 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Cardio = cardiovascular; d = day(s); F = female(s); (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage oil; GOT = glutamate-oxalacetate transaminase; Hemato = hematological; LD50 = lethal dose, 50% kill; LD_{LO} = lowest lethal dose; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; SAKT = serum alpha-ketoglutarate transaminase; SDH = sorbitol dehydrogenase; SGOT = serum glutamate-oxalacetate transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = water; yr = year(s)

FIGURE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral

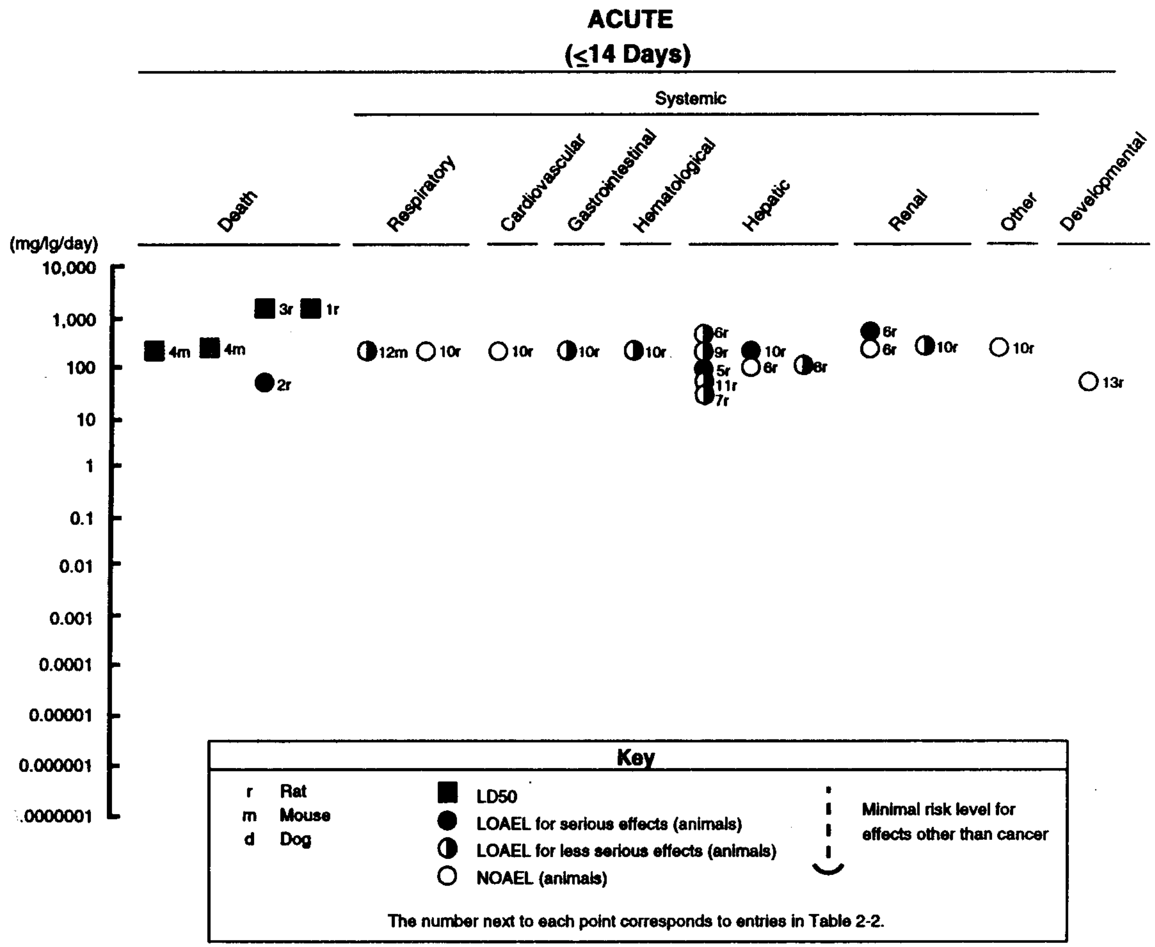
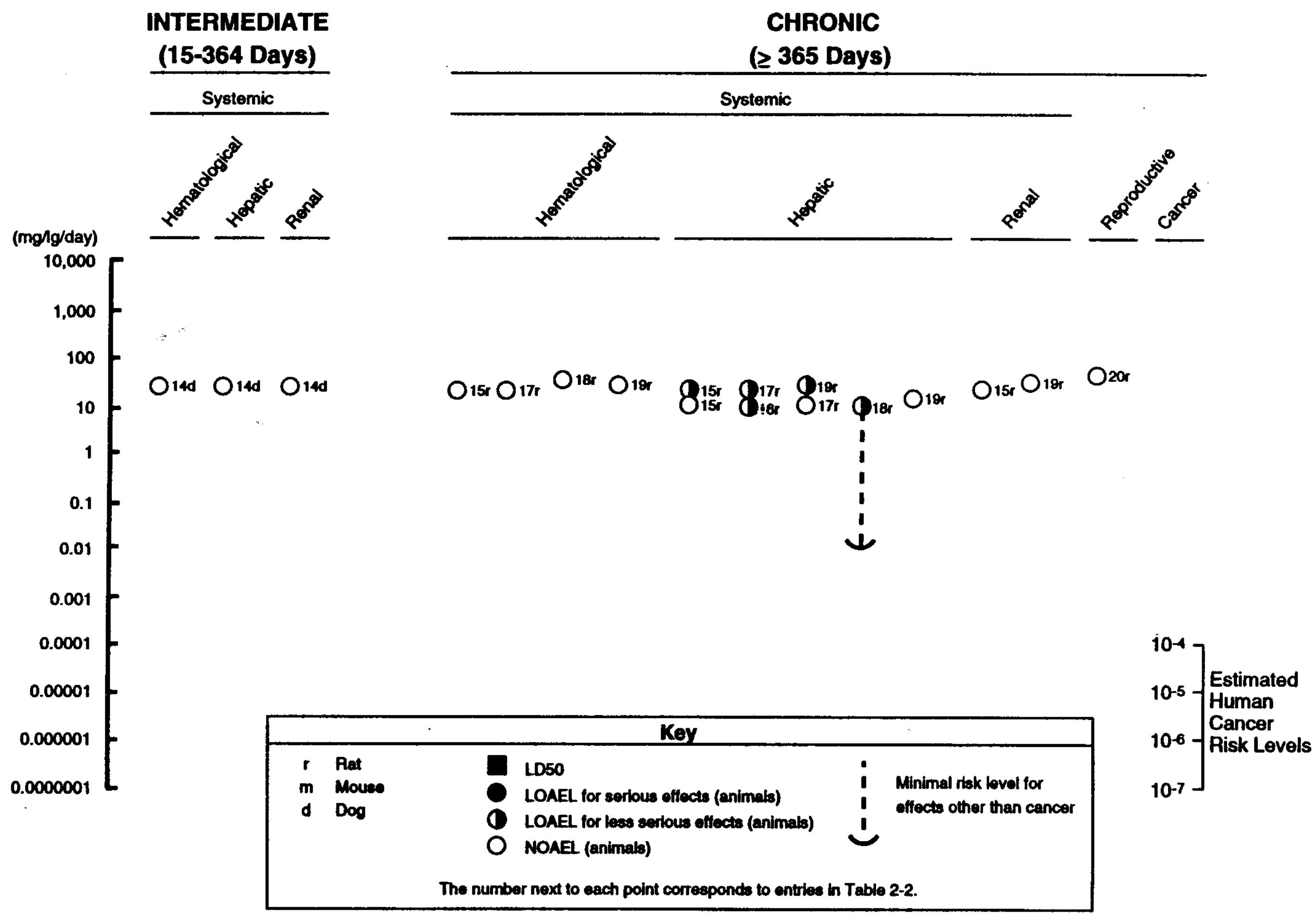


FIGURE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral *(continued)*



cellular regeneration was evident within 5 days of treatment. The relevance of these findings to human exposure is questionable.

Gastrointestinal Effects. Edema of the forestomach was observed in fasted and nonfasted rats after a single gavage dose of 200 mg/kg (Chieco et al. (1981). However, this alteration was not associated with any discernible degenerative changes, and its relevance to human exposure is unknown. No acute-duration studies of 1,1-dichloroethene administered in food were located.

Hematological Effects. A significant increase ($p<0.001$) in plasma free hemoglobin was observed in fasted rats administered a single dose of 200 mg/kg 1,1-dichloroethene in mineral oil or in corn oil (Chieco et al. 1981). The effect was not as marked, although still significant ($p<0.05$), when 1,1-dichloroethene was given to nonfasted rats in either vehicle. According to the investigators, the effect does not represent a true hematological effect but is due to hemolysis of red cells trapped in the congested sinusoids of the injured liver.

No significant changes in hematological or clinical chemistry parameters were observed in dogs exposed to 25 mg/kg/day 1,1-dichloroethene in drinking water for 97 days (Quast et al. 1983). Similar results were observed in rats exposed to ≤30 mg/kg/day in drinking water for 2 years (Quast et al. 1983; Rampy et al. 1977).

Hepatic Effects. 1,1-dichloroethene is hepatotoxic in laboratory animals, particularly after ingestion of an acute dose. A complete spectrum of effects indicative of liver toxicity has been observed in animals following acute oral administration of 1,1-dichloroethene, and their incidence and severity tend to be dose related. Significant increases in serum enzyme markers of liver damage or dysfunction (aspartate transaminase, ALT and alanine transaminase, AST) have been noted in fasted rats after the ingestion of a single dose of 50 mg/kg or more (Andersen and Jenkins 1977; Jenkins and Andersen 1978; Moslen et al. 1989b). Acute exposure to 25 mg/kg or more induced bile canalicular injury in fasted rats (Kanz and Reynolds 1986; Moslen et al. 1989a). Histological evidence of liver damage as seen by the presence of pyknotic cells was noted following oral administration of 100 mg/kg to rats (Kanz et al. 1991). Ultrastructural changes in hepatocellular organelles such as morphological changes in bile canaliculi and plasma membranes have also been noted in fasted rats after a single dose of 25 mg/kg (Kanz and Reynolds 1986).

The food intake of animals and the dosing vehicle influence the hepatotoxicity of orally administered 1,l -dichloroethene in animals. Fasting exacerbates 1,l -dichloroethene-induced hepatotoxicity; nonfasted animals exhibit only mild effects at comparable doses (i.e., increases in organ weight) (Andersen and Jenkins 1977; Andersen et al. 1980; Chieco et al. 1981; Jenkins and Andersen 1978). The hepatotoxic effects of 1,1-dichloroethene in rats tend to be more severe when administered in mineral or corn oil than in 0.5% aqueous Tween 80 (Chieco et al. 1981). Study authors have suggested that an aqueous solution of Tween 80 facilitates the clearance of 1,l -dichloroethene from the body.

One study was located regarding hepatic effects in animals after intermediate exposure to 1,1-dichloroethene. No exposure-related gross or histopathological changes were observed in the livers of beagle dogs given 25 mg/kg/day in drinking water for 97 days (Quast et al. 1983).

Chronic studies have been performed in rats ingesting low levels (9-20 mg/kg/day) of 1,l-dichloroethene for 2 years. The results indicated few treatment-related changes. After 1 year of treatment, only a minimal increase in cytoplasmic vacuolation of hepatocytes was noted (Rampy et al. 1977). After 2 years, a minimal amount of hepatocellular swelling with midzonal fatty change was reported (Quast et al. 1983). Slight hepatocellular changes were observed in rats exposed to 1,1-dichloroethene in the drinking water at levels of 9 mg/kg/day *in utero*, during lactation, and through weaning into adulthood (Nitschke et al. 1983). A chronic oral MRL of 0.009 mg/kg (Quast et al. 1983) was calculated for 1,1-dichloroethene, as described in the footnote in Table 2-2.

Renal Effects. Evidence for 1,1-dichloroethene-induced kidney dysfunction has been observed in laboratory animals following acute oral exposure. Fasted rats given single gavage doses of 200 mg/kg or more in corn oil exhibited increased plasma urea and creatinine levels (at 400 mg/kg) (Jenkins and Andersen 1978). Histopathological changes (vacuolizalion, pigmentation, tubular dilation, and necrosis) were observed at 400 mg/kg. These changes were more severe in females, though some recovery was evident in females 96 hours after exposure. Histological changes such as granular heme casts in Henle's loop were observed in the kidneys of nonfasted and fasted rats administered single doses of 200 mg/kg by gavage in either corn oil, mineral oil, or an aqueous solvent (Chieco et al. 1981). As noted for hepatic effects, fasting exacerbates

1,l -dichloroethene-induced nephrotoxicity in animals; no renal effects were observed in nonfasted animals administered single doses of 400 mg/kg (Jenkins and Andersen 1978).

No renal effects were noted in animals following intermediate (Quast et al. 1983) or chronic (Rampy et al. 1977) oral exposure to 1,1-dichloroethene at doses of 30 mg/kg/day or less.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to 1,1-dichloroethene.

No effect on body weight was reported in rats following acute oral exposure to 200 mg/kg/day (Chieco et al. 1981).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 1,1-dichloroethene.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,l -dichloroethene.

No adverse neurological effects on were identified after oral administration of 1,1-dichloroethene for any exposure duration in animals. The appearance and demeanor of the test animals were not affected in either an intermediate feeding study in dogs (25 mg/kg/day for 97 days) or a chronic study in rats (30 mg/kg/day or less for 2 years) (Quast et al. 1983). However, these results are only suggestive because no sensitive neurological tests were performed.

2.2.2.5 Reproductive Effects

Only one human study was located regarding neural tube defects in newborns after transplacental exposure to 1,l-dichloroethene via contaminated water (NJDH 1992a, 1992b). However, these data provide only suggestive evidence and therefore, should be interpreted with caution.

1,1-dichloroethene (99.5% purity) was administered in the drinking water of rats at dosages of 30 mg/kg/day or less for three generations. No dose-related changes were seen in reproduction or neonatal development (Nitschke et al. 1983). The study employed sufficient number of animals and used three dose levels. The NOAEL value for reproductive effects is listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

Only one human study was located regarding neural tube defects in newborns after transplacental exposure to 1,1-dichloroethene via contaminated water (NJDH 1992a, 1992b). However, these data provide only suggestive evidence and, therefore, should be interpreted with caution.

No effect on the number of implantations, live fetuses, or resorptions, sex ratio, or fetal weight were observed among the offspring of rats administered 40 mg/kg/day in the drinking water on gestation days 6 through 15 (Murray et al. 1979). The incidence of malformations, considered individually or collectively, among the rats given 1,1-dichloroethene was not significantly different from that of controls. There was, however, a marginal increase in crown-rump length in treated rats; the significance of this effect is unclear.

The highest NOAEL values for developmental effects in rats after acute exposure are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 1,l -dichloroethene.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to 1,1-dichloroethene.

A number of chronic studies in rats and mice have evaluated the carcinogenicity of 1,1-dichloroethene by oral exposure (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Dosages of 1,1-dichloroethene in these studies ranged from 0.5 to 150 mg/kg/day. Administration was by gavage with the exception of two studies in which 1,1-dichloroethene was administered daily in the drinking water (Quast et al. 19%; Rampy et al. 1977). Major organs and tissues of treated and control animals in these investigations were subjected to both gross and microscopic examination.

A trend toward increased incidence of malignant and nonmalignant tumors in 1,1-dichloroethene-treated animals has been reported (NTP 1982; Ponomarkov and Tomatis 1980; and Quast et al. 1983). For example, rats exposed in *utero* to a single dose of 150 mg/kg I,l-dichloroethene and given weekly gavage doses of 50 mg/kg 1,1-dichloroethene from weanilg until 120 weeks of age had increased incidences of meningiomas and liver cell adenomas and {arcinomas compared to controls, but the difference was not statistically significant (Ponomarkob and Tomatis 1980). However, hyperplastic nodules of the liver in these animals were significantly increased ($p=0.04$). No significant increase in tumor incidence was seen in dams receiving a single oral dose of 150 mg/kg 1,1-dichloroethene (Ponomarkov and Tomatis 1980). Another study showed that male rats treated by gavage with 5 mg/kg 1,1-dichloroethene for 2 years had an increased incidence of pheochromocytomas, but when compared with control animals, the difference was not statistically significant (NTP 1982).

Statistically significant increases in certain types of tumors and cancers have been reported in bioassays in which rats and beagles were orally exposed to 1,1-dichloroethene (Quast et al. 1983); however, investigators discounted these results for various reasons. In a 2-year study by Quast et al. (1983), doses of 7, 10, and 20 mg/kg/day and 9, 14, and 30 mg/kg/day were administered in the drinking water of male and female rats, respectively. A statistically significant increase ($p<0.05$) in the incidence of combined mammary gland fibroadenomas and adenofibromas was noted in low-dose females. Because the incidence of these types of tumors was within the normal range of historical control data and because these tumors were not observed in higher-dose females or in treated males, the study authors did not consider these increases to be related to 1,1-dichloroethene ingestion. Thus, the results of the study are of questionable biological significance.

Clinical signs of toxicity were not generally observed in the various oral carcinogenicity studies on 1,1-dichloroethene; consequently, maximum tolerated doses may not have been achieved (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Chronic-duration animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986e). Two of the oral carcinogenicity studies also used exposure periods that were less than lifetime (52-59 weeks); however, the animals were observed for 136 or 147 weeks allowing an adequate latency period for the development of lateappearing tumors (Maltoni et al. 1982, 1985).

EPA has derived an oral cancer slope factor (q_1*) of 0.6 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to l,l-dichloroethene based on the study by NTP (1982) in rats (IRIS 1992). The doses associated with the upper bound for individual lifetime cancer risk of 10^{-4} to 10^{-7} are $1.7x10^{-4}$ to $1.7x10^{-7}$ mg/kg/day. This range is plotted in Figure 2-2. At the highest dose level tested, 5 mg/kg/day, the incidence of pheochromocytomas increased in male rats, but the increase was not statistically significant.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to 1,l -dichloroethene. The dermal/ocular effects observed after dermal expostire are discussed below.

Dermal/Ocular Effects. Liquid 1,1-dichloroethene is irritating when applied to the skin of humans (EPA 1979b) and animals (Torkelson and Rowe 1981) after exposures lasting only a few minutes. Details concerning these studies are lacking, but it has been suggested that these irritant effects may be due to the inhibitor,*p*-hydroxyanisole (monomethyl ether of hydroquinone, MEHQ), present in these formulations. MEHQ is an antioxidant which on contact results in skin depigmentation at concentrations of 0.25% or more (Busch 1985). Similarly, 1,1-dichloroethene is an ocular irritant in humans (EPA 1979b); this effect has also been ascribed to MEHQ.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to 1,1-dichloroethene.

2.2.3.4 Neurological Effects

Two cases of persistent nerve disorders were reported in subjects involved in manually cleaning tanks used to transport 1,1-dichloroethene copolymers (Fielder et al. 1985). The study is limited by a small sample size, lack of details regarding concentration, and a possible exposure via inhalation route.

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

The carcinogenicity of 1,1-dichloroethene following dermal exposure has been evaluated by Van Duuren et al. (1979). In this study, 1,1-dichloroethene doses of 40 or 121 mg (1,333 or 4,033 mg/kg, respectively) in acetone were applied three times weekly for 588 days or less to the skin of Swiss mice. No skin tumors were noted in treated animals. Increased incidences of pulmonary papillomas and squamous-cell carcinomas of the forestomach were observed in treated mice; the incidences of these tumors, however, were not statistically different from controls. The results suggest 1,1-dichloroethene is inactive as a complete carcinogen (an agent that, if applied in sufficient concentrations, can induce tumors by itself) when applied repeatedly to the mouse skin.

The ability of 1,1-dichloroethene to act as a tumor initiator in the skin of Swiss mice was evaluated by Van Duuren et al. (1979). In two-stage tumorigenesis, a subthreshold dose of a tumor initiator is applied. An initiator does not generally produce tumors at this dose but causes “dormant” cell changes so that later repeated applications of a promoter (an agent that by itself will not produce tumors) will induce benign and malignant tumors at the site of application. 1,1-dichloroethene (121 mg or 4,033 mg/kg) in acetone was applied to the skin once, followed 2 weeks later by dermal application of the tumor promotor, phorbol myristate acetate (TPA), three times a week for 576 days or less. Untreated, vehicle-treated, and TPA-only-treated animals served as negative controls. A statistically significant ($p<0.005$) increase in the incidence of skin papillomas was recorded in treated mice compared to controls. These results indicate that 1,1-dichloroethene is a tumor-initiating agent in the Swiss mouse skin test.

2.3 TOXICOKINETICS

Data regarding toxicokinetics of 1,1-dichloroethene in humans are not available. Studies in animals indicate that 1,1-dichloroethene is readily absorbed and rapidly distributed in the body following inhalation and oral exposure. The oral absorption rate greatly depends on the type of vehicle used. Oily vehicles facilitate uptake. Uptake of 1,1-dichloroethene vapors is duration and dose dependent. However, the percentage of 1,1-dichloroethene uptake decreases as the exposure concentration increases, until an equilibrium is reached. 1,1-dichloroethene distributes mainly to the liver and kidney and does not appear to be stored or accumulated in the tissues. It is metabolized by the hepatic microsomal cytochrome P-450 system. This process gives rise to several possible reactive intermediates thought to be responsible for 1,1-dichloroethene toxicity. The major detoxification route for these intermediates are hydroxylation and conjugation with GSH. Therefore, metabolic interventions that deplete GSH (treatment with drugs, fasting, etc.) tend to increase 1,1-dichloroethene toxicity. Excretion of metabolites occurs primarily via the urine and exhaled air. Unmetabolized parent compound may also be eliminated via exhaled air. After high-level exposures, greater percentages of the dose are exhaled as unchanged 1,1-dichloroethene. The physical/chemical properties of 1,1-dichloroethene indicate that absorption of 1,l -dichloroethene via dermal exposure is possible in humans. Information on the disposition and metabolism of 1,1-dichloroethene following chronic-duration exposures was not available.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of 1,1-dichloroethene in humans following inhalation exposure.

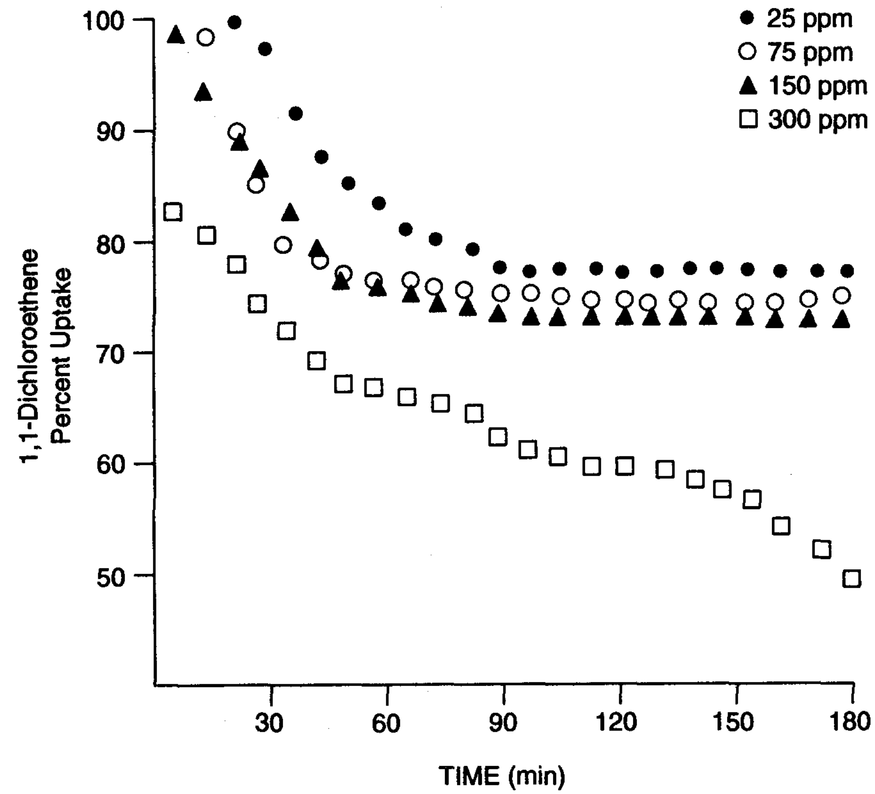
Studies in laboratory animals have demonstrated that 1,1-dichloroethene was rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978b). No studies were located that described transport mechanisms for 1,1-dichloroethene absorption. Since 1,1-dichloroethene is a small organic molecule with chemical and physical properties similar to lipid soluble anesthetics, it is expected to penetrate pulmonary membranes easily and to enter the blood stream rapidly. Substantial levels of the parent compound were found in the venous blood of rats within 2 minutes after inhalation exposure (Dallas et al. 1983). Absorption of 1,l-dichloroethene was duration and dose-dependent, as shown in Figure 2-3. The percentage of systemic uptake decreased with time from the onset of exposure until an equilibrium was reached within 1 hour. Once equilibrium was reached, percentage uptake varied inversely with dose. The cumulative uptake of 1,1-dichloroethene following inhalation exposure was linear for levels of 150 ppm or less. However, at 300 ppm a steady state was never achieved. This finding indicates that 1,1-dichloroethene absorption following inhalation exposure was saturable at high levels, and the kinetics at these levels are best described by a cubic curve (Dallas et al. 1983).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to 1,1-dichloroethene.

Studies in animals clearly indicated that doses of 1,1-dichloroethene ranging from 10 to 100 mg/kg were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; Putcha et al. 1986). Rapid

FIGURE 2-3. Percent Systemic Uptake of 1,1-Dichloroethene During Inhalation Exposures*



* Rats were exposed to 25, 75, 150, or 300 ppm 1,1-Dichloroethene for 3 hours. Percentage uptake was determined at 8-minute intervals. Each point represents the mean percentage uptake in four animals per group. Standard deviation brackets are omitted for the sake of clarity. Adapted from Dallas et al. 1983.

absorption occurred following oral administration of 200 mg/kg in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al, 1981). Peak blood levels were achieved in rats within 2-8 minutes after oral administration (Putcha et al. 1986). When 0.5-50 mg/kg of radiolabeled 1,1-dichloroethene was given to female rats, ≈10% of the parent compound was recovered in the expired air by 1 hour after exposure, indicating that oral absorption was rapid (Reichert et al. 1979). After oral administration to rats of 1,1-dichloroethene labeled with radioactive carbon (^{14}C), 81-99.8% of the administered radioactivity was recovered within 72 hours (Reichert et al. 1979). Studies have shown that 9-21% was recovered in the expired air, 53.9% in urine, 14.5% in feces, 2.8% in the carcass, and 7.5% in the cage rinse following oral administration of 1 or 5 mg ^{14}C-1,1-dichloroethene/kg (McKenna et al. 1978a; Reichert et al. 1979). After a dose of 50 mg ^{14}C-1,1-dichloroethene/kg, 19% and 29% of the parent compound was excreted via lungs in nonfasted and fasted rats, respectively (McKenna et al. 1978a). These results suggest that 1,1 -dichloroethene may be rapidly and completely absorbed in humans following oral exposure (e.g., via ingestion of contaminated groundwater).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 1,l -dichloroethene. Nonetheless, the physical/chemical properties of 1,l -dichloroethene indicate that dermal absorption of 1,1-dichloroethene is probable. 1,1-dichloroethene is a small organic molecule with properties similar to the lipid-soluble anesthetics. Thus, liquid 1,1-dichloroethene is expected to readily penetrate the skin, which is a lipid-rich tissue. However, with a vapor pressure of greater than 500 torr at room temperature, the rate of evaporation would be rapid leaving only a short time for skin penetration.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to 1,l-dichloroethene.

Following inhalation exposure of rats to 10 or 200 ppm of ^{14}C-labeled 1,1-dichloroethene, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues (McKenna et al. 1978b). These authors found that the tissue burden/g of tissue (mg equivalents of ^{14}C-1,1-dichloroethene/g of tissue/total mg equivalents recovered per rat) in the liver, kidneys, and lungs of fasted rats were significantly greater than in nonfasted rats at both exposure levels, even though the total accumulation of ^{14}C in fasted rats was less than in nonfasted rats. The results of this study suggest that in fasted rats the ^{14}C is retained in specific target tissues and not distributed randomly in all tissues.

Preferential accumulation of radioactivity was reported in the kidney and liver of rats exposed to 2,000 ppm radiolabeled 1,1-dichloroethene for 2 hours (Jaeger 1977a). Fasted rats had higher levels of label than nonfasted rats in these tissues. Examination of ^{14}C activity at the subcellular level in these two tissues revealed that significantly more water-soluble ^{14}C activity was present in the cytosolic fractions of fasted rats. This observation suggests that distribution pathways for metabolism differ according to the amount of food ingested by the animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 1,1-dichloroethene.

1,1-dichloroethene was rapidly distributed to all tissues examined following a single oral dose of the ^{14}C-labeled compound to rats (Jones and Hathway 1978b). The highest amount of radioactivity was found in the liver and kidneys within 30 minutes of administration. More general redistribution throughout the soft tissues of the body followed.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to 1.1-dichloroethene.

2.3.2.4 Other Routes of Exposure

In a study by Okine et al. (1985) in which mice were administered a single intraperitoneal injection of 125 mg/kg of ^{14}C-l ,l -dichloroethene, radioactivity was distributed to some extent to all examined tissues with peak levels seen 6 hours after administration. The highest levels of radioactivity were found in the kidney, liver, and lung with lesser amounts in the skeletal muscle, heart, spleen, and gut.

2.3.3 Metabolism

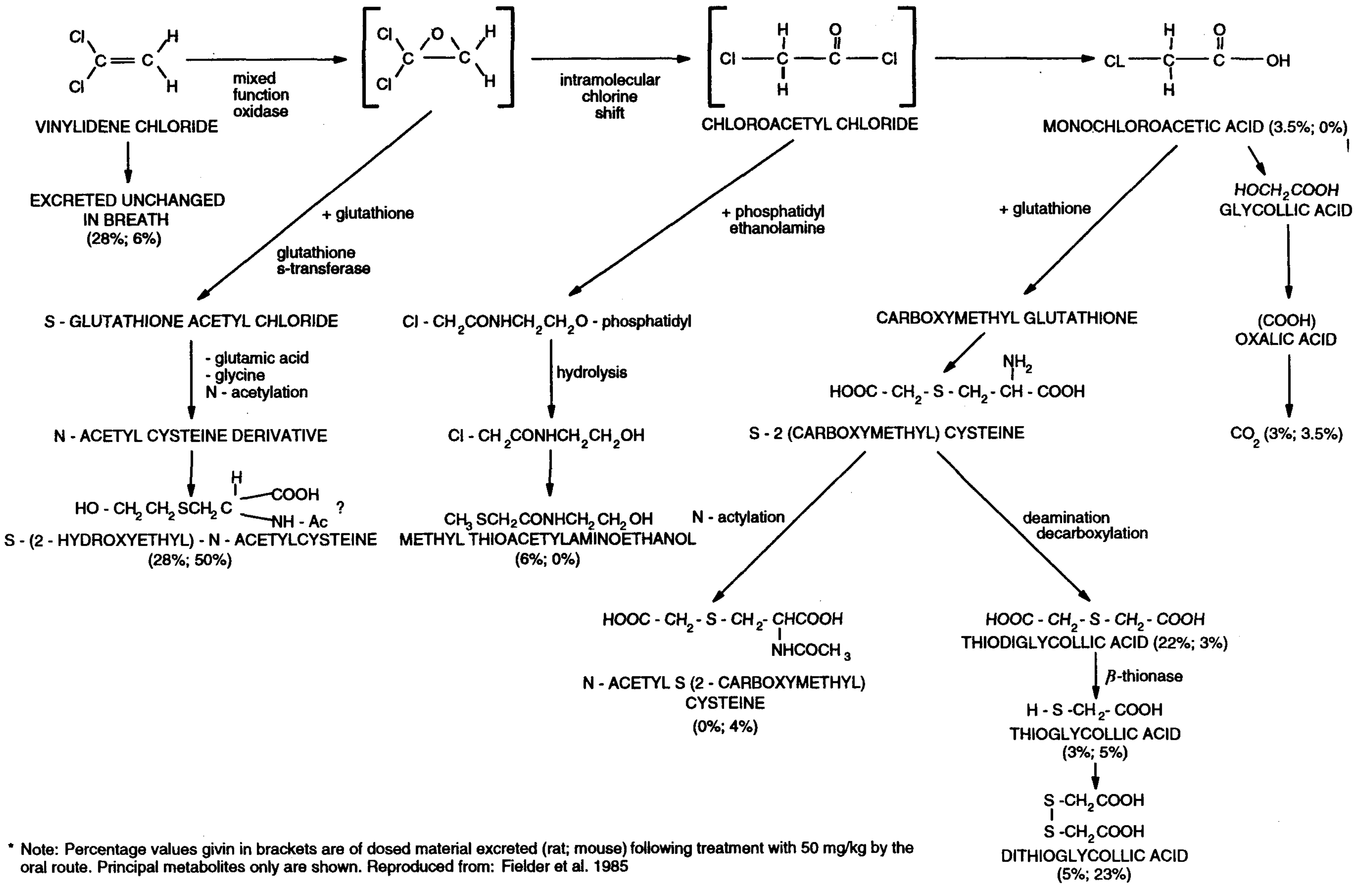
No studies were located regarding metabolism in humans following inhalation, oral, or dermal exposure to 1,1-dichloroethene.

Some evidence from animal studies suggests that at least the initial metabolic transformations in humans may be similar to those described in animals. Liver cells from a human subject together with Arochlor- pretreated S-9-activated 1,1-dichloroethene induced unspecified mutagenic metabolites in *Salrnonella typhimutium* assay (Jones and Hathway 1978c). This suggests that reactive metabolites may also be produced in humans.

The metabolism of 1,1-dichloroethene following oral administration in rats has been extensively studied (Jones and Hathway 1978a, 1978b; McKenna et al. 1978a; Reichert et al. 1979). These studies demonstrate that 1,l-dichloroethene undergoes biotransformation, and several metabolites have been identified. An overall summary of the metabolic pathway of 1,1-dichloroethene in animals is presented in Figure 2-4.

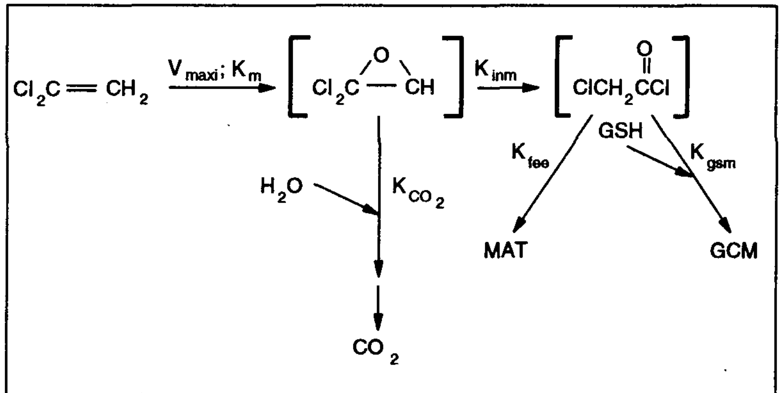
A physiologically based pharmacokinetic model for 1,1-dichloroethene based on its oxidative metabolism by the P-450 cytochrome system and subsequent conjugation with GSH, a principal pathway, was developed by D'Souza and Anderson (1988) (see Figure 2-5). Their model demonstrates that because 1,l-dichloroethene has a low blood-to-air partition coefficient and saturable metabolism, the metabolism of 1,1-dichloroethene is sensitive to the rate of absorption. Furthermore, 1,1-dichloroethene's metabolic pathway (i.e., the percentage of l,l-dichloroethenc exhaled, metabolized, and conjugated with GSH) is different for different routes of exposure and

FIGURE 2-4. Metabolic Pathway of 1,1-Dichloroethene in Animals*

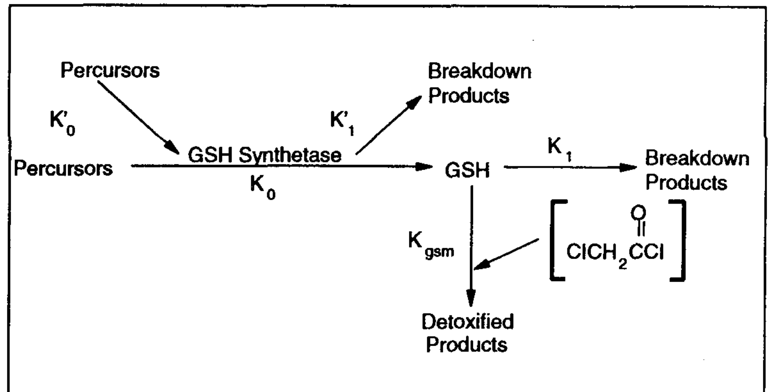


* Note: Percentage values givin in brackets are of dosed material excreted (rat; mouse) following treatment with 50 mg/kg by the oral route. Principal metabolites only are shown. Reproduced from: Fielder et al. 1985

FIGURE 2-5. Physiologically Based Pharmacokinetic Model for 1,1-Dichloroethene*



Scheme I. Model for 1,1-Dichloroethene metabolism pathways.



Scheme II. GSH synthesis and depletion by chloroacetyl chloride.

GCM Glutathione - conjugated metabolite.

GSH Glutathione concentration

K_{fee} First-order rate constant for formation of MAT.

K_{gsm} First-order rate constant for formation of GCM.

K_{inm} First-order rate constant for chloroacetyl chloride formation.

K_m Michaelis constant for oxidative pathway.

K_0 Zero-order glutathione synthesis, time and GSH dependent.

$K_{0'}$ Glutathione synthetase formation.

K_1 First-order rate constant for glutathione breakdown.

$K_{1'}$ First-order rate constant for glutathione synthetase breakdown.

MAT Metabolite available for toxicity.

V_{max} Maximum velocity of oxidative pathway.

* Reproduced from: D'Souza and Anderson 1988.

Parameters Used In The 1,1-Dichloroethene PB-PK Model	
Partition Coefficients	
Liver:blood	1.1
Richly perfused:blood	1.1
Slowly perfused:blood	0.6
Fat:blood	18.4
Blood:air	5.0
Kinetic Constants	
V_{max} (mg hr^{-1})	2.6
K_m (mg liter^{-1})	0.25
K_{gsm} ($\mu M^{-1} hr^{-1}$)	0.33
K_{fee} (hr^{-1})	50
K_{inm} (hr^{-1})	9000
K_{co_2} ($M^{-1} hr^{-1}$)	1.82×10^{-5}
H_2O (M)	55

dose levels. This model, which the study authors verified experimentally, is useful in predicting the kinetics and potential toxicity of 1,1-dichloroethene under various exposure conditions.

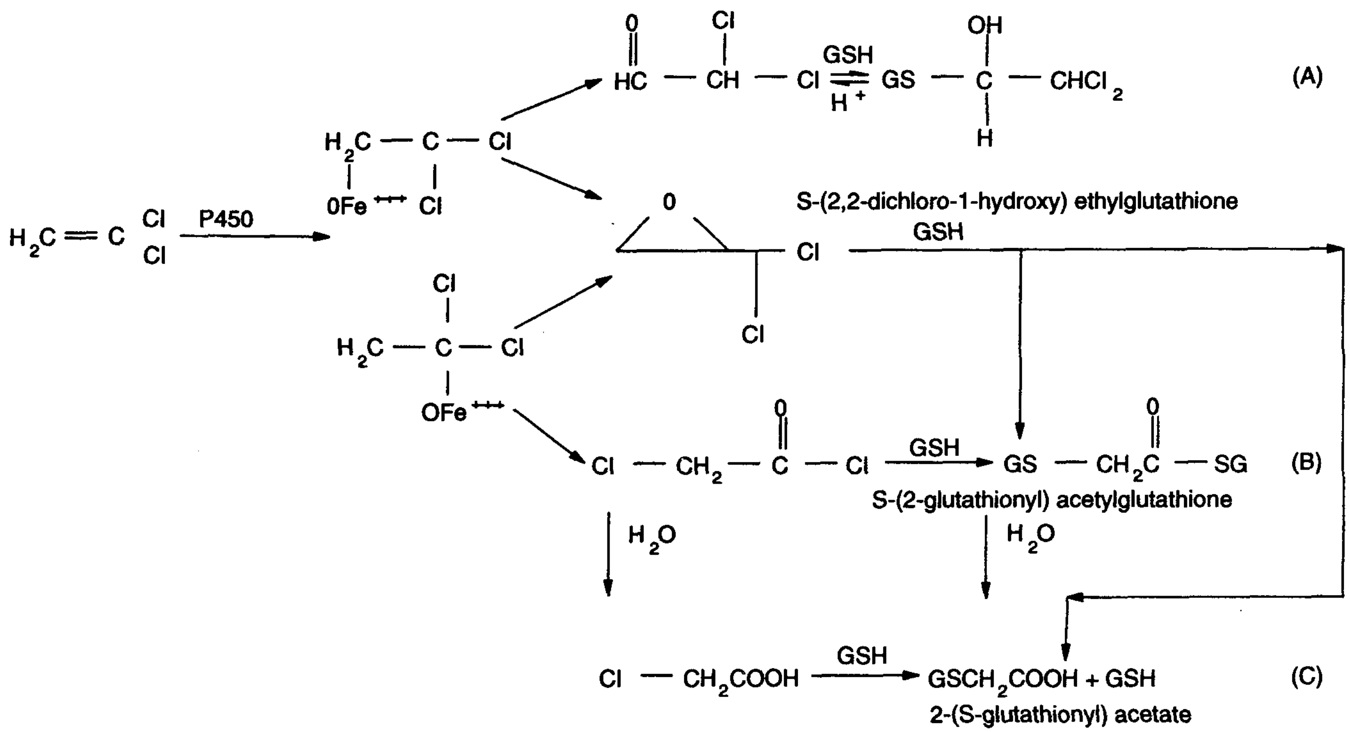
The hepatic cytochrome P-450 isozyme, P-450 2E1, is believed to play a role in the metabolic toxification of DCE in the liver (Kainz et al. 1993). An initial step in the metabolism of 1,1-dichloroethene may be the formation of the epoxide (oxirane) intermediate, 1,1-dichloroethylene oxide; however, this reactive compound has never been isolated after 1,1-dichloroethene administration in laboratory animals (Jones and Hathway 1978b; McKenna et al. 1977; Reichert et al. 1979).

An alternate metabolic scheme that does not go through the epoxide intermediate was proposed based on studies in isolated hepatocytes by Liebler et al. (1985, 1988) and is presented in Figure 2-6.

The main biotransformation pathways for 1,1-dichloroethene in the rat may involve conjugation with GSH, either with the epoxide or following rearrangement of the epoxide to chloroacetylchloride, with subsequent hydrolysis to monochloroacetic acid. This is consistent with the observation that exposure to 1,1-dichloroethene depletes GSH levels in the liver (Jaeger et al. 1974; Reichert et al. 1978; Reynolds et al. 1980). For example, Reynolds et al. (1980) reported a linear relationship in rats between intraperitoneally administered 1,1-dichloroethene and GSH depletion over the range of 20-100 mg/kg; above this level GSH depletion reached a plateau. The maximum reduction seen (70%) occurred 4 hours after treatment, with a subsequent gradual recovery to normal levels within 24 hours. These findings have led several investigators to suggest that 1,1-dichloroethene-induced hepatotoxicity is related to the depletion of hepatic GSH levels, thereby permitting the reactive intermediate to bind to and alkylate hepatic macromolecules instead of being detoxified, ultimately leading to cell death (Jaeger et al. 1974; McKenna et al. 1977, 1978a; Reynolds et al. 1980).

Conjugation of monochloroacetic acid with GSH followed by β-thionase activity appeared to be the major metabolic route on a quantitative basis in rats since thiodiglycollic acid was the predominant urinary metabolite (Jones and Hathway 1978a), this metabolite, however, only comprised 25% of ^{14}C urinary activity in another study (McKenna et al. 1978c). Forty-five percent of the activity was contributed by *S*-(2-hydroethyl)-*N*-acetylcysteine. Other metabolites

FIGURE 2-6. General Proposed Scheme for Oxidative Conjugative Metabolism of 1,1-Dichloroethene Not Metabolized Via the Epoxide Intermediate*



*Reproduced from Liebler et al. (1985)

identified in this pathway include monochloroacetic acid itself, thioglycolic acid, and dithioglycollic acid. However, direct GSH detoxication of the epoxide also apparently occurred to a significant degree, as demonstrated by the formation of glutathionyl acetyl chloride with subsequent breakdown to an *N*-acetyl cysteine derivative.

Evidence suggests that enzymatic hydration of the epoxide by epoxide hydrolase is a minor pathway in the metabolism of 1,1-dichloroethene in rats. Exacerbation of 1,1-dichloroetheneinduced toxicity in rats by diethyl maleate and various epoxide inhibitors following inhalation exposure was directly related to their ability to decrease GSH levels, rather than their ability to competitively inhibit epoxide hydrolase (Andersen et al. 1980).

An alternative metabolic pathway (i.e., one not involving GSH conjugation) to account for the presence of the metabolite methylthioacetylaminoethanol was proposed by Reichert et al. (1979). They suggested that chloroacetylchloride, instead of being hydrolyzed to monochloroacetic acid, reacts with membrane phosphatidyl ethanolamine, which is enzymatically cleaved to yield the ethanolamine derivative of chloroacetic acid. The thiomethyl group is then probably transferred from methionine to the metabolite as a result of direct nucleophilic attack.

The pathways of 1,1-dichloroethene metabolism in the mouse were similar to those seen in the rat except that the rate of metabolism was greater in the mouse (i.e., a greater proportion of administered 1,1-dichloroethene was metabolized per given dose level by the mouse than the rat) (Jones and Hathway 1978a). A predominant urinary metabolite of 1,1-dichloroethene found in mice was the *N*-acetylcysteine derivative produced by GSH conjugation to detoxify the epoxide intermediate. In mice there were quantitatively greater amounts of water-soluble urinary metabolites present in the urine (and consequently less parent compound in the expired air) attesting to a greater metabolic capacity. Furthermore, β-thionase activity was more pronounced since more dithioglycollic acid was found than thiodiglycollic acid (Jones and Hathway 1978a). In addition, Oesch et al. (1983) pointed out that 1,1-dichloroethene may have different effects on cytosolic GSH transferase activity and that this difference may have contributed to the species differences observed.

^{14}C- 1,1-DICHLOROETHENE covalently binds preferentially to liver and kidney tissues following administration, which may provide a basis f& the toxic effects seen in these organs (Jaeger et al.

1977a; McKenna et al. 1977, 1978a). A linear increase in the amount of covalently nound radioactivity in the liver of rats exposed to 10-200 ppm ^{14}C- 1,l -dichloroethene by inhalation for 6 hours was reported by McKenna et al. (1977). However, GSH depletion plateaued at about 200 ppm. Therefore, the actual amount of reactive metabolite formed and available for binding was probably determined by a combination of both activation and detoxication pathways.

The increased severity of hepatotoxic and nephrotoxic effects induced by 1,1-dichloroethene in the mouse, compared to the rat, may be partially explained by the observation that greater amounts of covalently bound reactive material were found in these two tissues in the mouse than in the rat following exposure to the same dose of 1,1-dichloroethene (McKenna et al. 1977). Levels of covalently bound material were six times higher in the mouse kidney than in the rat kidney (McKenna et al. 1977). Similar results were reported by Short et al. (1977d) when a single dose of ^{14}C-1,1-dichloroethene was injected intraperitoneally into mice. The highest level of covalently bound radioactivity was seen in the mouse kidney. The study authors found that pretreatment with disulfiram also reduced the amount of covalent binding. The study authors speculated that disulfiram may reduce the activation of 1,1-dichloroethene and increase the extent of its detoxification. Thus conjugation of reactive intermediates of l,l-dichloroethetle with GSH is a major detoxification mechanism in laboratory animals because it reduces the amount of reactive material available to covalently bind to cellular macromolecules.

1,1-dichloroethene can also potentially form adducts with hemoglobin, as has been observed with ethylene oxide (Tornyvist et al. 1986). Electrophilic intermediates, such as the epoxide formed in 1,1-dichloroethene metabolism, may bind to proteins in hemoglobin, similar to reactions demonstrated for liver and kidney (McKenna et al. 1977).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans following inhalation exposure to 1,l -dichloroethene.

Elimination of 1,1-dichloroethene by rats following inhalation exposure to low levels is rapid, with the majority of the compound eliminated as metabolites in the urine, and very little (1% of the administered dose) eliminated as the unchanged parent compound in the expired air (McKenna et al. 1973). After exposure to low levels (25-150 ppm) of 1,1-dichloroethene, steady-state levels of 1,1-dichloroethene in the expired air are achieved within 30-45 minutes, indicating that elimination is first-order at low levels of exposure (Dallas et al. 1983). Steady-state levels of 1,1-dichloroethene in expired air are never reached when exposure levels approach 200-300 ppm because metabolic processes are saturated. When metabolic processes become saturated, increased amounts of 1,1-dichloroethene can easily be eliminated unchanged via the lung, since 1,1-dichloroethene is volatile (VP=500 torr at 20°C) and relatively insoluble in blood. Following cessation of exposure, concentrations of 1,1-dichloroethene in both blood and breath were observed to fall rapidly (Dallas et al. 1983). Similar results were reported by McKenna et al. (1978b).

1, 1-dichloroethene exhibited a biphasic elimination profile following inhalation exposure in rats (McKenna et al. 1978b). The first phase had a half-life of about 20 minutes for the elimination of unchanged 1,1-dichloroethene in breath and 3 hours for the elimination of water-soluble metabolites in urine. The second phase had a half-life of about 4 hours in breath and 20 hours in urine. The bulk of the material was eliminated in both the breath and the urine during the rapid phase. Fasting did not appear to affect the elimination kinetics of 1,1-dichloroethene following inhalation exposure in rats (McKenna et al. 1978b).

Information is limited on elimination in mice following inhalation exposure to 1,1-dichloroethene. However, McKenna et al. (1977) reported that at low levels of exposure (10 ppm for 6 hours), somewhat smaller amounts of unchanged 1,1-dichloroethene were eliminated in the expired air of mice and larger amounts of water-soluble metabolites were found in the urine of mice compared to levels observed in rats. This indicates that mice metabolize 1,1-dichloroethene at a greater rate than rats.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,1-dichloroethene.

Elimination of 1,1-dichloroethene and its metabolites following oral administration in rats is very similar to that seen following inhalation exposure. Following oral administration of 1 mg/kg ^{14}C-1,1-dichloroethene in corn oil, less than 1% of the administered dose was excreted unchanged in the expired air, with 8-14% of the administered dose recovered as ^{14}C-carbon dioxide. The bulk of the administered ^{14}C-1,1-dichloroethene (44-W% of the administered dose) was eliminated in the urine within 3 days, most within the first 24 hours. Smaller amounts of water-soluble metabolites (8-16% of the administered dose) were found in the feces (Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979). Following the oral administration of higher doses to rats (50 mg/kg ^{14}C-1,1-dichloroethene), a higher proportion of unchanged parent compound (16-30% of the administered dose) was excreted in the breath with a concomitant reduction in the amount of expired carbon dioxide (3-6% of the administered dose) and urine metabolites (35-42% of the administered dose) (Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979). Similar but more marked trends were observed at even higher doses (Chieco et al. 1981; Jones and Hathway 1978b). Thus, metabolic processes become saturated at rather low dose levels.

The elimination of orally administered 1,1-dichloroethene is triphasic according to Putcha et al. (1986); however, McKenna et al. (1978b) and Reichert et al. (1979) reported that elimination is biphasic. The first phase identified by Putcha et al. (1986) occurred almost immediately, within the first few minutes after exposure, and the second two phases corresponded to those observed by the other investigators. Half-lives for the two phases of elimination after inhalation exposure were 20 minutes and 1 hour in the breath and 6 hours and 17 hours in the urine.

The amount of food ingested in the previous 24 hours slightly modifies the elimination of 1,1-dichloroethene by rats after oral administration. It was found that 19% of a 50-mg/kg dose was excreted unchanged via the lungs of nonfasted rats, whereas 29% was excreted by fasted rats (McKenna et al. 1978b). This finding provides evidence that fasted rats eliminate unchanged 1,1-dichloroethene to a greater extent than nonfasted rats. However, elimination of nonvolatile metabolites was slightly greater in nonfasted animals than in fasted animals, indicating a reduced capacity for metabolism in fasted rats.

Mice eliminate more 1,1-dichloroethene as water-soluble metabolites in the urine than do rats at comparable doses (Jones and Hathway 1978a). These results suggest that mice also metabolize orally administered 1,1-dichloroethene to a greater extent than rats.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of 1,1-dichloroethene in humans or animals following dermal exposure to 1,1-dichloroethene.

2.3.4.4 Other Routes of Exposure

Using the physiologically based pharmacokinetic model developed for 1,l -dichloroethene discussed in Section 2.33, D'Souza and Anderson (1988) demonstrated that the half-life of 1,1-dichloroethene in blood is not representative of metabolism rates, but rather more closely corresponds to reeyuilibration of 1,1-dichloroethene from fat. Consequently, rats with a greater amount of fat deposits had longer 1,1-dichloroethene blood half-lives following intravenous administration. This finding could have important implications for obese individuals exposed to high levels of 1,1-dichloroethene.

2.3.5 Mechanisms of Action

The specific mechanism by which 1,1-dichloroethene is transported across the gastrointestinal wall or across the pulmonary epithelium is not known. However, because of its high lipid solubility, it is expected that 1,1-dichloroethene will easily penetrate biological membranes following a concentration gradient. Similarly, no information was found regarding the mechanism by which 1,1-dichloroethene is transported in the blood; however, it is reasonable to assume that I,1 dichloroethene will dissolve in the lipid fraction of the blood.

It is well known that the toxicity of 1, 1-dichloroethene is due to biotransformed 1,1-dichloroethene and not to the parent compound (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978c). 1,1-dichloroethene is initially oxidized by the hepatic cytochrome P-450 system with the formation of reactive and electrophilic products such as epoxides, acyl chlorides, and halogenated aldehydes, which are responsible for the liver toxicity via alkylation of macromolecules (Forkert et al 1986). These reactive intermediates form GSH *S*-conjugates by the action of glutathione *S*-transferases located in the hepatic cytosol and microsomes. GSH *S*-conjugates that are primarily secreted from the hepatocytes into plasma and *S*-conjugates entering the circulation after reabsorption from the small intestine are ultimately delivered to the kidney where they undergo glomerular filtration (Dekant et al. 1989). In the kidney, GSH Sconjugates may be metabolized to the corresponding cysteine S-conjugate, which may be acetylated to form the corresponding mercapturic acid and excreted in the urine (Vamvakas and Anders 1990). However, cysteine S-conjugates may also be metabolized by β-lyase, an enzyme located in the renal proximal tubule cells; the resulting unstable thiols in turn yield electrophilic products whose interactions with macromolecules are associated with nephrotoxicity. In summary, GSH *S*-conjugate formation of nephrotoxic haloalkenes competes with hepatic cytochrome P-450 for substrates. The relative extent of these reactions *in vivo* appears to be decisive for the initiation of adverse effects either in the liver (via oxidation products generated by P-450 system) or in the kidney (via formation and renal processing of S-conjugates).

2.4 RELEVANCE TO PUBLIC HEALTH

Exposure to 1,l -dichloroethene in an occupational setting is most likely to occur via a combination of the inhalation and dermal routes. The general population is most likely to be exposed to 1,1-dichloroethene by inhalation of contamination and oral consumption of contaminated food or water. Limited information is available on the human health effects following exposure to 1,1-dichloroethene. This information comes primarily from case reports and/or insufficiently detailed mortality studies wherein the concentration and duration of exposure to 1,1-dichloroethene were not quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Nevertheless, the information available indicates that relatively high concentrations of inhaled 1,1-dichloroethene can induce adverse neurological effects after acute-duration exposure, and that 1,1-dichloroethene is associated with liver and kidney toxicity in humans after repeated, low-level exposure. Considerable information exists regarding the effects of 1,1-dichloroethene in animals after inhalation and oral exposure. The liver and kidney, and possibly the lungs, can be considered target organs for 1,1-dichloroethene by both routes of exposure. In addition, cardiovascular, neurological, developmental, and genotoxic effects were reported after inhalation of 1,1-dichloroethene, and gastrointestinal effects occurred after oral exposure. The evidence for 1,1-dichloroethene carcinogenicity is inadequate in humans and is limited in animals. Information regarding toxicokinetics in animals suggests that 1,1-dichloroethene does not tend to accumulate in the body. Background levels found in air and drinking water supplies (see Section 5.4) are not likely to cause adverse health effects in humans. For populations living near waste sites and/or facilities that manufacture or store 1,1-dichloroethene, the most likely routes of exposure are inhalation and oral (through contaminated water).

There is convincing evidence from animal studies to indicate that 1,1-dichloroethene toxicity is mediated by metabolism to reactive intermediates that act at the cellular level to ultimately compromise the viability of the target tissues. While the metabolic pathways for 1,l -dichloroethene are similar in the rat and mouse, the rate of metabolism is greater in the mouse, resulting in greater concentrations of toxic metabolites. Thus, the severity of 1,1-dichloroethene-induced toxicity in humans probably depends on the extent to which 1,1-dichloroethene is metabolized and which intermediates are formed.

Groups of people who should be specifically cautioned against exposure to 1,1-dichloroethene include the very young; the elderly; pregnant women; those who ingest alcohol; people using phenobarbital (or possibly other hepatic enzyme-inducing drugs); people who, for whatever reason, are fasting; and those with cardiac, hepatic, renal, and certain central nervous system dysfunctions.

Minimal Risk Levels for 1,1-Dichloroethene

Inhalation MRLs

- An MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to 1,1-dichloroethene. This MRL is based on a NOAEL of 5 ppm for hepatic effects in guinea pigs continuously exposed to 1,1-dichloroethene (Prendergast et al. 1967). Increased SGPT and alkaline phosphatase activity and decreased lipid content were observed at 48 ppm.

An MRL has not been derived for acute inhalation exposure (14 days or less) to 1,1-dichloroethene. A study by Reitz et al (1980) reported adverse kidney effects in mice exposed to 10 ppm for 6 hours. This appears to be the most sensitive end point identified; however, study limitations, such as the small number of animals used (three to six males) and the ambiguous description of the incidence of the lesions (0-20% of the animals), precluded derivation of an acute-duration inhalation MRL. In addition, an acute-duration MRL could not have been derived since the renal effects occurred at a lower concentration than did effects following intermediate-duration exposure to 1,l -dichloroethene.

An MRL has not been derived for chronic inhalation exposure (365 days or more) to 1,1-dichloroethene. Adverse hepatic effects were observed in rats exposed to a concentration of 25 ppm 1,1-dichloroethene 6 hours/day, 5 days/week, for 18 months (Quast et al. 1986). Few chronic inhalation studies were identified, and the one conducted by Quast et al. (1986) provided the most complete information and identified the most sensitive end point. However, a serious LOAEL of 15 ppm for developmental effects in rats and mice following acute exposure to 1,1-dichloroethene was reported by Short et al. (1977a) which precluded derivation of a chronic-duration inhalation MRL.

Oral MRLs

- An MRL of 0.009 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,1-dichloroethene. This MRL is based on the development of hepatocellular changes observed in rats exposed to 50 ppm 1,1-dichloroethene (converted by the investigators to a dose of 9 mg/kg/day based on body weight and water consumption data) in *utero*, during lactation, and through weaning into adulthood (Quast et al. 1983). These results are supported by several other chronic-duration studies that fc>und similar hepatic effects in rats at comparable doses of 1,1-dichloroethene.

An MRL has not been derived for acute oral exposure (14 days or less) to 1,1-dichloroethene. With the exception of a developmental study in rats (Murray et al. 1979), all the acute-duration studies administered a single dose of 1,1-dichloroethene, and although Murray et al. (1979) defined a NOAEL of 40 mg/kg/day, this NOAEL is too close to the 50-mg/kg dose that caused death in fasted rats (Andersen and Jenkins 1977).

An MRL has not been derived for intermediate oral exposure (15-364 days) to 1,1-dichloroethene. Only one study reported data after intermediate-duration exposure to 1,1-dichloroethene (Quast et al. 1983). This study could not define a dose-response relationship for any examined end point and reported a NOAEL of 25 mg/kg/day.

Death. No deaths have been reported in humans following 1,1-dichloroethene exposure.

1,1-dichloroethene was lethal to animals following acute exposures to high levels via the inhalation or oral routes. 1,1-dichloroethene-induced lethality appeared to be influenced by the fasting of the animal regardless of exposure route, with LD_{50} values for fasted animals generally significantly lower than those reported for nonfasted animals (e.g., Chieco et al. 1981; Jaeger et al. 1973c; Jenkins and Andersen 1978; Siegel et al. 1971). Young males appeared to be affected to a greater extent by fasting than females. Experimental evidence suggests that this enhanced toxicity in fasted animals resulted from increased levels of reactive intermediates of 1,1-dichloroethene available for binding to macromolecules in target tissues after fasting (McKenna et al. 1978b). Nonfasted rats that were exposed to 20,000 or 32,000 ppm of 1,1-dichloroethene by inhalation for 1 hour survived for at least 24 hours (Carlson and Fuller 1972). However, when comparable animals were pretreated with the microsomal enzyme inducers phenobarbital or methylcholanthrene, these exposure levels were lethal to nearly all of the animals within 2 hours, suggesting that lethality was due to increased formation of toxic metabolites. However, Carlson and Fuller (1972) found that pretreating rats with two different inhibitors of microsomal metabolism, which presumably would reduce the formation of reactive intermediates (SKF 525A and Lilly 18947), prior to inhalation exposure to 1,1-dichloroethene also reduced the survival time. Other inhibitors of microsomal metabolism (carbon disulfide and diethyldithiocarbamate) were found to protect mice against all 1,1-dichloroethene-induced toxic effects at low doses following intraperitoneal injection (Masuda and Nakayama 1983). These results indicate that biotransformation plays an important role in the expression of 1,1-dichloroethene-induced effects. Increased susceptibility of fasted animals to the lethal effects of 1,1-dichloroethene may occur because fasting depleted GSH in the target tissues and less GSH was available to bind to the active intermediate (Jaeger et al. 1973a).

Mice are more sensitive than rats to the lethal effects of inhaled 1,1-dichloroethene (see Figure 2-1) (Jaeger et al. 1974). This differential sensitivity also has been observed by the oral exposure route (Jenkins et al. 1972; Jones and Hathway 1978a). Pharmacokinetic studies suggest that, relative to rats, the rate of metabolism is higher in mice, resulting in a greater degree of damage from the increased levels of electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

Although animal studies indicate that amount of food ingested affects 1,1-dichloroethene-induced lethality, how the amount of food ingested prior to exposure affects the susceptibility of humans to the toxic effects of 1,1-dichloroethene is not known. Human subpopulations probably exist with differing biochemical capacities for 1,1-dichloroethene metabolism and thereby are more or less able to form reactive intermediates. It is not known whether these differing biochemical capacities would affect an individual's susceptibility to 1,1-dichloroethene-induced lethality. Orally ingested 1,l-dichloroethene at sufficiently high doses is likely to cause death in humans, and younger members (particularly males) of the population at hazardous waste sites may be at higher risk.

Systemic Effects

Respiratory Effects. No information regarding respiratory effects in humans was located.

Irritation of the mucous membranes of the upper respiratory tract and pulmonary congestion, hyperemia, and morphological changes were seen at necropsy in rats and mice acutely exposed to high levels of 1,1-dichloroethene via inhalation (Henschler 1979; Klimisch and Freisberg 1979a; Zeller et al. 1979b). Chronic inhalation exposure to 1,1-dichloroethene was associated with similar adverse respiratory effects (Gage 1970; Prendergast et al. 1967; Quast et al. 1986). These effects appeared to be rather nonspecific and probably resulted from 1,1-dichloroethene's irritating properties. Therefore, these data suggest that any possible nongenotoxic respiratory effects associated with inhalation exposure to 1,1-dichloroethene (particularly acute exposure) in humans may be a consequence of local nonspecific irritation.

However, a local nonspecific irritant effect cannot explain the pulmonary injury observed in mice following the oral administration of a single-dose of 1,1-dichloroethene. The effects seen included histopathological changes in Clara cells. These effects were considered reversible since cellular regeneration was evident within 3 days of treatment (Forkert et al. 1985). Clara cell degeneration, increases in covalent binding, and decreases in GSH content were also seen in mice following acute intraperitoneal administration of 1,1-dichloroethene (Forkert et al. 1986, 1990; Krijgsheld et al. 1984; Moussa and Forkert 1992). The relevance of these findings to prolonged human exposure is not known because the findings in the one oral study are not substantiated by other studies and because intraperitoneal administration is not a relevant route of administration in humans.

Cardiovascular Effects. No information was located regarding cardiovascular effects of 1,1-dichloroethene in humans.

Results obtained in experimental animals suggest that at high concentrations the myocardium is sensitized by 1,1-dichloroethene (Siletchnik and Carlson 1974). However, the relevance of these findings to prolonged human exposure is not known because the findings are not substantiated by other studies.

Hematological Effects. No information was found regarding hematological effects of 1,1-dichloroethene in humans.

Increased hemoglobin levels were reported in an acute oral study in rats fed 200 mg/kg/day 1,1-dichloroethene (Chieco et al. 1981). Given the lack of effects noted in animals in chronic-duration studies by the inhalation (Lee et al. 1977; Quast et al. 1986) and oral routes (Quast et al. 1983; Rampy et al. 1977), it seems unlikely that 1,1-dichloroethene would cause adverse hematological effects in humans.

Hepatic Effects. Information regarding hepatic effects of 1,1-dichloroethene in humans was limited to a reports of increased serum enzymes (indicative of liver injury) in occupationally exposed workers (Ott et al. 1976; EPA 1976). However, because of the incomplete reporting of the results, a clear relationship between exposure to 1,1-dichloroethene and development of adverse hepatic effects in humans could not be established.

Results from animal as well as human studies indicate that the liver is a primary target organ for 1,1-dichloroethene-induced toxicity. Hepatotoxicity in animals following both inhalation and oral exposure to 1,1-dichloroethene was manifested by biochemical changes (i.e., increases in serum enzyme markers of liver damage and induction of hepatic enzymes), and mild to marked histological changes (e.g., midzonal and/or centrilobular vacuolization, swelling, degeneration and necrosis). More severe hepatotoxic effects were seen in fasted animals (particularly males), compared to fed animals (Andersen and Jenkins 1977; Andersen et al. 1978, 1980; Chieco et al. 1981; Jaeger et al. 1974, 1975b; Jenkins and Andersen 1978; McKenna et al. 1978a; Reynolds et al. 1980). The increased susceptibility to 1,1-dichloroethene-induced hepatotoxicity seen in fasted rats is probably related to the depletion of GSH levels. The hepatotoxic effects of 1,1-dichloroethene were also found to be dependent on the vehicle used. For example, increased liver toxicity was observed in fasted rats given 1,1-dichloroethene in mineral oil or corn oil compared to administration of 1,1-dichloroethene in an aqueous solution (Chieco et al. 1981). This information has important implications with regard to humans, since oral exposure to 1,1-dichloroethene, particularly in individuals in close proximity to hazardous waste sites, will most likely be from groundwater.

Indirect evidence of the role of GSH in 1,1-dichloroethene-induced hepatotoxicity is provided by Jaeger et al. (1974) who demonstrated that diethyl maleate, a substance that depletes liver GSH levels, potentiates liver toxicity in nonfasted rats exposed to 1,1-dichloroethene via inhalation. Decreased levels of hepatic GSH were also reported in mice treated with 1,1-dichloroethene intraperitoneally (Forkert and Moussa 1991). In addition, thyroidectomy, a surgical procedure that results in increased liver GSH levels, has protected against 1,1-dichloroethene-induced hepatotoxicity and lethality, whereas thyroxine replacement restored or even potentiated the susceptibility of thyroidectomized animals to 1,1-dichloroethene-induced hepatotoxicity (Jaeger et al. 1977b; Szabo et al. 1977).

Results from *in vivo* studies suggest that 1,1-dichloroethene-induced hepatic injury may result from the formation of a reactive epoxide or other intermediate *in vivo* (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978c), which in turn binds to macromolecules in the target tissues. These intermediates are believed to be generated via the cytochrome P-450 mixed function oxidase system (Forkert et al. 1986).

Other subcellular mechanisms of 1,1-dichloroethene-induced toxicity have been proposed. For example, it has been suggested that 1,1-dichloroethene-induced inhibition of calcium-dependent ATPase may be the initial biochemical insult that triggers a sequence of events that may culminate in cell death (Luthra et al. 1984). Results of *in vitro* studies in liver perfusates have suggested that 1,1-dichloroethene metabolism reduces the viability of liver cells (Reichert et al. 1978). This was demonstrated by Kainz et al. (1993) who determined that mouse hepatocytes incubated with 1,1-dichloroethene experienced a concentration-dependent leakage of lactate dehydrogenase (LDH) into the cellular medium. Histochemical and biochemical evidence support the concept that plasma membranes and mitochondrial membranes may be the primary foci of acute hepatocellular injury in fasted rats (Jaeger 1977; Reynolds et al. 1980). Phospholipase A2 activation may also be part of the sequence of events (Glende and Recknagel 1992).

In conclusion, 1,1-dichloroethene induces hepatotoxicity in humans. This is supported by evidence in animals following both inhalation and acute and repeated oral exposures. However, humans, particularly those exposed by inhalation to high levels of 1,1-dichloroethene in occupational settings or in areas surrounding hazardous waste sites and those with compromised hepatic function, may be at risk for 1,1-dichloroethene-induced liver toxicity.

Renal Effects. No studies were located regarding renal effects in humans after exposure to 1,1-dichloroethene.

Renal toxicity (e.g., enzyme changes, hemoglobinuria, increases in organ weight, and tubular swelling, degeneration, and necrosis) has been observed following both inhalation and oral exposure to 1,1-dichloroethene in animals (Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978a; Oesch et al. 1983; Short et al. 1977d). Fasted animals (particularly males) were again more susceptible to these effects than nonfasted animals (Chieco et al. 1981; McKenna et al. 1978b), and mice were more susceptible than rats, as was seen for 1,1-dichloroethene-induced hepatotoxicity (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). There is some evidence that the kidney damage induced by acutely inhaled or ingested 1,1-dichloroethene may be reversible (Jenkins and Andersen 1978; Reitz et al. 1980), and the amount of reversibility is concentration and duration dependent. As indicated in Section 23.5, kidney toxicity has been attributed to the formation of cysteine S-conjugates that may be metabolized by β-lyase, located in the proximal tubule cells, to unstable thiols that yield electrophilic products that interact with macromolecules.

Though data on kidney toxicity in humans following exposure to 1,1-dichloroethene do not currently exist, evidence from animal studies in two species suggest that nephrotoxicity may also occur in humans, particularly following acute exposure to 1,1-dichloroethene. The fact that adverse renal effects were rarely seen following more prolonged exposure to 1,l-dichloroethene (except in male mice), coupled with the observation that the acute nephrotoxic effects at lower doses were reversible, suggest that up to a point the damaged cells can be replaced. The renal effects of chronic-duration exposure to 1,1-dichloroethene in humans are not known but are probably minimal at concentrations generally experienced.

Immunological Effects. No studies were located regarding immunological effects in humans and animals after 1,1-dichloroethene exposure by any route. Therefore, the potential for 1,1-dichloroethene to cause immunological effects in humans exposed in the environment or at hazardous waste sites cannot be assessed.

Neurological Effects. Central nervous system toxicity has been observed in humans acutely exposed to high concentrations (≈4,000 ppm) of inhaled 1,1-dichloroethene (EPA 1979b). Complete recovery occurred if exposure was not prolonged.

In addition, signs of central nervous system toxicity were the predominant effects observed in animals after acute inhalation exposure to high concentrations of 1,1-dichloroethene. These signs and symptoms observed in humans and in animals are consistent with a narcotic effect of 1,1-dichloroethene, which is observed with many other organic solvents. Effects on the nervous system were not observed following lower oral dose or repeated inhalation exposures to 1,1-dichloroethene in animals. However, these studies did not utilize comprehensive neurological testing that may have detected subtle neurological effects. The available information is insufficient to predict whether or not exposure to low levels of 1,1-dichloroethene by the inhalation, oral, or dermal routes of exposure represent a neurological hazard for humans.

Reproductive Effects. The only study reported in humans regarding reproductive effects of 1,1-dichloroethene provides only suggestive evidence of neural tube defects in newborns (NJDH 1992a, 1992b). Therefore, these data should be interpreted with caution.

Premating exposure of male rats to 1,1-dichloroethene by the inhalation route had no effect on reproductive end points (Anderson et al. 1977; Short et al. 1977b). Similarly, no reproductive effects were reported in a three-generation drinking water study with 1,1-dichloroethene in rats (Nitschke et al. 1983). The biological significance of these findings in animals with regard to potential reproductive effects of 1,1-dichloroethene in humans is not known.

Developmental Effects. The only study reported in humans regarding reproductive effects of 1,1-dichloroethene provides very weak suggestive evidence of neural tube defects in newborns (NJDH 1992a, 1992b). Therefore, these data should be interpreted with caution. An increased incidence of congenital cardiac malformations was observed in infants born to mothers who had consumed water contaminated mainly with trichloroethylene and to a lesser extent with 1,1 dichloroethene and chromium during the first trimester of pregnancy (Goldberg et al. 1990).

Although exposure to other chemicals was simultaneous, this finding may be relevant since 1,1-dichloroethene induced a dose-related increase in various congenital cardiac defects in rat fetuses after intrauterine administration of 1,1-dichloroethene to the dams (Dawson et al. 1990). Since 1,1-dichloroethene was not supplied by a natural route of exposure, the results of this study should be interpreted with caution (Dawson et al. 1990). Based on studies by Short et al. (1977a), 1,1-dichloroethene has weak teratogenic effects in laboratory animals (rats and mice). Developmental toxicity was enhanced following inhalation exposure to 1,1-dichloroethene, compared to oral exposure. Developmental toxicity was often observed at doses of 1,1-dichloroethene that also induce maternal toxicity in animals. Studies by Murray et al. (1979) demonstrated that the sensitivity of pregnant rats to 1,1-dichloroethene was greater by inhalation than by ingestion. After inhalation exposure at 80 and 160 ppm for 7 hours/day on gestation days 6-18, 1,1-dichloroethene produced maternal toxicity, increased resorption and skeletal alterations. Except for a marginal increase in mean fetal crown-rump length in the offspring, no adverse effects were noted in rats receiving 40 mg/kg/day in drinking water. The author hypothesized a possible mechanism to explain the route-dependent differences in 1,1-dichloroethene-induced toxicity was as follows: since detoxication of 1,1-dichloroethene occurred via conjugation of its active metabolites with GSH (McKenna et al. 1977) and GSH levels undergo diurnal variations (Jaeger et al. 1973a), was speculated that sufficient GSH levels were available to detoxify 40 mg/kg administered in drinking water over a 24-hour period, but not when the animals were exposed via inhalation between 8:30 am and 3:30 pm (Murray et al. 1979). When

1,l -dichloroethene doses are converted into equivalent units, animals exposed by inhalation received ≈76.6 and 153 mg/kg/day (assuming all 1,1-dichloroethene was absorbed by the lungs) compared to 40 mg/kg/day in drinking water. Thus, a difference in total dose may also explain the greater toxicity seen following inhalation exposure.

Based on studies in laboratory animals, it is prudent to consider that potential adverse maternal and developmental effects could occur in humans exposed to 1,1-dichloroethene.

Genotoxic Effects. The available data suggest that 1,1-dichloroethene produces genotoxic effects in a number of test systems. The results of *in vitro* and *in vivo* studies indicate that 1,1 -dichloroethene exhibited mutagenic properties upon metabolic activation (i.e., the presence of an exogenous mammalian metabolic system was required) in bacteria and yeast and that it induced gene conversion in yeast. It was also widely mutagenic in plant cells without activation by mammalian metabolic systems. 1,1-dichloroethene induced chromosome aberrations and sister chromatid exchanges in cultured mammalian cells *in vitro* and DNA damage in mice *in vivo.*

1,1-dichloroethene was genotoxic in several *in vitro* test systems. A metabolic activation system is usually required for activity. Results of *in vitro* genotoxicity studies are shown in Table 2-3. Gene mutations were observed in bacteria, yeast, and plant cells (Bartsch et al. 1975, 1979; Bronzetti et al. 1981; Greim et al. 1975; Jones and Hathway 1978c; Oesch et al. 1983; Van't Hof and Schairer 1982) and it induced gene conversion in yeast (Bronzetti et al. 1981; Koch et al. 1988). Dose-dependent increases in the frequency of euploid whole chromosome segregants were noted in *Aspergillus nidulans* (Crebelli et al. 1992). Both base-pair substitution and frameshift mutations were reported in *Salmonella typhimurium* after continuous exposure to 1,1-dichloroethene vapors (Bartsch et al. 1975, 1979; Jones and Hathway 1978c; Oesch et al. 1983). Another study reported negative results from tests in *Salmonella* (Mortelmans et al. 1986). However, the Mortelmans et al. (1986) study incorporated single doses of 1,1-dichloroethene into warmed incubation medium instead of exposing the bacteria continuously to vapor. Given that l,l-dichloroelhene is very volatile and would be expected to escape from the culture, continuous exposure to vapor is considered a mere reliable method. 1,1-dichloroethene was mutagenic in *Salmonella* after metabolic activation with an exogenous activation system derived from human liver cells (Jones and Hathway 1978c), thus supporting the ccmcept that the human liver is capable of activating 1,1-dichloroethene into mutagenic metabolites.

TABLE 2-3. Genotoxicity of 1,1-Dichloroethene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (desiccator test for exposure to gases)	Gene mutation	+	No data	Bartsch et al. 1979
S. typhimurium (gas exposure)	Gene mutation	+	-	Oesch et al. 1983
S. typhimurium (gas exposure)	Gene mutation	+	-	Bartsch et al. 1975
S. typhimurium (gas exposure)	Gene mutation	+	No data	Jones and Hathway 1978c
S. typhimurium (liquid preincubation test)	Gene mutation	-	-	Mortelmans et al. 1986
S. typhimurium (liquid preincubation test)	Gene mutation	+	-	Roldan-Arjona et al. 1991
Escherichia coli WP2	Gene mutation	+	-	Oesch et al. 1983
E. coli K12	Gene mutation	+	-	Greim et al. 1975
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	+	-	Bronzetti et al. 1981
S. cerevisiae D7	Gene conversion	+	-	Bronzetti et al. 1981
S. cerevisiae D7	Gene conversion	-	-	Koch et al. 1988
S. cerevisiae D7	Gene mutation	+	-	Koch et al. 1988
S. cerevisiae D61.M	Mitotic malsegregation	+	+	Koch et al. 1988
Aspergillus nidulans	Chromosome segregation	+	No data	Crebelli et al. 1992
Plant:				
Tradescantia clone 4430	Gene mutation	No data	(+)	Van't Hoff and Schairer 1982
Mammalian cells:				
Chinese hamster V79 cells	Gene mutation	-	No data	Drevon and Kuroki 1979
Chinese hamster CHL cells	Chromosomal	+	-	Sawada et al. 1987
Chinese hamster CHL cells	Sister chromatid exchange	(+)	-	Sawada et al. 1987
Mouse L5178Y lymphoma cells	Gene mutation	+	(+)	McGregor et al. 1991

- = negative result; + = positive result; (+) = weakly positive result

In cultured mammalian cells, 1,1-dichloroethene was negative in a point mutation assay in 8-azaguanine and ouabain-resistant V79 Chinese hamster lung cells (Drevon and Kuroki 1979), but it produced chromosomal aberrations and sister chromatid exchanges in a Chinese hamster lung fibroblast cell line (Sawada et al. 1987) and in mouse lymphoma cells (McGregor et al. 1991) in the presence of a metabolic activation system.

1,1-dichloroethene has also been tested in several *in vivo* studies in animals. Results of *in vivo* genotoxicity studies are shown in Table 2-4. Negative results were reported in assays for dominant lethal mutations in mice (Anderson et al. 1977) and rats (Short et al. 1977b) and in a micronucleus test in mice using both the bone marrow assay system following gavage administration and the transplacental assay system following intraperitoneal administration to pregnant mothers (Sawada et al. 1987). 1,1-dichloroethene inhalation was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats, compared to dimethylnitrosamine-treated controls. Furthermore, DNA repair mechanisms were induced in the kidneys of mice in cells in which normal replicative DNA synthesis had been inhibited. A significant increase in DNA repair rates was not observed in 1,1-dichloroethene treated mouse liver nor in the kidneys or liver of rats (Reitz et al. 1980). In a mouse host-mediated assay system, 1,1-dichloroethene was mutagenic and induced gene conversion in yeast (Bronzetti et al. 1981).

In vitro and *in vivo* studies indicate that 1,1-dichloroethene exhibits some mutagenic properties upon metabolic activation. But there is no direct evidence that exposure to 1,1-dichloroethene causes genotoxic effects in humans. However, the evidence that a metabolizing enzyme system derived from human liver could activate 1,1-dichloroethene into mutagenic metabolites (Jones and Hathway 1978c) suggests that 1,1-dichloroethene may be considered a potential genotoxic threat to humans. It must be mentioned, however, that human liver cells overlaid with mammalian tissue post-mitochondrial SC) (prepared from Aroclor 1254-induced rats) were activated, and human tissue not overlaid with S9 did not activate 1,1-dichloroethene into mutagenic metabolites (Jones and Hathaway 1978c).

Cancer. Data regarding carcinogenic effects of 1,1-dichloroethene in humans were limited to results from an occupational exposure study (Ott et al. 1976). The assumption is made that

TABLE 2-4. Genotoxicity of 1,1-Dichloroethene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse	Dominant lethals	-	Anderson et al. 1977
Rat	Dominant lethals	-	Short et al. 1977b
Mouse bone marrow	Micronuclei	-	Sawada et al. 1987
Mouse fetal liver and blood	Micronuclei	-	Sawada et al. 1987
Mouse kidney (DNA repair)	DNA damage	(+)	Reitz et al. 1980
Host-mediated assays:			
Saccharomyces cerevisiae (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1981
S. cerevisiae (mouse host-mediated assay)	Gene conversion	+	Bronzetti et al. 1981

- = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid exposure occurred mainly via inhalation, although dermal contact cannot be ruled out. Limitations in these studies, such as small cohort size and short observation periods greatly diminished their usefulness for assessing the carcinogenic potential of 1,1-dichloroethene in humans.

The carcinogenicity of 1,1-dichloroethene following inhalation, oral, dermal, and subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979) rats (Hong et al. 1981; Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986; Rampy et al. 1977; Viola and Caputo 1977) and Chinese hamsters (Maltoni et al. 1985). Of the carcinogenicity bioassays conducted to date, only the results of a single inhalation study in mice by Maltoni et al. (1985) provide evidence of a positive carcinogenic effect from 1,1-dichloroethene exposure. In this study, increases in renal adenocarcinomas were noted in male Swiss mice exposed to 25 ppm 1,1-dichloroethene via inhalation. Mammary gland carcinomas and lung tumors, most of which were benign pulmonary adenomas, were also observed in this study. Results of all other carcinogenicity studies with laboratory animals have been negative. Increases in a variety of malignant and nonmalignant tumors were reported in studies involving inhalation and oral exposure; however, these increases either were not statistically significant or were not considered by the respective authors to be exposure related (Lee et al. 1977, 1978; Maltoni et al. 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986). Study limitations for several of the investigations included less than lifetime exposure, use of doses below the maximum tolerated dose, small numbers of animals, and limited gross and microscopic examinations. Such limitations reduce the sensitivity of a bioassay system to detect a carcinogenic response.

The carcinogenicity of 1,1-dichloruethene in mice treated by dermal application and by subcutaneous injection was evaluated by (Van Duuren et al. 1979). 1,1-dichloroethene was inactive as a complete carcinogen when applied repeatedly for a lifetime to the skin of mice and did not induce local malignancies when administered chronically to mice by subcutaneous injection. However, a dermal initiation-promotion study with Swiss mice has shown that 1,1-dichloroethene was active as a tumor-initiating agent. A statistically significant increase in the incidence of skin papillomas was noted in Swiss mice treated dermally initially with 1,1-dichloroethene and subsequently with the tumor-promoting agent phorbol myristate acetate (Van Duuren et al. 1979).

On the basis of the suggestive inhalation study by Maltoni et al. (1985), 1,1-dichloroethene should be regarded as a possible animal carcinogen and, therefore, as a possible human carcinogen. Results of studies with laboratory animals indicating nonsignificant or non-dose-related increases in various malignant and nonmalignant tumors following oral or inhalation exposure provide limited but suggestive support that 1,1-dichloroethene may be a weak carcinogen (Lee et al. 1978, 1977; Maltoni et al. 1985; Ponomarkov and Tomatis 1980; Quast et al. 1986, 1983). The positive initiation-promotion study by Van Duuren et al. (1979) also suggests that 1,1-dichloroethene in concert with tumor-promoting agents can induce cancer, but a relationship between this test and human cancer has not been demonstrated.

In experimental studies with mice, it has been observed that doses of 1,1-dichloroethene that induce renal tumors also induce renal tissue damage (degeneration and necrosis) (Maltoni et al. 1985; Reitz et al. 1980; Watanabe et al. 1980). These tumorigenic doses, however, are associated in mice with only minimal DNA alkylation and DNA repair (Reitz et al. 1980). These findings suggest that kidney toxicity may play a contributing role in the induction of renal tumors (Watanabe et al. 1980), and that tumors observed in mice exposed to 1,1-dichloroethene may be the result of the chemical's toxic effect upon nongenetic carcinogenic mechanisms (Reitz et al. 1980). However, 1,1-dichloroethene is mutagenic in lower organisms and the same nephroses present in males was present in females but no tumors developed.

It has been suggested that the toxic and carcinogenic effects of 1,1-dichloroethene may depend on species, strain, and sex of the tested animals (Maltoni et al. 1985). Results of studies suggest that male Swiss mice are more susceptible to the toxic effects of 1,1-dichloroethene than female Swiss mice, rats, or hamsters (Maltoni et al. 1985; Oesch et al. 1983). Pharmacokinetic studies also suggest that compared to rats, mice have a greater rate of 1,1-dichloroethene activation to electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

NTP originally described the carcinogenic effects of oral administration of 1,1-dichloroethene in both sexes of Fischer-344 rats and B6C3F_1 mice as negative. This term has subsequently been changed to no evidence. EPA (IRIS 1992) has classified 1,1-dichloroethene as a Group C agent (possible human carcinogen). This category applies to chemicals for which there is limited evidence of carcinogenicity in animals and inadequate evidence in humans. IARC (1987) has classified 1,1-dichloroethene as a Group 3 chemical (not classifiable as to human carcinogenicity). 1,1-Dichloroethene is not included in the Sixth Annual Report on Carcinogens, which is a list of compounds that may reasonably be anticipated to be carcinogens published by the U.S. Public Health Service (NTP 1991).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time 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,l -dichloroethene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are 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 1,1-dichloroethene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to 1,1-dichloroethene

Exposure to 1,1-dichloroethene can be determined by the appearance of 1,1-dichloroethene in exhaled air and/or the appearance of metabolites such as dithioglycollic acid in urine (see Section 6.1). However, because 1,1-dichloroethene is rapidly eliminated from the body, such determinations can prove useful only for detecting recent exposure (within days). Furthermore, because other structurally similar compounds such as vinyl chloride can give rise to the same metabolic products as 1, 1-dichloroethene, formation of adducts with hemoglobin and detection of urinary metabolites cannot be considered as specific biomarkers of exposure to 1,l-dichloroethene.

Data from available studies have been insufficient to correlate levels of 1,1-dichloroethene in the environment with levels in breath. In an investigation of trace organic compounds in human breath, a 60-minute: sampling period yielded 13.0 μg of 1,1-dichloroethene in the breath (volume unspecified) of one individual (Conkle et al. 1975). This value was corrected for the amount of 1,l-dichloroethene in the air supplied to the individual during the sampling period. The study authors attributed the amount of 1,1-dichloroethene in the individuals's breath to previous exposure; however, no levels of previous exposure to 1,1-dichloroethene were reported for the test subject. The breath of 1 out of 12 subjects tested by Wallace et al. (1984) contained 1,1-dichloroethene; however, the levels were not specified. No environmental levels of 1,l-dichloroethene were reported for this study. Twelve percent of breath samples from 50 residents of New Jersey contained measurable amounts of 1,1-dichloroethene, ranging from 0.2 to 2 μg/m^3 of expired air (Wallace et al. 1986). Increased liver enzyme (AST, ALT) activities were reported in two workers exposed to 1,1-dichloroethene (Ott et al. 1976). However, these enzyme markers are not specific to 1,1-dichloroethene induced liver toxicity because they can be indicative of the detoxification process.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1 ,I -Dichloroethene

As indicated in Sections 2.2 and 2.3, the liver and kidney are primary target organs for 1,l -dichloroethene exposure. Exposure to 1,1-dichloroethene (depending on dose and duration of exposure) increases serum levels of certain liver enzymes such as SGOT (AST), SGPT (ALT), and others, which is taken as an indication of liver injury. However, this effect is caused by other halogenated alkenes as well such as vinyl chloride, and cannot be considered as a specific indicator of 1,l -dichloroethene effects.

Occupational exposure studies have investigated health effects associated with exposure to 1,1-dichloroethene. Because of the small cohort size and concurrent exposure to other compounds, the information from these studies is not sufficient to correlate levels of 1,1-dichloroethene in the environment with health effects. A study of 138 workers exposed to 1,1-dichloroethene (time-weighted-average concentrations ranging from <5 to 70 ppm) and copolymers other than 1,l -dichloroethene reported no statistically-related changes attributable to 1,l -dichloroethene in long-term mortality or health-inventory findings (Ott et al. 1976). No association between occupational exposure to 1,1-dichloroethene (with concurrent exposure to other chemicals) and incidence of angiosarcomas of the liver in workers was found by Waxweiler (1981).

Inhalation exposure to 50 ppm 1,1-dichloroethene was associated with minimal rates of DNA alkylation in liver and kidney cells of experimental rats and mice (Reitz et al. 1980).

Additional details regarding biomarkers of effects for 1,1-dichloroethene may be found in the CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990) or in the Office of Technology Assessment report on neurotoxicity (OTA 1990). A more detailed discussion of health effects attributed to exposure to 1,1-dichloroethene can be found in Section 2.2 of Chapter 2 in this document.

2.6 INTERACTIONS WITH OTHER CHEMICALS

As discussed in previous sections, it is apparent that the toxicity of 1,1-dichloroethene is largely due to the formation of toxic intermediates during metabolism *in vivo*. The production and biotransformation of toxic metabolic intermediates of 1,1-dichloroethene can be greatly influenced by various metabolic inhibitors and inducers, and by the availability of precursors of compounds involved in detoxication, such as GSH.

Microsomal mixed-function oxidases (MFOs) are a group of enzymes involved in the biotransformation and detoxication of xenobiotics such as 1,1-dichloroethene. Inhibitors of some microsomal MFOs include the compound SKF-525-A, disulfiram, and other dithiocarbamates, such as thiram and diethyldithiocarbamate. These compounds reduce the toxic effects of 1,1-dichlorethene in the liver, probably by inhibiting the enzymes responsible for the formation of reactive toxic intermediates (Masuda and Nakayama 1983; Short et al. 1977c). Pretreatment with intracellular cysteine precursor, L-2-oxothiazolidine-4-carboxylate is also used to protect against 1,1-dichloroethene toxicity in this way (Moslen et al. 1989b). Inhibitors of metabolic enzymes responsible for the breakdown of these reactive intermediates may also enhance the toxicity of 1,1-dichloroethene. For example, 1,1,1-trichloropropane and other inhibitors of epoxide hydrolase can potentiate the toxicity of 1,1-dichloroethene (Jaeger 1977). Other chemicals that reduce the activity of metabolic enzymes and show some protective effects against the toxicity of 1,1-dichloroethene include pyrazole, 3-aminotriazol (Andersen et al. 1978).

Pretreatment of rats with acetaminophen greatly increased lethality and the hepatotoxic effects of 1,1-dichloroethene (Wright and Moore 1991). Although the depletion of glutathione was not discussed, the study authors concluded that acetaminophen produces alterations that make hepatocytes more susceptible to 1,l-dichloroethene injury.

Enzyme inducers (enhancers) may either protect against or exacerbate the toxicity of 1,1-dichloroethene. Induction of enzymes involved in the formation of toxic intermediates potentiates 1,l -dichloroethene-induced toxicity following 1,1-dichloroethene exposure; conversely, induction of enzymes responsible for the biodegradation of the toxic intermediate(s) decreases toxicity. Examples of compounds that induce MFOs and increase toxic effects upon exposure to 1,1-dichloroethene include ethanol and acetone (Charbonneau et al. 1991; Hewitt and Plaa 1983;

Kainz et al. 1993; Sato et al. 1983). In acetone-pretreated rats, mixtures containing chloroform or carbon tetrachloride plus 1,1-dichloroethene increased hepatotoxic responses additively (Charbonneau et al. 1991).

Many inducers of MFO enzymes (e.g. P-450) do not increase the hepatotoxicity of l,l-dichlorocthene, perhaps because they stimulate enzyme systems not involved in the metabolism of 1,1-dichloroethene. An example of a P-450 inducer is phenobarbital (Carlson and Fuller 1972). Jenkins et al. (1971) found that pretreatment of rats with phenobarbital followed by oral administration with 1,1-dichloroethene had a protective effect against liver damage, while Carlson and Fuller (1972) found that pretreatment of rats with phenobarbital followed by inhalation exposure to 1,1-dichloroethene increased mortality but had no effect on hepatotoxicity. This discrepancy may be due to differences in routes of administration and indicators of toxicity examined.

Thyroidectomy protected rats from the hepatotoxic effects of 1,1-dichloroethene, probably by increasing the amount of hepatic GSH (Szabo et al. 1977). Thyroxine replacement in thyroidectomized rats exacerbated the liver damage seen upon subsequent exposure to 1,1-dichloroethene (Szabo et al. 1977).

Pretreatment of animals with compounds that deplete GSH levels (such as buthionine sulfoximine) increases the amount of liver damage caused by 1,1-dichloroethene exposure (Reichert et al. 1978). Conversely, pretreatment of animals with supplements containing high concentrations of the amino acids cysteine and/or methionine, both of which are metabolic contributors of the sulfhydryl group required for GSH biosynthesis, has had a protective effect against the toxicity of 1,1-dichloroethene (Short et al. 1977d).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1-dichloroethene than will most persons exposed to the same level of 1,1-dichloroethene in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the preexisting compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Specific information regarding human subpopulations that are unusually susceptible to the toxic effects of 1,1-dichloroethene were not located. However, animal studies have suggested that there are factors that may predispose some groups of the population to an increased risk for the toxic effects of 1,1-dichloroethene. These factors are discussed below.
The influence that dietary intake can have upon the metabolism and detoxification of xenobiotics

has been well documented. Fasting is known to modify the metabolism and toxicity of a variety of halogenated alkenes (Andersen et al. 1978; Nakajima et al. 1982). As discussed in previous sections, the liver MFO activity in fasted animals or animals kept on a low carbohydrate diet was enhanced when exposed to 1,1-dichloroethene, compared to that in similarly exposed control (carbohydrate-fed) animals (McKenna et al. 1978a; Nakajima et al. 1982). Fasting prior to 1,1-dichloroethene exposure resulted in an earlier appearance of hepatic lesions, a more extensive distribution of lesions and a reduced ability to metabolize high doses of 1,1-dichloroethene when compared to control (nonfasted) rats (Jaeger et al. 1974; McKenna et al. 1978a; Reynolds and Moslen 1977).

Sex differences in the toxic response to 1,1-dichloroethene have been observed in animals. For example, in a chronic inhalation exposure study in rats, hepatotoxic effects occurred at lower 1,1-dichloroethene concentrations in female rats than in male rats (25 and 75 ppm, respectively) (Quast et al. 1986). Fasted male animals, particularly young males, appear to be more susceptible to the toxic effects of 1,1-dichloroethene than fasted females, as evidenced by their enhanced responses at lower doses of 1,1-dichloroethene.

Individuals taking certain drugs or who have pre-existing liver, kidney, thyroid, or cardiac disease may be at greater risk for 1,1-dichloroethene-induced toxicity. Acetaminophen is prescribed to some rheumatic patients at doses up to 4 grams per day (Insel 1990). Such individuals may be highly susceptible to the effects of 1,l-dichloroethene (Wright and Moore 1991). Phenobarbital, even though somewhat protective against 1,1-dichloroethene-generated liver damage (Carlson and Fuller 1972), has sensitized the heart to 1,l -dichloroethene-induced arrhythmias (Siletchnik and Carlson 1974). Since phenobarbital is sometimes used as a soporific, and by those with various forms of epilepsy or seizure disorders, people who are taking this medication or those with pre-existing arrhythmic heart conditions should not be exposed to high levels of 1,l-dichloroethene. Ethanol increases the amount of 1,1-dichloroethene-induced hepatotoxicity observed in rats, which suggests that alcohol ingestion could exacerbate 1,1-dichloroethene-induced toxicity in exposed individuals. Therefore, individuals taking medicine that contains alcohol or individuals drinking alcoholic beverages may be more susceptible to the toxic effects of 1,1-dichloroethene. Thyroidectomy, either chemical or surgical, can protect against the hepatotoxicity associated with inhalation of 1,1-dichloroethene. Conversely, thyroxine treatment to replace or supplement normal thyroid function increases the amount of liver damage upon subsequent exposure to 1,1-dichloroethene in animals (Szabo et al. 1977). Individuals with liver or kidney disease or those with an acute hypersensitivity to 1,1-dichloroethene should avoid exposure to 1,1-dichloroethene.

Specific data concerning teratogenicity in humans exposed to 1,l-dichloroethene were not found in the literature. 1,1-dichloroethene has been described as a possible teratogen responsible for soft-tissue anomalies in rats and skeletal defects in mice, rats, and rabbits, often at levels that produced clear evidence of toxicity in the dam. It would be prudent for pregnant women to avoid exposure to 1,1-dichloroethene.

To conclude, groups of people who should be specifically cautioned against exposure to 1,1-dichloroethene include the very young; the elderly; the pregnant; those ingesting large amounts of acetaminophen as medication; those that ingest large amounts of alcohol; people using phenobarbital (or possibly other hepatic enzyme-inducing drugs); those receiving thyroid replacement therapy or those who are hyperthyroid; people who, for whatever reason, are fasting; and those with cardiac, hepatic, renal, and certain central nervous system dysfunctions.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,l -dichloroethene. 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 1,1-dichloroethene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Treatment for exposure to 1,1-dichloroethene is essentially supportive after the individual is removed from the contaminated environment (Haddad and Winchester 1990). The following steps have been suggested in an acute exposure situation to reduce the possibility of 1,1-dichloroethene absorption. If 1,1-dichloroethene is swallowed and the victim is conscious, water or milk can be administered to minimize mucosal irritation (Anonymous 1991). Activated charcoal can be administered to inhibit absorption in the intestine. Following dermal contact, the affected areas are flushed with water. No specific information was located regarding reducing peak absorption of 1,l -dichloroethene following inhalation exposure.

2.8.2 Reducing Body Burden

No information was located regarding retention of 1,1-dichloroethene or its metabolites in humans exposed to 1,1-dichloroethene. However, if the toxicokinetic mechanisms described in animals are suggestive for humans, the metabolites are eliminated mainly in the urine. Therefore, increasing diuresis may be a way of reducing the body burden of 1,1-dichloroethene metabolites.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located in the available literature regarding clinical or experimental methods that can block the mechanism of toxic action of 1,1-dichloroethene in humans.

Although the exact mechanism of action of 1,1-dichloroethene in humans is not known both humans and animal studies have identified the liver as the target organ for 1,1-dichloroethene. In experimental animals, 1,1-dichloroethene-induced hepatotoxicity is primarily due to reactive metabolic products that arise from biotransformation reactions initiated by the cytochrome P-450 enzymatic system. It is, therefore, not unreasonable to assume that 1,1-dichloroethene-induced liver toxicity in humans is also caused by 1,1-dichloroethene metabolites. If this premise is accepted, then two general types of biochemical manipulations could be envisioned to reduce 1,1-dichloroethene-induced toxicity. The first one would be to prevent biotransformation into reactive intermediates. This could be done by inhibiting enzymes responsible for these processes. The second alternative would be to ensure that adequate amounts of GSH are available (for example by administering precursors of GSH) in the liver in order to form S-conjugates with metabolic intermediates that can be eliminated in the urine. In fact, such interventions have been shown to protect against 1,1-dichloroethene-induced liver damage in rats (Moslen et al. 1989c). Based on the fact that I,l-dichloroethene does not appear to accumulate in tissues, these experimental procedures are likely to be more useful shortly after exposure to 1,1-dichloroethene rather than after prolonged exposure to low levels of 1,1-dichloroethene, which may occur to populations near waste sites.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1-dichloroethene 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 1,1-dichloroethene.

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

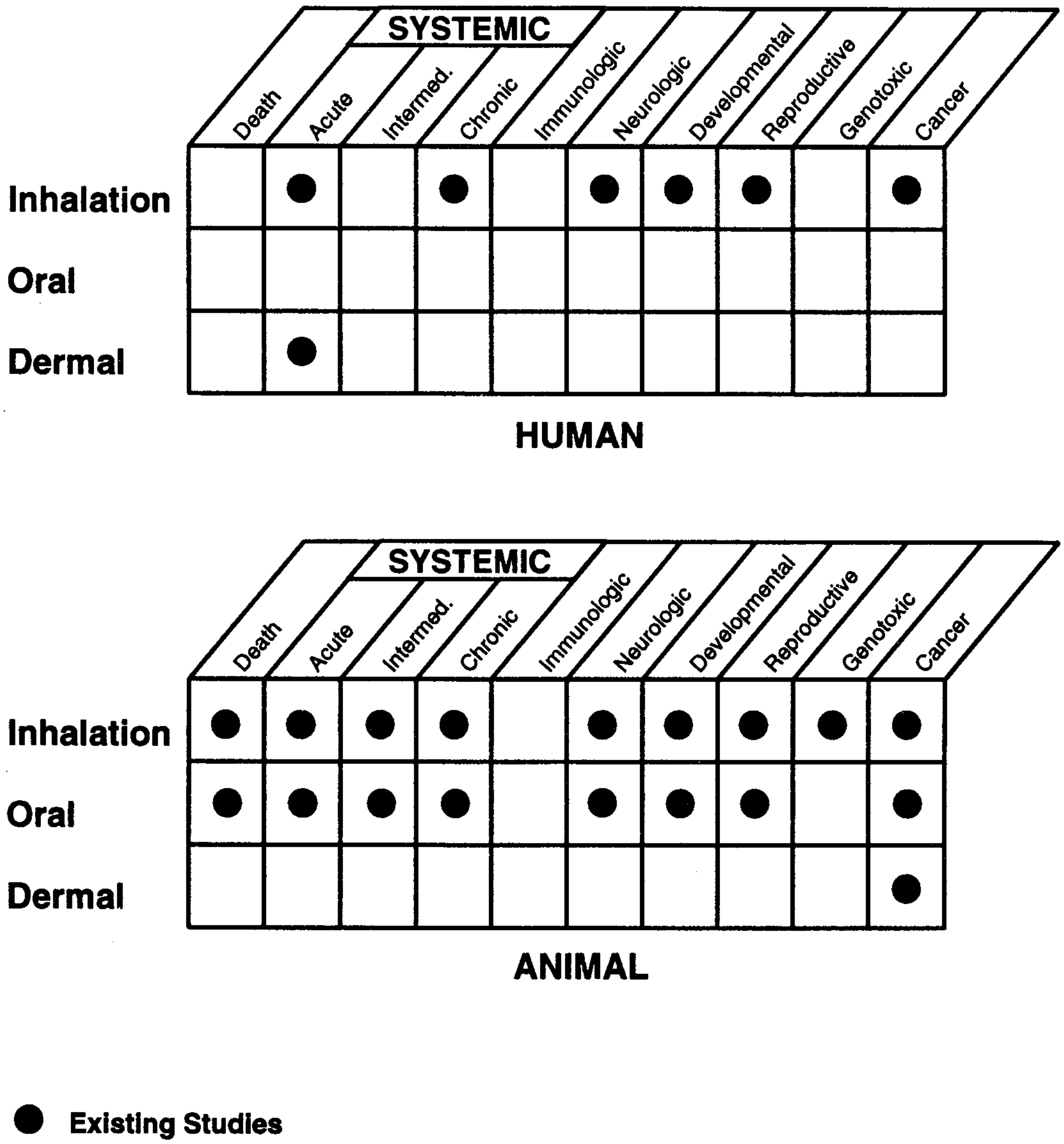
2.9.1 Existing Information on Health Effects of 1,1-Dichloroethene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethene are summarized in Figure 2-7. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1-dichloroethene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." 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.

Figure 2-7 depicts the existing health effects information on 1,1-dichloroethene for a specific route and duration of exposure. There is little information available concerning the long-term health effects of 1,1-dichloroethene in humans following inhalation exposure. Most of the information concerning health effects in humans is reported in occupational studies that are difficult to interpret because of limitations in study design (e.g., exposure levels and duration cannot be quantified and concurrent exposure to other toxic substances cannot be ruled out). No information concerning oral or dermal exposure to 1,1-dichloroethene in humans was found in the reviewed literature.

The systemic effects of 1,1-dichloroethene in animals following inhalation and oral exposure have been studied in a variety of species following acute, intermediate, and chronic exposure durations. No studies were located regarding immunological effects in humans or animals following inhalation or oral exposure. One oral exposure study reported observations of the "appearance" and "demeanor" of test animals, but this was not considered a good analysis of possible neurological or behavioral effects. Genetic effect end points were examined following inhalation exposure only. Carcinogenicity studies in animals following exposure by the oral, inhalation, and dermal routes are available.

FIGURE 2-7. Existing Information on Health Effects of 1,1-Dichloroethene



2.9.2 Identification of Data Needs

Acute-Duration Exposure. No data were located indicating specific organs or systems as targets for 1,l -dichloroethene in humans by any route of exposure. The data in experimental animals such as rats and mice suggest that the liver and kidneys are the primary targets for acute-duration exposure to 1,1-dichloroethene by inhalation and oral routes of exposure (Anderson et al. 1980; Chieco et al. 1982; Henck et al. 1979; Jenkins and Anderson 1978; McKenna et al. 1975; Moslen et al. 1989b; Reynolds et al. 1980). Data regarding the dermal route of exposure were not located. Although the kidney was. identified as the most sensitive organ in acute inhalation studies (Henck et al. 1979; McKenna et al. 1978b; Reitz et al. 1980), these studies were considered inadequate for derivation of an acute inhalation MRL, largely because of the small numbers of animals used and lack of clarity in the presentation of the results. The data in experimental animals were insufficient to derive an acute oral MRL mainly because the lowest dose associated with systemic effects (Moslen et al. 1989a) was also found to cause lethality in fasted rats (Anderson and Jenkins 1977). Information regarding the cause of death in the acuteduration studies would be useful. Acute-duration studies by the dermal route using ^{14}C-1,l -dichloroethene would provide useful information regarding absorption, distribution and kinetics of excretion. Results of these studies coupled with available knowledge on the toxicity and toxicokinetics should suffice. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for brief periods. Acute industrial exposure is, however, more likely. Pharmacokinetic data do not suggest route-specific target organs. Since 1,1-dichloroethene is rapidly excreted, it is not expected to accumulate in tissues.

Intermediate-Duration Exposure. No data were located that identified target organs in humans following intermediate exposure to 1,1-dichloroethene by any route of exposure. Information is available on the systemic toxicity of 1,1-dichloroethene following inhalation and oral exposure in rats, guinea pigs, dogs, and monkeys. These data indicate that the liver and kidneys are target organs for intermediate exposure to 1,1-dichloroethene (Prendergast et al. 1967). An MRL was derived for inhalation exposure based on hepatic effects in guinea pigs (Prendergast et al. 1967). Only one study was identified that described the effects of 1,1-dichloroethene in animals (dogs) after oral intermediate exposure (Quast et al. 1983). The lack of supporting data precluded derivation of an oral MRL. Additional studies conducted in rats via oral route for intermediate exposure would be useful for setting the maximum tolerated dose for oral chronic studies. Data on dermal exposure in animals are not needed. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for brief periods. There are no pharmacokinetic data that would suggest route-specific target organs.

Chronic-Duration Exposure and Cancer. No data were located that identified target organs in humans following chronic exposure to 1,1-dichloroethene by the oral and dermal routes. Hepatic effects described in occupationally exposed humans (EPA 1976) are supported by data in animals (Quast et al. 1983, 1986) but data from animal studies are sparse. An MRL was derived for oral exposure based on hepatic effects in rats (Quast et al. 1983). There are no pharmacokinetic data that would suggest route-specific target organs. Dermal exposure data are lacking. Studies with well-designed experiments and complete dose and time protocols, and measuring all sensitive toxicological end points, would provide valuable information on the health effects associated with long-term exposure to 1,l-dichloroethene. These chronic studies could provide information on subtle toxicological changes in organs associated with prolonged exposure to low levels of 1,l-dichloroethene. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for long periods.

Available data are insufficient to permit an evaluation of the carcinogenic risk of 1,1-dichloroethene in humans. The data from animal studies are limited in their usefulness because of flaws in the experimental design (e.g., doses that are too low) (Maltoni et al. 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). An inhalation study in mice described a positive carcinogenic response in the kidney (Maltoni et al. 1985). This study, however, has been regarded as inconclusive since it appears that tumors were not observed in the absence of nephrotoxicity. Swiss mice, in fact, are much more susceptible to the nephrotoxic effects of 1,1-dichloroethene than other species, or even other strains of mice. Additional information of the carcinogenicity of 1,1-dichloroethene from well conducted animal bioassays and epidemiological studies using various routes of exposure would be useful in predicting the likelihood that such a response occurs in humans.

Genotoxicity. No studies were identified that evaluated genotoxic effects of 1,1-dichloroethene in humans following any route of exposure, or in animals following oral or dermal exposure. Studies by the oral and dermal routes could help develop dose-response relationships for these routes. Several *in vitro* studies (Table 2-3 in Section 2.3.1.1) suggest that 1,1-dichloroethene, only in the presence of activating systems, is mutagenic in both prokarydc and eukatydc organisms. These results are consistent with the idea that a reactive metabolic intermediate(s), and not the parent compound, is (are) responsible for the genotoxic properties of 1,1-dichloroethene. With the exception of a weakly positive response in mouse kidney cells (Reitz et al. 1981), 1,1-dichloroethene tested negative in *in vivo* rodent assays following acute and intermediate inhalation or acute oral exposure to 1,1-dichloroethene (Anderson et al. 1977; Sawada et al. 1987; Short et al. 1977b). Cytogenetic analysis of human populations exposed to 1,1-dichloroethene in occupational settings would provide an opportunity to assess the genotoxic potential of this chemical in humans.

Reproductive Toxicity. The only study reported in humans regarding reproductive effects following oral exposure to 1,1-dichloroethene provides evidence of neural tube defects in children (NJDH 1992a, 1992b). However, these data are only suggestive and therefore, should be interpreted with caution. No information is available regarding reproductive effects of I,l-dichloroethene in humans following inhalation or dermal routes of exposure or in animals following dermal exposure. Only one multigeneration study was identified in rats (Nitschke et al. 1993). This study was conducted by the oral route, and the results were negative. Studies were identified that examined the reproductive effects of 1,1-dichloroethene after acute inhalation exposure in rats (Short et al. 1977b) and mice (Anderson et al. 1977). No adverse reproductive effects were observed in either one of these studies. Available pharmacokinetic data do not suggest route-specific target organs. Multigeneration studies by the inhalation and dermal routes would add information that could be relevant to humans.

Developmental Toxicity. The only study available in humans following oral exposure to 1,1-dichloroethene provides evidence of neural tube defects in children (NJDH 1992a, 1992b). However, these data are only suggestive and therefore, should be interpreted with caution. No relevant information is available indicating that 1,1-dichloroethene affects development in humans by any route of exposure or in animals following dermal exposure. Numerous studies have been conducted in rats by the inhalation route (Murray et al. 1979; Short et al. 1977a, 1977b). Based on the results of these studies no-observed-effect level could not be identified because the study authors did not use concentrations below those that produced adverse effects. Therefore, studies using lower exposure concentrations of 1,1-dichloroethene would provide useful information.

Only one oral exposure study in rats was located (Murray et al. 1979), and this study used only one exposure level. No pharmacokinetic data are available that would indicate the transplacental transfer of 1, l-dichloroethane. However, the available developmental toxicity studies suggest that l,l-dichloroethane can be potentially toxic to the developing fetus. Therefore, additional oral studies using a range of doses would provide useful information.

Immunotoxicity. No information is available indicating that the immune system is a target f& 1,1-dichloroethene in humans or animals. Batteries of immune function tests have not been performed in the available acute-, intermediate-, and chronic-duration studies. Studies conducti tests for immunocompetence and histopathological observations of organs and tissues involved il immunological response would provide valuable information. Dermal sensitization studies in animals might provide information on whether 1,1-dichloroethene is likely to cause an allergic response. Available toxicokinetic data do not suggest route-specific target organs.

Neurotoxicity. Neurobehavioral toxicity studies of acute inhalation exposures to 1,1-dichloroethene in both humans (EPA 1979b) and animals (Henschler 1979; Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979a, 1979b) are inadequate. This limited information suggests that the nervous system can be affected by exposure to rather high concentrations of 1,1-dichloroethene. Information by other routes of exposure is lacking. Available toxicokinetics data do not suggest route-specific target organs. Studies by the inhalation, oral, and dermal routes, as well as tests for neurological impairment in animals, might provide information that could be relevant to humans.

Epidemiological and Human Dosimetry Studies. Most of the available information on the adverse effects of 1,1-dichloroethene in humans comes from cases of acute poisoning occurring primarily in the workplace. Limitations inherent in these studies include unquantified exposures, concentrations and durations, as well as concomitant exposure to other toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods, and/or brief exposure periods. Despite their inadequacies, studies in humans indicate that 1,1-dichloroethene can cause central nervous system toxicity and irritation of the mucous membranes (EPA 1979b; Quast et al. 1986). There is also some evidence to suggest that repeated exposure to 1,1-dichloroethene is associated with liver damage in humans (EPA 1976). Well-controlled epidemiological studies of people living near areas where 1,1-dichloroethene has been detected in surface water and groundwater, in the vicinity of industries releasing 1,1-dichloroethene, near hazardous waste sites, and of people occupationally exposed could add to and clarify the existing database on 1,l-dichloroethene-induced human health effects. However, such studies would probably be very difficult to conduct since the majority of exposed workers are carpenters, warehousemen, and machine operators for whom exposure information and health follow-up is difficult to obtain, and the exposed population is either decreasing or difficult to define. Furthermore, a study of human populations residing near hazardous waste sites or production sites would also be difficult to conduct because of the difficulty in obtaining meaningful historical estimates of exposure, historical medical data, and comprehensive follow-ups.

Biomarkers of Exposure and Effect

Exposure. Information regarding populations exposed specifically to 1,1-dichloroethene is not available; therefore, no known biomarker of exposure to 1,1-dichloroethene has been identified in humans. However, if 1,1-dichloroethene is metabolically disposed of by humans in a way similar to that observed in animals, 1,1-dichloroethene in expired air could be a biomarker of recent exposure to relatively high concentrations of 1,1-dichloroethene.Similarly, urinary excretion of metabolites such as thioglycollic acid could also be considered a biomarker of recent exposure. It must be mentioned, however, that the urinary metabolites would not be specific biomarkers for 1,1-dichloroethene exposure since other chemicals have similar urinary metabolites. Hence, the development of methods to detect alternative biomarkers, specific to 1,l -dichloroethene exposure would be useful.

Effect. Information regarding populations exposed specifically to 1,1-dichloroethene is not available. Limited information indicate that serum levels of certain enzymes indicative of liver damage may be elevated in humans exposed to 1,1-dichloroethene (EPA 1976). However, the elevation of liver enzymes is triggered by exposure to many other chemicals; hence, elevation of these enzymes cannot be considered a specific biomarker for 1,1-dichloroethene. Research leading to the identification of specific DNA adducts formed after 1,1-dichloroethene exposure would be valuable. This would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation, oral, or dermal route. The animal data indicate that 1,1-dichloroethene is efficiently absorbed by the inhalation (Dallas et al. 1983; McKenna et al. 1978b) and oral routes (Jones and Hathway 1978a; McKenna et al. 1978a; Putcha et al. 1986). These studies have been conducted mostly in rats and mice. Dermal absorption data are lacking, but absorption by this route should be suspected based on the physical and chemical properties of 1,1-dichloroethene and the fact that the fact that the Sencor mouse test was positive for initiation of papillomas.

No data were located regarding distribution of 1,1-dichloroethene or its metabolites in humans. Animal data regarding inhalation exposure (Jaeger et al. 1977a) and oral exposure (Jones and Hathway 1978b) to 1,1-dichloroethene indicate that 1,1-dichloroethene (or metabolites) distributes preferentially to the liver, kidney, and lung and that in general 1,1-dichloroethene does not accumulate in tissues. Additional data on the distribution of 1,1-dichloroethene following dermal exposure would be useful since humans can be exposed via this route as well. Studies regarding distribution through the placenta were not available.

Data regarding biotransformation of 1,1-dichloroethene in humans are not available. The use of human cell systems in culture might be considered a useful alternative to studying the metabolic fate of 1,l dichloroethene in individuals. The metabolism of 1,l -dichloroethene has been extensively studied in rats and mice following inhalation and oral exposure (Jones and Hathway 1978a, 1978b; McKenna et al. 1977, 1978a; Reichert et al. 1979). Experimental evidence indicates that the metabolism of 1,1-dichloroethene is a saturable process. Although information regarding metabolism following dermal exposure is lacking, there is no reason to believe that other pathways would operate after exposure by this route.

Data regarding excretion of 1,1-dichloroethene in humans are not available. Urinary excretion of metabolites is the main route of elimination of 1,1-dichloroethene metabolites in animals after inhalation (McKenna et al. 1978b) and oral exposure (McKenna et al. 1978a; Reichert et al. 1979). After exposure to high concentrations of 1,l -dichloroethene, however, elimination of unchanged 1, 1-dichloroethene in expired air was observed (Jones and Hathway 1978b; McKenna et al. 1978a, 1978b; Reichert et al. 1979). No studies were located regarding excretion following dermal exposure to 1,l -dichloroethene.

Comparative Toxicokinetics. No direct information exists to assess whether humans handle 1,1-dichloroethene in a way similar to that observed in animals. Toxicokinetics studies have been performed mainly in rats and mice, and the results suggest that no qualitative differences exist between these two species, although mice seem to metabolize 1,1-dichloroethene to a greater extent than rats (Jones and Hathway 1978a, 1978b; McKenna et al. 1977, 1978a; Reichert et al. 1979). Experiments in animals (mostly rats and mice) indicate that the liver, kidney, and lungs are common target organs across species. Data from occupationally exposed humans suggest that the liver is a target organ in humans (EPA 1976). Once reliable end points are determined in species other than rats and mice, it would be important to verify that primates are affected in a similar manner, in order to ensure that no unforeseen health effects might occur in humans.

Methods for Reducing Toxic Effects. There are no specific established methods or treatment for reducing absorption of 1,l -dichloroethene. Studies aimed at elucidating this mechanism would provide useful information. No information is available regarding the mechanism by which 1,1-dichloroethene distributes to tissues in the body. There are no well-established methods or treatment for reducing the body burden of 1,1-dichloroethene or metabolites or for prevention of toxicity following long-term exposure. The mechanism of toxicity of 1,1-dichloroethene in humans is not known, but there is evidence that 1,1-dichloroethene toxicity in animals is due to a reactive intermediate and not the parent compound (Dekant et al. 1989; Vamvakas and Anders 1990). Experimental methods exist that can prevent the toxic action of 1,1-dichloroethene in animals (i.e., administration of precursors of GHS) (Moslen et al. 1989b), but it is not known whether these methods are relevant to humans. Studies in primates could provide information regarding the mechanism of action of 1,1-dichloroethene that may be more relevant to humans than data obtained in rats and mice. Methods for mitigation of the adverse health effects induced by 1,1-dichloroethene in animals have involved administering the substance prior to exposure (Anderson et al. 1978).

2.9.3 On-going Studies

Studies being conducted by C.H. Tamburro and coworkers at the University of Louisville School of Medicine will continue medical surveillance of chemical industry workers exposed to vinylidene chloride with regard to gastrointestinal, pulmonary, brain, and hematopoietic cancers (IARC lW2).

Studies by Mary T. Moslen and coworkers at the University of Texas Medical Branch at Galveston are using 1,1-dichloroethene to selectively damage bile canaliculi to study liver function (Moslen 1993).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for 1,1-dichloroethene are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of 1,1-dichloroethene are listed in Table 3-2.

TABLE 3-1. Chemical Identity of 1,1-Dichloroethene

Characteristic	Information	Reference
Chemical name	1,1-Dichloroethene	HSDB 1992
Synonym(s)	DCE; 1,1-dichloroethylene; 1,1-DCE; asym-dichloroethylene; VDC; vinylidene chloride; vinylidene chloride (II); vinylidene dichloride; vinylidine chloride	HSDB 1992
Registered trade name(s)	No data	
Chemical formula	$C_2H_2Cl_2$	Budavari 1989

Chemical structure	Cl — C = C — H
	        | |
	       Cl H
		Budavari 1989

Identification numbers:		
CAS registry	75-35-4	HSDB 1992
NIOSH RTECS	KV9275000	HSDB 1992
EPA hazardous waste	U078/D029	HSDB 1992
OHM/TADS	7216949	HSDB 1992
DOT/UN/NA/IMCO shipping	UN 1303; IMO 3.1	HSDB 1992
HSDB	1995	HSDB 1992
NCI	C54262	HSDB 1992

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 Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of 1,1-Dichloroethene

Property	Information	Reference
Molecular weight	96.95	Budavari 1989
Color	Colorless	Grayson 1985
Physical state	Liquid	Budavari 1989
Melting point, °C	-122.5	Budavari 1989
Boiling point, °C	31.7 at 760 mmHg	Budavari 1989
Density:		
at 20°C	1.213 g/cm^3	Budavari 1989
Odor	Mild sweet odor resembling that of chloroform	Budavari 1989
Odor threshold:		
Air	500 ppm	Torkelson and Rowe 1981
Solubility:		
Water at 25°C	2.5 g/L	HSDB 1992
Organic solvent(s)	Soluble in organic solvents	Budavari 1989
Partition coefficients:		
Log K_{ow}	1.32	HSDB 1992
Log K_{oc}	1.81	EPA 1982
Vapor pressure:		
at 20°C	500 mmHg	Verschueren 1983
at 25°C	591 mmHg	Torkelson and Rowe 1981
Henry's law constant:		
at 20–25°C	0.19 atm-m^3/mol	Pankow and Rosen 1988
Autoignition temperature	570.0°C	HSDB 1992
Flashpoint	-16°C (open-cup)	EPA 1985a
	-19°C (closed-cup)	EPA 1985a
Flammability limits	7.3–16%	Weiss 1986
Conversion factors	1 ppm = 3.97 mg/m^3	Verschueren 1983
	1 mg/m^3 = 0.25 ppm	Verschueren 1983
Explosive limits	5.6–11.4% v/v in air	Sax and Lewis 1987

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

4.1 PRODUCTION

1,1-dichloroethene does not occur naturally (EPA 1985a), but it is found as the result of the breakdown of polyvinylidene chloride products in landfills. It is produced commercially by the dehydrochlorination of 1,1,2-trichloroethane with excess lime or caustic. As an inhibitor of the polymerization reaction, 200 ppm γ-hydroxyanisole is added, then later removed by distillation or washing (Grayson 1985). Typically, a commercial grade contains 99.8% 1,1-dichloroethene (EPA 1985a).

1,1-dichloroethene polymerizes after the addition of an initiator by either an ionic or a free radial reaction. 1,1-dichloroethene can polymerize spontaneously at room temperature following addition of peroxides (Grayson 1985).

1,1-dichloroethene is manufactured in chemical plants located in Texas and Louisiana. Currently, there are two major producers, Dow Chemical and Pittsburgh Paint and Glass (PPG) Industries (Burke 1987; EPA 1977; SRI 1991). Production capacity in 1985 was 178 million pounds/year (EPA 1985a). This has decreased from 1977, when production capacity was estimated at 270 million pounds (EPA 1977). In 1988, plant capacity at PPG Industries was estimated at 64 million pounds/year (PPG Industries 1988). Estimated 1989 production is 230 million pounds (CMA 1989).

According to the 1991 Toxic Chemical Release Inventory (TRI), 23 facilities manufactured or processed 1,1-dichloroethene in 1991 (TRI91 1993). All 23 of these facilities reported the maximum amount of 1,1-dichloroethene that they would have on site. These data are listed in Table 4-l. The TRI data should be used with caution since only certain types of facilities are required to report.. This is not an exhaustive list.

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

Facility	Location[b]	Range of maximum amounts on site in pounds	Activities and uses
3M	DECATUR, AL	1,000-9,999	As a reactant
MONSANTO CO. CHEMICAL GROUP	DECATUR, AL	100,000-999,999	As a reactant
EASTMAN KODAK CO. KODAK COLORADO DIV.	WINDSOR, CO	1,000-9,999	As a reactant
DOW CHEMICAL DALTON SITE	DALTON, GA	0-99	As a reactant
MORTON INTERNATIONAL INC. (RIN)	RINGWOOD, IL	1,000,000-9,999,999	As a reactant
BF GOODRICH CO. LOUISVILLE PLANT	LOUISVILLE, KY	10,000-99,999	As a reactant
W. R. GRACE & CO.	OWENSBORO, KY	100,000-999,999	As a reactant
MARINE SHALE PROCESSORS INC.	AMELIA, LA	10,000-99,999	As a reactant
VULCAN MATERIALS CO. CHEMICAL DIV.	GEISMAR, LA	10,000-99,999	Produce; as a byproduct; as an impurity; as a reactant
DOW CHEMICAL CO. LOUISIANA DIV.	PLAQUEMINE, LA	1,000-9,999	Produce; as a byproduct; as a reactant; in ancillary or other uses
PPG INDUSTRIES INC.	WESTLAKE, LA	10,000,000-49,999,999	Produce; for sale/distribution; as a byproduct; as an impurity
DOW CHEMICAL USA MIDLAND SITE	MIDLAND, MI	10,000,000-49,999,999	As a reactant; in ancillary or other uses
RHONE-POULENC INC. WALSH DIV.	GASTONIA, NC	10,000-99,999	As a reactant
ALLIED-SIGNAL INC. ELIZABETH	ELIZABETH, NJ	10,000-99,999	As a reactant
DU PONT PARLIN PLANT IMAGING SYSTEMS DEPT.	PARLIN, NJ	1,000-9,999	As a reactant
ALLIED-SIGNAL INC.	BUFFALO, NY	10,000,000-49,999,999	As a reactant
EASTMAN KODAK CO. KODAK PARK	ROCHESTER, NY	1,000-9,999	As a reactant
GENCORP POLYMER PRODUCTS LATEX	MOGADORE, OH	100,000-999,999	As a reactant
OCCIDENTAL CHEMICAL CORP. VCM PLANT	DEER PARK, TX	10,000-99,999	Produce; as a byproduct
DOW CHEMICAL CO. TEXAS OPERATIONS	FREEPORT, TX	1,000,000-9,999,999	Produce; for sale/distribution; as a byproduct; as an impurity; in re-packaging; as a processing aid; in ancillary or other uses
OCCIDENTAL CHEMICAL CORP. CORPUS CHRISTI PLANT	GREGORY, TX	100-999	Produce; as a byproduct
HERCULES INC.	COVINGTON, VA	100,000-999,999	As a reactant
ARCO CHEMICAL CO.	SOUTH CHARLESTON, WV	100,000-999,999	As a reactant

[a] Derived from TRI91 (1993)
[b] Post Office state abbreviations used

4.2 IMPORT/EXPORT

In 1986, 217,000,000 pounds of 1,1-dichloroethene were imported into the United States (SRI 1987). No data are available on the export levels.

4.3 USE

Monomeric 1,1-dichloroethene is used as an intermediate for captive organic chemical synthesis and in the production of polyvinylidene chloride copolymers. These polymers, which have been commercially important since their introduction in the early 1940s are used extensively in many types of flexible packing materials (including barrier, multilayer, and monolayer), as flame retardant coatings for fiber and carpet backing, and in piping, coating for steel pipes, and adhesive applications (EPA 1977). The major application of polyvinylidene chloride copolymers is the production of flexible films for food packaging (SARAN and VELON wraps). 1,1-dichloroethene is found in many food and other packaging materials. At one time, SARAN wrap was found to contain up to 30 ppm 1,1-dichloroethene (Birkel et al. 1977). The plastic packaging films can contain no more than 10 ppm 1,1-dichloroethene (FDA 1988). The coating applicable to fresh citrus fruit (minimum amount required for intended use) is <25% aqueous solution (FDA 1982). Because of the instability of the polymer, 1,1-dichloroethene is usually used as a copolymer with acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate (Grayson 1985; Rossberg et al. 1986).

4.4 DISPOSAL

1,1-dichloroethene is classified as a llammable liquid (Weiss 1986). As such, the EPA (1987a) requires compliance with the regulations of the Resource Conservation and Recovery Act (RCRA) when producing, treating, transporting, storing, or disposing of this substance. Current disposal regulations of 1,1-dichloroethene require dissolving it in combustible solvents and scatter spraying the solvent into a furnace with an afterburner and alkaline scrubber. However, the criteria for land treatment and burial is undergoing significant revision (HSDB 1992). The waste mother liquor probably contains higher concentrations (>200 ppm) of the inhibitor, MEHQ.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

The primary sources of 1,1-dichloroethene in the environment are related to the synthesis, fabrication, and transport of 1,1-dichloroethene and the fabrication of its polymer products. Because of the volatile nature of the chemical, releases to the atmosphere are the greatest source of ambient 1,1-dichloroethene. Smaller amounts of the chemical are released to surface water and soil, primarily as a result of waste disposal. 1,1-dichloroethene in waste water should partition to the atmosphere as a result of volatilization during treatment processes. Most of the 1,1-dichloroethene released to the environment partitions to air or water, including groundwater (Table 5-l).

1,1-dichloroethene has been identified in at least 492 of the 1,350 hazardous waste sites on the EPA National Priorities List (NPL) (HAZDAT 1992). However, the number of sites evaluated for 1,1-dichloroethene is not known. The frequency of these sites can be seen in Figure 5-l. Of these sites, 1 is located in the Commonwealth of Puerto Rico (not shown).

1,1-Dichloroethene is rapidly transformed in the troposphere, where oxidation by hydroxyl radicals is the dominant transformation process. Biotransformation is believed to be the dominant transformation process for 1,1-dichloroethene in groundwater, although this process is probably not important in aerobic surface waters. Biotransformation in soil has not been studied extensively, but it has been shown to occur by methanogenic organisms. Biotransformation will be more important in subsurface soils, because 1,1-dichloroethene in surface soils will volatilize to the atmosphere. 1,1-dichloroethene has been detected in air, surface water, groundwater, and soil, with the frequency of detection and the concentrations greatest near source areas (e.g., industrial areas, landfills, hazardous wastes sites).

The potential for human exposure to 1,1-dichloroethene is greatest for those at its point of production, formulation, or transport. Occupational exposure to 1,l -dichloroethene may occur by inhalation or dermal contact. Members of the general public may be exposed by inhalation or by ingesting contaminated drinking water. Those who live near hazardous waste sites contaminated

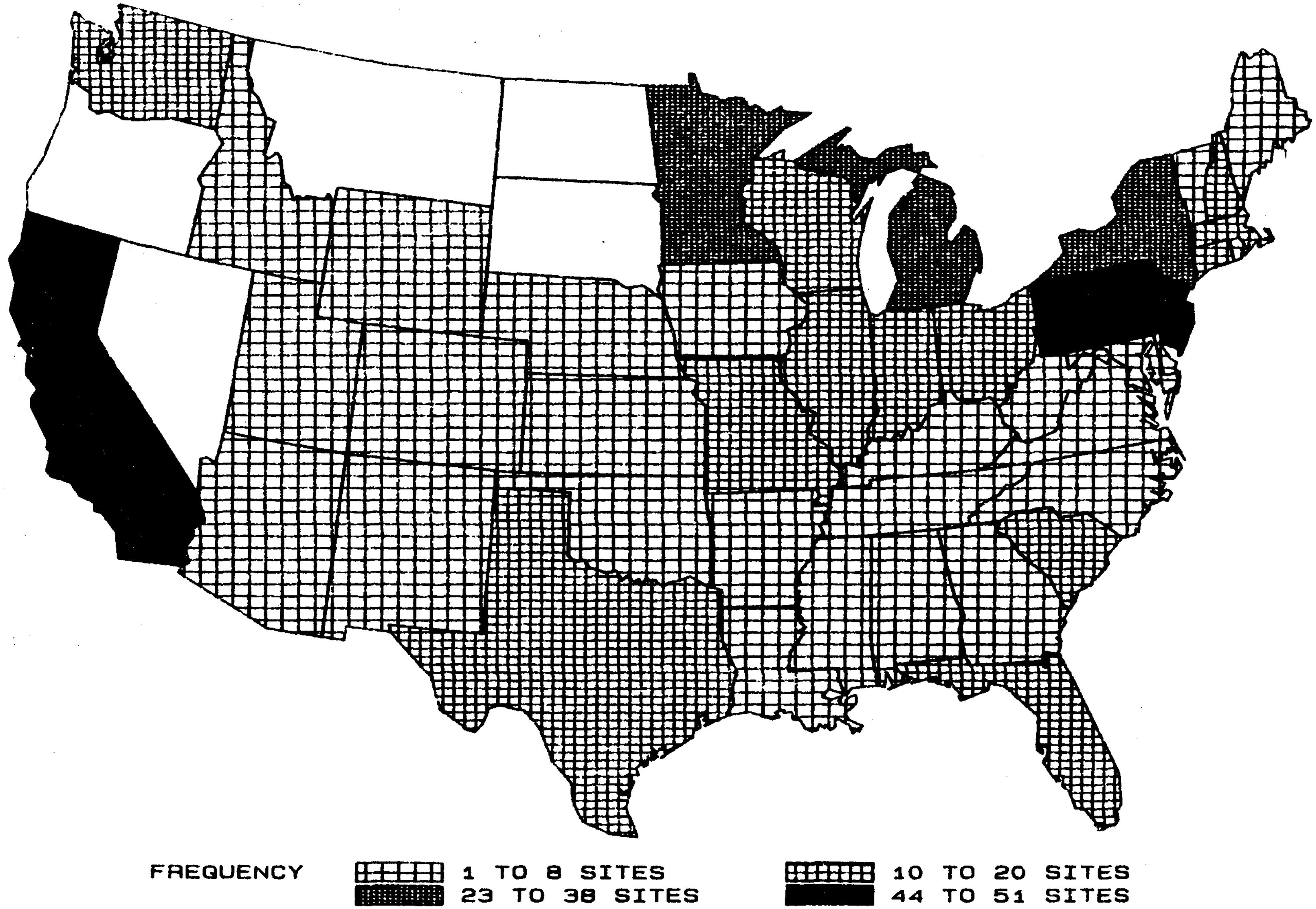
TABLE 5-1. Releases to the Environment from Facilities that Manufacture or Process 1,1-Dichloroethene[a]

Facility	Location[b]	Reported amounts released in pounds: Air	Underground injection	Water	Land	Total environment[c]	POTW transfer	Off-site waste transfer
3M	DECATUR, AL	1,750	0	1	0	1,751	0	0
MONSANTO CO. CHEMICAL GROUP	DECATUR, AL	2,170	0	0	0	2,170	0	0
EASTMAN KODAK CO. KODAK COLORADO DIV.	WINDSOR, CO	85	0	19	0	104	0	0
DOW CHEMICAL DALTON SITE	DALTON, GA	2,910	0	0	1	2,911	0	53,100
MORTON INTERNATIONAL INC.	RINGWOOD, IL	11,100	0	0	0	11,100	0	0
BF GOODRICH CO.	LOUISVILLE, KY	920	0	0	0	920	0	0
W. R. GRACE & CO.	OWENSBORO, KY	127,700	0	31	14	127,745	0	0
MARINE SHALE PROCESSORS INC.	AMELIA, LA	120	0	0	0	120	0	0
VULCAN MATERIALS CO.	GEISMAR, LA	163	0	2	0	165	0	0
DOW CHEMICAL CO. LOUISIANA DIV.	PLAQUEMINE, LA	43	0	38	0	81	0	0
PPG INDUSTRIES INC.	WESTLAKE, LA	92,434	0	389	0	92,823	0	158
DOW CHEMICAL USA MIDLAND	MIDLAND, MI	25,762	0	150	0	25,912	0	0
RHONE-POULENC INC. WALSH DIVISION	GASTONIA, NC	146	0	0	0	146	0	0
ALLIED-SIGNAL INC.	ELIZABETH, NJ	500	0	0	0	500	0	8
DU PONT PARLIN PLANT IMAGING SYSTEMS DEPT.	PARLIN, NJ	15	0	0	0	15	14	248
ALLIED-SIGNAL INC.	BUFFALO, NY	108	0	0	0	108	0	0
EASTMAN KODAK CO.	ROCHESTER, NY	879	0	200	0	1,079	0	7
GENCORP POLYMER PRODUCTS	MOGADORE, OH	540	0	0	0	540	49	1
OCCIDENTAL CHEMICAL CORP. VCM PLANT	DEER PARK, TX	0	0	0	0	0	0	5
DOW CHEMICAL CO.	FREEPORT, TX	15,300	0	2	0	15,302	0	0
OCCIDENTAL CHEMICAL CORP. CORPUS CHRISTI PLANT	GREGORY, TX	5	0	0	0	5	0	0
HERCULES INC.	COVINGTON, VA	1,189	0	0	0	1,189	0	0
ARCO CHEMICAL CO.	SOUTH CHARLEST, WV	1,351	0	0	0	1,351	31	21,000
Totals		285,190	0	832	15	286,037	94	74,527

[a]Derived from TRI91 (1993)
[b]Post office state abbreviations used
[c]The sum of all released of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

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



*Derived from HazDat 1993

with 1,1-dichloroethene, especially those who receive their drinking water from underground sources, may potentially be exposed to 1,1-dichloroethene, the levels of which cannot be established at present. Quantitative data that address levels of human exposure to 1,1-dichloroethene are limited.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Air releases are the largest source of 1,1-dichloroethene releases to the environment, and emissions from polymer synthesis and fabrication industries contribute most to overall atmospheric loading. Singh et al. (1981) have estimated that air emissions of 1,1-dichloroethene from polymer synthesis in the United States range between 2% and 5% of the annual production. EPA (1985a) estimated total annual air emissions of 1,1-dichloroethene of ≈650 tons/year, which was 0.8% of the production volume for that year. Over one-half of that total (355 tons) was from the polymer production/fabrication industries. The remaining emissions were from monomer synthesis (223 tons/year; 34%) and monomer storage, handling, and transportation (73 tons/year; 11%). Small amounts of 1,1-dichloroethene (not quantified) were estimated to be released during the incineration (disposal) of polymer products containing the 1,1-dichloroethene monomer, 1,1,1-trichloroethane, and other chlorinated solvents (Oki et al. 1990; Yasuhaka and Morita 1988). Crume (1991) reported that 1,1-dichloroethene can be released to the atmosphere by air stripping contaminated groundwater. This process transfers groundwater contaminants into the gaseous phase and subsequently releases them into the atmosphere with no further treatment (the releases were not quantified). However, more recent data indicate that both the number of emission point sources and the total amount of 1,1-dichloroethene released to the atmosphere are much less than EPA's earlier estimates. This decrease is the result of shifts away from the use of the compound by processors and improvements in control technology. For example, survey data submitted by the Chemical Manufacturers Association to EPA indicate that ≈103.4 tons of 1,1-dichloroethene per year are released from manufacturing and processing facilities (CMA 1989).

According to the TRI91 (1993), an estimated total of 285,190 pounds (129.3 metric tons) of 1,1-dichloroethene, amounting to 99.7% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1991. The data listed in TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Hazardous waste sites and landfills where 1,1-dichloroethene have been improperly disposed of are additional potential sources of release of the chemical to the atmosphere because of volatilization (see Section 5.4.1).

5.2.2 Water

Industrial releases of 1,1-dichloroethene to surface water contribute to the overall environmental loading of the chemical but to a much lesser extent than atmospheric emissions. Liquid effluents produced during polymerization operations are estimated to contribute ≈2 tons of waste 1,1-dichloroethene each year (Neufeld et al. 1977). Other potential industrial sources of waste 1, 1-dichloroethene in surface water are metal finishing and nonferrous metals manufacturing industries, soap and detergent manufacturers, electric coil coating and battery manufacturers, coal mines, laundries, and industries involving paint and ink formulation. 1,1-dichloroethene has been measured in raw waste water from these industries at mean concentrations of 3-760 μg /L (EPA 1981).

According to TRI91 (1993), an estimated total of 832 pounds (0.4 metric tons) of 1,1-dichloroethene, amounting to 0.29% of the total environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1991 (TRI91 1993). An estimated total of 94 pounds (0.043 metric tons), amounting to 0.03% of the total environmental release, was discharged to publicly owned treatment works. The TRI data should be used with caution since only certain types of facilities are required to report.

Hazardous waste sites where 1,1-dichloroethene has been improperly disposed are additional potential sources of the chemical, although there are no quantitative data available to address how much 1,1-dichloroethene enters the environment from this source. In addition, surface water or groundwater contaminated with l,l,l-trichloroethane, tetrachloroethylene, 1,1,2-trichloroethylene, and 1,2-dichloroethane can be an additional source of 1,1-dichloroethene through biotic or abiotic elimination or dehydrochlorination transformations (Baek et al. 1990; Cline and

Viste 1985; Lesage et al. 1990; McCarty et al. 1986). Hydrolysis of 1,1,1-trichloroethane in water or water/sediment systems will result in the formation of 1,1-dichloroethene by elimination, although it is a very slow process, with a half-life of -1 year (Haag and Mill 1988). Total releases of 1,1-dichloroethene from these sources have not been quantified or estimated.

5.2.3 Soil

Limited information is available on the releases of 1,1-dichloroethene to soil. An estimated total of 180 pounds/year of 1,1-dichloroethene are disposed of in municipal landfills as residual monomer in some consumer products on a national basis (Neufeld et al. 1977).

According to TRI91 (1993), an estimated total of 15 pounds (0.007 metric tons) of 1,1-dichloroethene, amounting to 0.005% of the total environmental release, was discharged to soil from manufacturing and processing facilities in the United States in 1991 (TRW1 1993). The TRI data should be used with caution since only certain types of facilities are required to report.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The tendency of a chemical to partition between soil, water, sediment, air, and biota can be inferred from its physical/chemical properties. Based on a vapor pressure of 592 mmHg (Verschueren 1983), most of the 1,1-dichloroethene released into the environment will ultimately partition into the atmospheric compartment as shown by the vapor partitioning model of Mackay and Paterson (1981) although other factors such as water solubility may affect the rate at which the partitioning will occur. In localized situations, intervening processes such as biotransformation, may alter this outcome.

As the magnitude of the Henry's law constant for 1,1-dichloroethene, 0.19 atmospheres m^3/mole (Pankow and Rosen 1988), indicates, 1,1-dichloroethene is likely to partition readily into the atmosphere from water. Because of this, 1,1-dichloroethene is generally not found in surface water in high concentrations. Studies on atmospheric removal processes indicate that once in the atmosphere, 1,1-dichloroethene is unlikely to be removed by physical processes such as wet deposition (e.g., rain) or by adsorption to atmospheric particulates (EPA 1980d).

1, 1-Dichloroethene spilled onto surface soil will also tend to partition to the atmosphere, while some of the chemical may percolate into the subsurface soil. Once in the subsurface soil, 1,1-Dichloroethene will partition between soil and water. 1,1-dichloroethene has high water solubility and a small log soil organic carbon sorption coefficient (K_{oc}) value of 1.81 (EPA 1982) indicating that 1, 1-dichloroethene will migrate through soil without significant retardation by adsorption to organic carbon. Similarly, 1,1-dichloroethene will migrate relatively freely within groundwater.

1,1- Dichloroethene in surface water is unlikely to partition significantly into aquatic organisms. Although measured bioconcentration factors were not located in the available literature, partitioning of 1,1-dichloroethene from water into aquatic organisms can be predicted in part by the magnitude of the octanol/water partition coefficient (K_{ow}) value. The chemicals with a log K_{ow} of <4.0 are unlikely to bioaccumulate to hazardous levels in human food chains (Veith et al. 1985). The log K_{ow} is 2.13 (Veith et al. 1985) and based upon this calculation, bioaccumulation in the human food chain is not expected to be significant for this compound.

5.3.2 Transformation and Degradation

Transformations of 1,1-dichloroethene can occur from the reaction with radical species in the atmosphere and from biodegradation under anaerobic conditions in soil or water.

5.3.2.1 Air

Atmospheric degradation of 1,1-dichloroethene is expected to be dominated by gas-phase oxidation with photochemically produced hydroxyl radicals. An experimental rate constant for this process of 8.11×10^{-12} cm^3/molecule-second at 25°C has been determined (Tuazon et al. 1988) and has been recommended as the best value in an extensive review of the reaction of hydroxyl radicals with organic compounds (Atkinson 1989). Using an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm^3, a half-life of 2-3 days can be calculated for this process (EPA 1980d; Tuazon et al. 1988). A higher atmospheric concentration of hydroxyl radicals

(10^6 molecules/cm^3) will reduce the half-life of 1,1-dichloroethene to 4-20 hours (Grosjean 1990). The products from this reaction are phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988).

Atmospheric degradation of 1,1-dichloroethene may also occur by a gas-phase reaction with other atmospheric oxidants, namely ozone and nitrate radicals, although these processes are too slow to successfully compete with the reaction of 1,1-dichloroethene with hydroxyl radicals (Grosjean 1990). An experimental rate constant for the gas-phase reaction of ozone with 1,1-dichloroethene of $3.7x10^{11}$ cm^3/molecule-second at 25°C (Atkinson and Carter 1984) translates to an atmospheric half-life of more than 10 years for this process using an average atmospheric ozone concentration of $7x10^{11}$ molecule/cm^3. Nitrate radicals are destroyed by sunlight, and the oxidation of organic compounds by this oxidant is only important at night. The rate constant for the oxidation of 1,1-dichloroethene by nitrate radicals, $1.78x10^{-15}$ cm^3/molecule-second at 25°C (Sabljic and Gusten 1990), translates to a half-life of 19 days in a moderately polluted atmosphere, although at nitrate concentrations of 50 ppt the half-life may be reduced to 6 days (Grosjean 1990). Reaction products of 1,1-dichloroethene with hydroxyl radicals and nitrates in air include chloroacetyl chloride, phosgene, formaldehyde, carbon monoxide, and nitric acid (EPA 1983a).

Another process for release of organic compounds in the atmosphere is by direct photolytic degradation; however, because chloroethenes do not adsorb radiation at wavelengths <300 nm to any significant extent (EPA 1980d; Tuazon et al. 1988), this process is not an important degradation pathway for 1,1-dichloroethene.

5.3.2.2 Water

Biotransformation under anaerobic conditions is believed to be the dominant transformation process for 1,1-dichloroethene in groundwater. However, Ensign et al. 1992 observed that 1,1-dichloroethene was not degraded efficiently by propylene-grown *Xanthobacter-* cells (strain Py2) under anaerobic conditions. The environmental media was not reported. The importance of this process under aerobic conditions, such as those normally found in ambient surface water, has not been determined. Conflicting results have been obtained for the aerobic degradation of 1,1-dichloroethene. Several investigations (Bouwer et al. 1981; McCarty et al. 1986; Pearson and McConnel 1975) have uncovered no evidence for biotransformation of chlorinated ethenes such as 1,1-dichloroethene under aerobic conditions. In contrast, Tabak et al. (1981) reported transformation of 54% of 5 mg/L and 30% of 10 mg/L test concentrations of 1,1-dichloroethene under aerobic conditions within 1 week after incubation with a domestic waste water seed; these removal figures were adjusted to account for volatilization losses from control flasks of 24% for the 5 mg/L and 15% for the 10 mg/L test concentrations.

Under anaerobic conditions (such as those that occur in groundwater), the importance of biotransformation is more clearly defined. McCarty et al. (1986) found that 1,1-dichloroethene was nearly quantitatively reduced to vinyl chloride under methanogenic conditions after 108 days. In another study, vinyl chloride was produced from the reductive dechlorination of 1,1-dichloroethene by microorganisms in anoxic microcosms after l-2 weeks of incubation (Barrio-Lage et al. 1986). Wilson et al. (1986) studied the behavior of 1,1-dichloroethene in authentic aquifer material known to support methanogenesis. The disappearance of this compound was observed with an initial long lag time, and vinyl chloride, a daughter product of degradation, was found in trace amounts. Baek et al. (1990) also observed the formation of vinyl chloride under anaerobic conditions when 1,1-dichloroethene was incubated with digested sludge under both fermentive am methanogenic conditions. Vinyl chloride has been classified as a possible human carcinogen by EPA (EPA 1985a); ATSDR has produced a toxicological profile on this compound (ATSDR 1990).

Photolysis and hydrolysis of 1,1-dichloroethene in natural aquatic media are not significant processes (EPA 1982). The estimated half-life for hydrolysis of 1,1-dichloroethene at 25°C under neutral (or slightly basic) conditions is 1.2×10^8 years (Jeffers et al. 1989). Similarly, oxidation is not a significant transformation mechanism for 1,1-dichloroethene in aqueous environments. Degradation rates due to reactions with singlet oxygen and the peroxy radical are not estimated to be environmentally significant in aquatic systems (EPA 1980e).

5.3.2.3 Sediment and Soil

A methane-utilizing culture isolated from lake sediment was able to degrade 600 ng/mL 1,l-dichloroethene to 200 ng/mL under aerobic conditions within 2 days. The end products were nonvolatile and did not include vinyl chloride which is known to be formed under anaerobic conditions (Fogel et al. 1986).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The National Ambient Volatile Organic Compound Database, updated in 1988 to include ambient and indoor volatile organic compounds (VOCs) concentrations in urban, rural, remote, source-dominated and indoor environments, reports an ambient daily average concentration for 1,1-dichloroethene of 4.6 ppb (Shah and Heyerdahl 1988). The ambient average concentration represents contributions from rural, suburban, urban, and source-dominated sites. In a survey of the indoor air of 26 homes and apartments near Research Triangle Park, North Carolina, 1,1-dichloroethene was found in 4 of 15 summer samples at a mean concentration of 47.3 ppb and 4 of 16 winter samples at a mean concentration of 7.1 ppb (EPA 1985). The EPA TEAM (Total Exposure Assessment Measurement) studies measured 1,1-dichloroethene concentrations in 1,085 personal air samples collected from 350 New Jersey residents (discrepancy in the actual number of residents sampled) over three seasons. Only 77 (7%) of the samples had measurable concentrations of 1,1-dichloroethene, and 107 (10%) of the samples had trace levels. The detection limit ranged from 3 to 14 μg /m^3 (Wallace 1991).

The results of an on-site field data collection program based on short-term studies conducted in seven U.S. cities indicated that 1,1-dichloroethene was present in air at an average concentration range of 0.005-0.03 ppb in various cities (Singh et al. 1981, 1982). 1,l -Dichloroethene was detected in 24 of 79 ambient air samples (collected from 1986 to 1987 in the Kanawha Valley, West Virginia; Los Angeles, California; and Houston, Texas) at a mean concentration of 0.84 ppb (Pleil et al. 1988). It was also found in 33 of 35 ambient air samples (collected in Newark, New Jersey, July-August 1981) at a geometric mean concentration of 0.38 ppb (Harkov et al. 1987). Corresponding values for Elizabeth and Camden, New Jersey, were 33 of 34 samples at a mean concentration of 0.35 ppb and 28 of 30 samples with a mean concentration of 0.36 ppb, respectively (Harkov et al. 1987).

1,1-Dichloroethene has been measured in air in the vicinity of five of six hazardous waste sites as well as a sanitary landfill in New Jersey (1983-1984), with arithmetic mean concentrations ranging from 0.39 to 38.9 ppb measured at waste sites, and an arithmetic mean concentration of 2.6 ppb measured at the sanitary landfill. The highest concentration measured at these six sites was

97 ppb (Harkov et al. 1985; LaRegina et al. 1986). Although quantitative information on the air concentrations of 1,1-dichloroethene at hazardous waste sites on the NPL is not available, 1,1-dichloroethene is probably present in air at those NPL sites where it has been measured in either the soil, surface water, or groundwater.

5.4.2 Water

1,1-dichloroethene concentrations >5 mg/L have been measured in raw waste water from the metal finishing and nonferrous metals manufacturing industries (EPA 1981). Lower concentrations (<l mg/L) have been measured in raw waste water from industries involving paint and ink formulation, soap and detergent manufacturing, coil coating, battery manufacturing, coal mining and laundries (EPA 1981). Treated waste waters from all these industries ranged from < 1 to 4 mg/L (EPA 1981). According to the STORET database maintained by the EPA, 1,1-dichloroethene has been detected in 3.3% of 1,350 effluent samples monitored nationwide (Staples et al. 1985).

1,1-dichloroethene has been detected in surface waters sampled near industrial sites at concentrations ranging from less than 1 to 550 μg/L (Going and Spigarelli 1977). According to the STORET database maintained by the EPA, 1,1-dichloroethene has been detected in 6% of 8,714 surface water samples monitored nationwide (Staples et al. 1985). However, no 1,1-dichloroethene was detected in raw surface water during a 105-city survey of U.S. cities (Coniglio and Miller 1980). 1,1-dichloroethene has been detected infrequently at low concentrations in urban runoff that will contribute to surface water concentrations. The Nationwide Urban Runoff Program (NURP), initiated to evaluate the significance of priority pollutants in urban storm water runoff, report a detection frequency of only 3%, with a concentration range of 1.5-4 μg/L (Cole et al. 1984).

About 3% of the drinking water supplies in the United States have been found to contain 1,1-dichloroethene at 0.2-0.5 μg/L (estimated mean 0.3 μg /L) concentration in an EPA survey (EPA 1985a). 1,1-dichloroethene was also detected (quantification limit of 0.2 ppb) in 2.3% of the 945 samples of finished drinking water taken from community-based groundwater sources in a nationwide survey (Rajagopal and Li 1991, Westrick et al. 1984). The maximum concentration of 1, 1-dichloroethene detected in the positive samples was 6.3 μg/L (subset median values were

0.28-1.2 µg/L). 1,1-dichloroethene was detected in 9 of 466 U.S. drinking water wells sampled in the 1982 Ground Water Supply Survey at a median concentration of 0.3 µg/L (Cotruvo 1985).

1,1-dichloroethene has been detected in 25.2% of 178 contaminated sites monitored under the Comprehensive Emergency Response, Compensation, and Liability Act (CERCLA) making it the fifth most frequently detected organic contaminant at these sites (Plumb 1987). Contamination of groundwater at an industrial site in Waite Park, MN, resulting from the mishandling of waste product, paint, and solvent led to a maximum 1,1-dichloroethene concentration of 88 µg/L in deep monitoring wells and 22 µg/L in shallow wells (ATSDR 1990). This aquifer contamination led to a maximum 1,1-dichloroethene concentration of 94 µg/L in Waite Park municipal wells resulting in this city's water supply being listed as an NPL site. The disposal of organic chemicals in trenches at a waste disposal site near Ottawa, Canada, resulted in 1,1-dichloroethene groundwater concentrations ranging from 0.9 to 60 µg/L in 43% of samples taken from a 37-well monitoring network in 1988 (Lesage et al. 1990). Leachate originating from the Orange County and Alachua Municipal Landfills in north central Florida resulted in groundwater contamination near the landfills. The average concentration of 1,1-dichloroethene in wells sampled near the Orange County Landfill and the Alachua Municipal Landfill was 0.12 and < 1.0 µg/L, respectivel (Hallbourg et al. 1992). 1,1-dichloroethene has also been detected in groundwater sampling surveys conducted in New Jersey (Cain et al. 1989; Fusillo et al. 1985).

The concentration of 1,l -dichloroethene in leachate from the Moyer Landfill in Collegeville, Pennsylvania, classified as an NPL site by the EPA in 1982, ranged from 1 to 2 ppb (Varma 1985). In a 1987-1988 survey of groundwater contamination at 19 municipal and 6 industrial landfills in Wisconsin, 1,l-dichloroethene was detected at 1 site at an average concentration of 3.4 µg/L (Battista and Connelly 1988).

5.4.3 Sediment and Soil

No information is available on ambient concentrations of 1,1-dichloroethene in soil, although this chemical is often found at hazardous waste sites. Because of the tendency of 1,1-dichloroethene to partition into the atmosphere, with remaining material having the potential to percolate into groundwater, ambient concentrations in surface soil are expected to be low. No information is available on the concentration of l-l-dichloroethene in sediment.

5.4.4 Other Environmental Media

1,1-dichloroethene copolymers are used in the manufacture of films used in food packaging. Residual 1,1-dichloroethene monomer has been detected at concentrations of <0.02-1.26 ppm in retail food packaging films containing polyvinylidene chloride; residues in a variety of foodstuffs wrapped with the films were in the range of ≤0.005-0.01 ppm (Gilbert et al. 1980). Concentrations of residual 1,1-dichloroethene in household films used to package food were reported by Birkel et al. (1977) to be 6.5-10.4 ppm (average 8.8 ppm). At one time, some films contained as much as 30 ppm 1,1-dichloroethene (Birkel et al. 1977). No information on the levels of 1,1-dichloroethene in humans was located.

1,1-dichloroethene was detected in a composite sample of Rigolets clams obtained from Lake Pontchartrain, Louisiana, in 1980 at a concentration of 4.4 ppb wet weight (Ferrario et al. 1985).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Information on exposure of the general population to 1,1-dichloroethene is limited. An EPA TEAM study conducted from 1980 to 1987, reported that the average exposure of the general population to 1,1-dichloroethene is 6.5 $\mu g / m^3$ based on personal air samples from 350 homes in New Jersey (Wallace 1991).

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH), estimated that 56,857 workers in 3,853 plants were potentially exposed to 1,1-dichloroethene in the workplace in 1970 (NIOSH 1976). These estimates were derived from observation of the actual use of 1,1-dichloroethene (1%), the use of trade-name products known to contain 1,1-dichloroethene (19%), and the use of generic products suspected of containing the compound (80%). The largest numbers of exposed workers were special trade contractors or in the fabricated metal products industry or wholesale trade industry. The occupational groups of exposed workers consisted of carpenters, warehousemen (not otherwise classified), and miscellaneous machine operators.

Data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 2,679 workers, including 291 women, in

97 plants were potentially exposed to 1,1-dichloroethene in the workplace in 1980 (NIOSH 1984). The greatest number of exposed workers were chemical technicians. All estimates were derived from observations of the actual use of the compound.

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. Rather, they only provide estimates of workers potentially exposed to the chemicals.

Varying occupational exposure levels can be found in the literature. Reported ranges of concentrations associated with the monomer and polymer plants are ≈23-25 ppb and 6-12 ppb, respectively (Walling 1984). Exposure concentrations ≤1,900 ppm have been reported in a copolymer monofilament fiber production plant (Ott et al. 1976). However, in polymer manufacturing plants, worker exposure has been reported as <5 ppm (Jaeger 1975). Wallace (1991) reported an exposure concentration of 120 ppm for a cabinet maker; however, the concentration decreased to 14 ppm when measured during a different season (the seasons were not reported).

1,1-dichloroethene was produced in significant amounts that under certain conditions may approach 100%, from the thermal degradation of methyl chloroform (Glisson et al. 1986). This implies that inadvertent exposure to 1,1-dichloroethene may occur in many industrial situations when methyl chloroform is used in the vicinity of operations involving heat, such as welding or soldering and metal cleaning. 1,1-dichloroethene has also been detected as a pyrolysis product of the pesticide endosulfan in tobacco smoke (Chopra et al. 1978).

The Occupational Safety and Health Administration (OSHA) recently reduced the 8-hour timeweighted-average (TWA) permissible exposure level (PEL) to 1 ppm (OSHA 1989), which should limit future workplace exposures to low levels of this compound.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to 1,1-dichloroethene is potentially highest in workplace settings and among populations residing in the vicinity of hazardous waste sites where the compound may contaminate environmental media.

The presence of residual monomeric 1,1-dichloroethene in polymeric food wraps and other consumer products is another potential source of human exposure. Exposure from these sources is difficult to estimate. However, there is no evidence in the literature to implicate consumer products as major sources of 1,1-dichloroethene exposure (EPA 1985a).

In addition to releases from hazardous waste sites, ambient air and water may be contaminated with 1,l -dichloroethene by releases from industrial production and polymerization processes (EPA 1977, 1985a; Wang et al. 1985a, 1985b). Levels are significantly higher in areas surrounding production sites (EPA 1977, 1985a).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1-dichloroethene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1-dichloroethene.

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

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Available data adequately characterize the physical and chemical properties of 1,1-dichloroethene (HSDB 1992; Merck 1983) (see Chapter 3).

Production, Import/Export, Use, and Disposal. 1,1-dichloroethene is produced commercially. The estimated production of the compound in 1989 totalled 230 million pounds, up from an estimated production capacity of 178 million pounds/year in 1985. 1,1-dichloroethene is used as an intermediate in the synthesis of other organic chemicals and polymers, including flexible films for food packaging. Monomeric 1,1-dichloroethene has been detected in many food packaging materials and foodstuffs. 1,1-dichloroethene is released mainly to the atmosphere. EPA requires compliance with RCRA regulations when producing, treating, storing, or disposing of 1,1-dichloroethene. Current disposal regulations require dissolving the compound in combustible solvents and scatter spraying the solvent into a furnace with an afterburner and alkaline scrubber. Additional information on the current criteria for land treatment and burial and on the amounts of 1,1-dichloroethene disposed of by incineration versus landfilling would be helpful.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1990, became available in May of 1992. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The available data suggest that 1,1-dichloroethene can undergo transformation due to the reaction with radical species in the atmosphere and biodegradation under anaerobic conditions in water and under aerobic conditions in soil (Ensign et al. 1992; Foget et al. 1986; Grosjean 1990; Tabak et al. 1981; Tuazon et al. 1988). The atmospheric halflife of 1,1-dichloroethene in air following hydroxyl radical reaction is estimated to be 4-20 hours, and the products of this reaction are phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). The estimated half-life for hydrolysis of 1,1-dichloroethene at 25°C under neutral conditions is 1.2×10^8 years (Jeffers et al. 1989). 1,1-dichloroethene is reduced to vinyl chloride under methanogenic conditions (McCarty et al. 1986). In a methane-utilizing culture from lake sediment, 1,1-dichloroethene was degraded under aerobic conditions within 2 days; the end products, although unspecified, did not include vinyl chloride. More information is needed to define these processes and to quantify degradation rates. Such information would be helpful in understanding the fate of nonvolatilized 1,1-dichloroethene in these media.

Bioavailability from Environmental Media. The monitoring data available indicate that 1,1-dichloroethene is present in some samples of air, water, soil, and foodstuffs (EPA 1981, lW5a; Gilbert et al. 1980; Shah and Heyerdahl 1988; Singh et al. 1981; Verma 1985). Animal studies indicate that 1,l -dichloroethene is absorbed following inhalation and oral exposure. 1,l -dichloroethene and its metabolites can be measured in the breath, blood, urine, and adipose tissue of humans. Thus, it can be concluded that 1,1-dichloroethene is bioavailable from the environment. Good quantitative data that correlate varying levels in the environment with levels in the body and health effects and data on the extent to which 1,1-dichloroethene can be absorbed from various media (i.e., soil) are lacking. This information may be difficult to obtain since environmental levels can fluctuate widely and exposure may be sporadic.

Food Chain Bioaccumulation. No information was found regarding the bioconcentration of 1,1-dichloroethene in plants, aquatic organisms, or animals. On the basis of the log octanol/water partition coefficient value of 2.13 (EPA 1982), bioconcentration of the compound to significant levels by terrestrial or aquatic organisms is not expected. No data were located regarding the biomagnification of 1,1-dichloroethene in terrestrial or aquatic food chains. Given the expected limited bioconcentration (Barrio-Lage et al. 1986; Wilson et al. 1986) of the compound in the tissues of terrestrial and aquatic organisms, and the extent to which 1,1-dichloroethene undergoes biotransformation, biomagnification in terrestrial and aquatic food chains is not expected. Additional experimental data to confirm this predicted limited food chain bioaccumulation of 1,1-dichloroethene would be helpful in evaluating the relative significance of this route of exposure.

Exposure Levels in Environmental Media. Data on the concentrations of 1,1-dichloroethene in surface water, soil, and food, are limited (EPA 1981, 1985a; Gilbert et al. 1980; Shah and Heyerdahl 1988; Singh et al. 1981; Verma 1985). More data are needed to provide a more complete characterization of human exposure. The concentration of 1,1-dichloroethene in the air above hazardous waste sites and in groundwater near them is not well documented. The available data indicate that human exposure may occur because of 1,1-dichloroethene's presence in these environmental media. Additional monitoring data will better address the degree to which it occurs.

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

Exposure Levels in Humans. Although an analytical method is available to detect 1,1-dichloroethene in human tissue, no studies were found that measured its levels in human tissues. Most of the data on exposure levels of 1,1-dichloroethene are based on occupational studies conducted under controlled environmental conditions (Walling 1984), and these data are not current. More current information on the potential exposure resulting from residence in the vicinity of hazardous waste sites would provide a more accurate characterization of human exposure in the United States.

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

Exposure Registries. No exposure registries for 1,l -dichloroethene were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 On-going Studies

One on-going study on the environmental fate, including the accumulation and biodegradation of 1,1-dichloroethene was located. The study is being conducted by the EPA, and further details are not available (EXICHEM 1993). Remedial investigations and feasibility studies at NPL sites known to have 1,1-dichloroethene contamination (NPLTD 1988) should be completed in the near future and may add to the current knowledge regarding the transport and degradation of 1,l -dichloroethene in the environment.

Environmental monitoring conducted in conjunction with remedial investigation/feasibility studies at hazardous waste sites on the NPL should add to the current database on environmental levels of 1,1-dichloroethene.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), 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 1,1-dichloroethene and other volatile organic compounds.

Studies being conducted at the University of California, Riverside, will use *cis-* and *trans*-1,2-dichloroethene as surface probes to evaluate interactive mechanisms with individual soil constituents (CRIS USDA 1993). These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring 1,1-dichloroethene, its metabolites, and other biomarkers of exposure and effect to 1,1-dichloroethene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

The analytical methods used to quantify 1,1-dichloroethene in biological samples are summarized below. Table 61 lists the applicable analytical methods for determining 1,1-dichloroethene in biological specimens.

1,1-Dichloroethene exposure can be monitored by measuring the levels in blood, expired air and urine (Ashley et al. 1992; McKenna et al. 1978a; Pellizari et al. 1985; Raymer et al. 1990, 1991; Wallace et al. 1984). 1,1-dichloroethene also distributes preferentially to liver, kidney, and to a lesser extent, adipose tissue. Methods are available to measure 1,1-dichloroethene and/or its metabolites in these tissues as well (Lin et al. 1982). Purge-and-trap gas chromatography/mass spectrometry (GC/MS) is the most commonly used method to detect 1,1-dichloroethene in biological samples. The purge-and-trap technique involves bubbling an inert gas through the sample to purge the volatile compounds out of solution. The compounds are then trapped in a cold trap (cry&rapping) or adsorbed on a suitable adsorbent such as Tenax. The next step is thermal desorption of the trapped solutes and their subsequent transfer to an analytical column. GC/MS allows the detection of compound at the ppb level. Capillary GC affords the highest resolution of complex mixtures, even when other volatile organic compounds are present that could conceivably mask or interfere with the detection of 1,1-dichloroethene. Furthermore, specific GC-detectors, as well as mass selective detectors, enable the quantitation of 1,1-dichloroethene even when it is not fully separated from other compounds. It is difficult to accurately measure biological concentrations of 1,1-dichloroethene and correlate these measurements to actual exposure concentrations because of the chemical's short half-life and conversion into metabolites. The concentration of 1,1-dichloroethene in biological media is continually changing by virtue of its rapid release into the air or biotransformation into other compounds. More information on methods for the analysis of 1,1-dichloroethene in biological materials, including sample preparation techniques, can be found in the references cited in Table 6-1.

Environmental exposure to 1,1-dichloroethene at hazardous waste sites may often include exposure to other chlorinated hydrocarbons. 1,1-dichloroethene exposure can be monitored by direct measurement of the parent compound or its metabolites. It is difficult to distinguish metabolites of 1,1-dichloroethene in the body because some of the same metabolites may be formed as a result of exposure to other chlorinated hydrocarbons.

Determination of 1,1-dichloroethene in breath samples by GC/MS is the most commonly used method of monitoring exposure to 1,1-dichloroethene (Pellizzari et al. 1985; Raymer et al. 1990, 1991). Sensitivity is in the low ppb range. Recovery is adequate. Various other techniques are being studied and developed to monitor 1,1-dichloroethene in expired air using reversible adsorption (Contant et al. 1984) and impregnated tape methods for continuous monitoring (Denenberg and Miller 1974). Recently, a portable device for measuring 1,1-dichloroethene in alveolar breath was described (Raymer et al. 1990).

1,1-dichloroethene has been measured in whole blood samples using purge-and-trap GC/MS (Ashley et al. 1992). This method shows excellent sensitivity (low ppt levels) and good precision (<20% coefficient of variation). Recoveries were high (> 100%). The reason for the high recoveries was not clear but was suggested to be due to the inability to accurately assess the levels of the volatile compounds in the unspiked blood which served as a baseline for recovery calculation. The measurement of 1,1-dichloroethene adducts with DNA in lymphocytes or hemoglobin may also be useful in monitoring exposure to 1,1-dichloroethene. Such a method has been established in hemoglobin for another volatile organic compound, ethylene oxide (Tornqvist et al. 1986). Because human hemoglobin has a half-life of ≈60 days (although half-lives of

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human tissue (adipose, kidney, liver, and brain)	Mince tissue, add isooctane/water; extract, purge-and-trap	GC/ECD	≈50 pg	>50	Lin et al. 1982
Human Breath	Thermal desorption	GC/MS	1 $\mu g/m^3$	40–60	Pellizari et al. 1985; Wallace et al. 1984
Human Breath	Collect alveolar breath samples in 6-L cannister using a spirometer followed by cryogenic trapping; collect whole breath samples in Tedlar bags; preconcentrate onto Tenax; thermally desorb	GC/MS	NR	NR	Raymer et al. 1991
Human alveolar breath	Breath collection in evacuated 1.8-L canister using a spirometer, cryogenic concentration	GC/MS	<5 $\mu g/m^3$	95	Raymer et al. 1990
Human blood	Purge-and-trap volatile compounds from blood	GC/MS	3.1 ppt	>100	Ashley et al. 1992
Rat urine	None	GC/MS	No data	≥35	McKenna et al. 1978b

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; NR = not reported hemoglobin adducts are somewhat reduced), monitoring of 1,1-dichloroethene adducts with hemoglobin can be a valuable tool for estimating exposure over longer periods.

1,1-dichloroethene has been detected in urine using GC/MS; however, low recoveries were obtained (McKenna et al. 1978a). Sensitivity and precision data were not reported.

6.2 ENVIRONMENTAL SAMPLES

The analytical methods used to quantify 1,1-dichloroethene in environmental samples are listed in Table 6-2. The analytical methods required by EPA (1984a, 1984b, 1984c) for the analysis of 1,1-dichloroethene in water and waste water are described in procedures 601 (GC/ECD), 624 (GC/MS), and 1624 (GC/MS). The sensitivity for these methods is in the ppb range. These are testing procedures required under the Clean Water Act for sites discharging municipal and industrial waste water. The method required by the EPA Contract Laboratory Program (CLP) for analysis of 1,1-dichloroethene and other volatile organic compounds is hexadecane extraction, fc>llowed by determination of approximate concentration using GC and flame ionization detection (FID), and final quantitative analysis using GC/MS (EPA 1986a, 1986b).

GC/FID is used to detect 1,1-dichloroethene in air samples (Foerst 1979; NIOSH 1984; Taylor 1978). The sensitivity of this procedure is in the low ppm range. Recovery is good. GC/MS is used to determine 1,1-dichloroethene in water, waste water discharges, and soil samples with sensitivities in the ppb-range. DeLeon et al. (1980) measured levels of 1, 1-dichloroethene in soil and chemical waste; this method had a limit of detection of 10 ppm. In addition, GC/MS is used to determine levels of 1,1-dichloroethene in fish tissue (Easley et al. 1981 and Hiatt 1983). GC/ion trap detection (ITD) is used for drinking water. Sensitivity is in the ppb range and recovery is good. Purge-and-trap GC/MS is used for measuring volatile chlorinated hydrocarbons in ground water (Barber et al. 1992). The detection limit for this method is 0.2 µg /L. At concentrations 1, 1-dichloroethene ranging from 0.2 to 100 µg /L, recoveries were good, ranging from 85% to 142%. The high recoveries (>100%) o were the result of using a calibration curve that spanned more than three orders of magnitude. Precision was excellent (33% RSD). Purgeable organic chloride (POCl) analysis can be used as a complimentary method for use with GC/MS. Purge-and-trap CC/MS and POCl analysis gave data of similar accuracy and precision at spiked concentrations of >l µg /L. Lower recoveries and poor precision were obtained at a

TABLE 6-2. Analytical Methods for Determining 1,1-Dichloroethene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery[a]	Reference
Air	Adsorb (charcoal); desorb carbon disulfide	GC/FID	1 mg/m^3	85	Foerst 1979; NIOSH 1984 (method 1015); Taylor 1978
Air	Solid sorbent collection	GC/FID	7 μg/sample	>80	Foerst 1979
Air	Reversible adsorption	GC/MS	No data	No data	Coutant 1984
Water	Purge-and-trap method	GC/HECD	0.13 $\mu g/L$	0.98C–0.87	EPA 1984a (method 601)
Water	Purge-and-trap method	GC/MS	2.8 $\mu g/L$	1.12C+0.61	EPA 1984c (method 624)
Water	Isotope dilution	GC/MS	10 $\mu g/L$	No data	EPA 1984c (method 624)
Tap water	Purge-and-trap method	GC/FID	NR	76.6	Driss and Bouguerra 1991
Drinking water	Purge-and-trap on solid absorbent, thermal desorption, capillary column GC separation	GC/ITD	<0.2 $\mu g/L$	87	Eichelberger et al. 1990 (EPA method 524.2)
Groundwater	Purge-and-trap method	GC/HECD	0.13 $\mu g/L$	0.98C–0.87	EPA 1986a (method 8010)
Ground water	Purge-and-trap method	GC/MS	0.2 $\mu g/L$	85–142	Barber et al. 1992
Groundwater	Purge-and-trap method	GC/MS	5 $\mu g/L$	1.12C+0.61	EPA 1986b (method 8240)

TABLE 6-2. Analytical Methods for Determining 1,1-Dichloroethene in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery[a]	Reference
Solids/sludges/ soils/sediments/ wastes	Purge-and-trap method	GC/MS	Soil, sediment, 5 μg/L (ww); wastes, 0.5 mg/kg	1.12C+ 0.61	EPA 1986b (method 8240)
Soil/chemical waste	Hexane extraction; temperature programmed GC determination	GC/MS	10 ppm	80–90	DeLeon et al. 1980
Fish tissue	Homogenize, add liquid N_2 to prevent evaporation of volatiles, vacuum distillation	GC/MS using a fused-silica capillary column	No data	No data	Hiatt 1983
Fish tissue	Purge-and-trap method to release volatile compounds trapped in the fish tissue	GC/MS	10 μg/kg	70	Easley et al. 1981
Packaging films	Heat hypovials containing film at 120°C; collect headspace vapor	GC/ECD	0.04 ppm	No data	Crosby 1982; Gilbert et al. 1980
Food (potato crisps, cakes, snack products, cheeses, biscuits)	Crush or grind and heat food samples	GC/ECD	<0.005 ppm	No data	Gilbert et al. 1980

[a]Recovery is sometimes expressed as a function of C which denotes the true value for the concentration

ECD = electron capture detection; FID = flame ionization detection; GC = gas chromatography; HECD = Hall electrolytic conductivity detector; ITD = ion trap detection; MS = mass spectrometry; N_2 = nitrogen; ww = wet weight spiked concentration <1 µg /L. Detection limits using POCL analysis were 0.2 µg /L as well. POCI analysis is useful for screening samples for volatile chlorinated hydrocarbons; however, it is not suitable as an independent method of analysis. Purge-and-trap GC/flame ionization detector (ECD) has also been used to measure 1,1-dichloroethene in tap water (Driss and Bouguerra 1991). Recovery (76.6%) and precision (1.6% RSD) for this method were good. The detection limit was not reported. Gilbert et al. (1980) detected 1,1-dichloroethene in food at levels <5 ppm using headspace GC/ECD. These food products were packaged in polyvinylchloride films. Birkel et al. (1977), using GSC/MS, detected levels of between 6.5 and 10.4 ppm of 1,1-dichloroethene in Saran® food packaging films. Complete descriptions of these techniques can be found in the references cited in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1-dichloroethene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1-dichloroethene.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Except for the measurement of 1,l-dichloroethene in breath within a short period after exposure, there are no other biomarkers of exposure or effect unique to 1,1-dichloroethene. Analytical methods exist for determining 1,1-dichloroethene in breath (Contant et al. 1984; Denenberg and Miller 1974;

Pellizzari et al. 1985; Raymer et al. 1990; Wallace et al. 1984), blood (Ashley et al. 1992), and urine (McKenna et al. 1978a). These methods have acceptable quantification limits and are capable of determining exposure.

There are few analytical methods used to determine 1,1-dichloroethene in biological samples. The current emphasis is on (a) measuring the compound of interest at the ppb level accurately and consistently, (b) refining sample preparation techniques, and (c) modifying the analytical procedure to obtain better resolution with higher sensitivity. Analytical methodology to distinguish exposure to 1,1-dichloroethene from compounds with similar metabolic profiles is not available. Accuracy, precision, and recovery data are also lacking since the available information concentrates on the extension of detection limits of 1,1-dichloroethene rather than meeting quality control objectives necessary for analytical method standardization.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. There are media-specific standardized methods available for detecting 1,1-dichloroethene in environmental samples. Accuracy data and sample detection limit data are available for the EPA-approved methods; however, this information is incomplete for other analytical methods. This may be because of the lack of adequate data to determine method accuracy, precision, or recovery values. A better resolution and sensitivity are achievable with the application of the proper GC capillary column and selection of the correct detector or detector combination (Kirshen 1984).

Methods are available to detect 1,1-dichloroethene in air, water, sediment, soil, sludge, liquid waste, food, and fish (Barber et al. 1992; Coutant 1984; DeLeon et al. 1980; Driss and Bouguerra 1991; Easley et al. 1981; Eichelberger et al. 1990; EPA 1984a, 1984c, 1986a, 1986b; Foerst 1979; Gilbert et al. 1980; Hiatt 1983; NIOSH 1984; Taylor 1978). The standardized methods can detect 1,l-dichloroethene at ppt levels in air and mg/L levels in water. In addition, numerous techniques for the analysis of 1,1-dichloroethene are reported in the open literature (Constant et al. 1984; EPA 1986a, 1986b; Gilbert et al. 1980; Pellizzari et al. 1985; Tornqvist et al. 1986).

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

6.3.2 On-going Studies

No on-going studies concerning techniques for measuring and determining 1,1-dichloroethene in environmental samples were identified.

One on-going study on the development of analytical methods for human monitoring exposure to 1,1-dichloroethene was located (EXICHEM 1993). The study is being conducted by the EPA. Further details are not available .

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 1,1-dichloroethene and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion (ppt) range.

7. REGULATIONS AND ADVISORIES

Table 7-1 summarizes international, national, and state regulations and guidelines on human exposure to 1,l dichloroethene.

ATSDR has derived an MRL of 0.02 ppm for intermediate-duration inhalation exposure based on a NOAEL of 5 ppm for liver effects in guinea pigs (Prendergast et al. 1967).

ATSDR has derived an MRL of 0.009 mg/kg/day for chronic-duration oral exposure based on a LOAEL of 9 mg/kg/day for liver effects in rats (Quast et al. 1983).

A oral reference dose (RfD) of 0.009 mg/kg/day has been verified by EPA for 1,1-dichloroethene (IRIS 1992). The RfD is based on a LOAEL of 50 ppm of 1,1-dichloroethene in the drinking water for liver effects in rats (Quast et al. 1983). EPA has given 1,1-dichloroethene a Group C weight-of-evidence carcinogenicity classification (probable human carcinogen) (IRIS 1992).

The Clean Water Effluent Guidelines regulate 1,1-dichloroethene for the following industrial point sources: electroplating, organic chemicals production, rubber manufacturing, asbestos product manufacturing, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum and wood chemicals manufacturing, carbon black manufacturing, coil coating, and electrical and electronic components manufacturing (EPA 1986).

The FDA has limited the amount of 1,1-dichloroethene that can be present in foodwrap to 10 ppm (FDA 1988).

TABLE 7-1. Regulations and Guidelines Applicable to 1,1-Dichloroethene

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
WHO	Guideline for drinking water	0.3 µg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA	1 ppm	OSHA 1989 (29 CFR 1910.1000)
b. Water:			
EPA ODW	MCL in drinking water	0.7 µg/L	EPA 1985c (40 CFR 141)
EPA OWRS	General pretreatment regulations for existing and new sources of pollution waste water; effluent guidelines for point source categories	Yes	EPA 1988d (40 CFR 403); EPA 1987b (40 CFR 414)
	Rayon fibers, other fibers, thermoplastic resins, thermosetting resins, commodity organic chemicals, bulk organic chemicals, specialty organic chemicals:		
	Maximum for 1 day	60 µg/L	
	Maximum for monthly average	22 µg/L	
	Direct discharge point sources that use end-of-pipe biological treatment (effluent limitations BAT and NSPS):		EPA 1987b (40 CFR 414)
	Maximum for one day	25 µg/L	
	Maximum for monthly average	16 µg/L	
	Direct discharge point sources that do not use end-of-pipe biological treatment (BAT effluent limitations and NSPS):		EPA 1987b (40 CFR 414)
	Maximum for one day	60 µg/L	
	Maximum for monthly average	22 µg/L	
FDA	Proposed uses of vinyl chloride polymers: deletion of vinyl chloride-1,1-dichloroethene copolymers from the list of materials that may be used on fruits	Yes	FDA 1986
	Coatings applicable to fresh citrus fruit (minimum required for intended use) on plastic packaging films	25% or less aqueous solution ≤10 ppm	FDA 1977 (21 CFR 1172.210); FDA 1988 (21 CFR 177)
c. Other:			
EPA OERR	Reportable quantity	5000 pounds	EPA 1989 (40 CFR 302.4)
EPA OSW	Designation of hazardous substances	Yes	EPA 1985c (4O CFR 302.4)
	Listing as toxic wastes: discarded commercial chemical products, off-specification species, container residues, and spill residues of 1,1-dichloroethene	Yes	EPA 1980a (40 CFR 261.33)
	Listing as a hazardous waste constituent (Appendix VIII)	Yes	EPA 1991 (40 CFR 261)

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

Agency	Description	Information	References
NATIONAL (cont.)			
EPA OTS	Toxic Chemical Release Reporting; Community Right-to-Know; (proposed rule)	Yes	EPA 1987c
Guidelines:			
a. Air:			
ACGIH	TLV TWA	5 ppm	ACGIH 1986
	STEL	20 ppm	
NIOSH	REL TWA	C_a; lowest feasible concentration	NIOSH 1992
b. Water:			
EPA ODW	MCLG	0.007 mg/L	EPA 1985c (40 CFR 141)
	Health Advisories		EPA 1987a
	1 day	2.0 mg/L	
	10 days	1.0 mg/L	
	Longer Term		EPA 1987a
	Adult	3.5 mg/L	
	Child	1.0 mg/L	
	Lifetime	0.007 mg/L	
EPA OWRS	Ambient water quality criteria for protection of human health:		EPA 1980b
	Ingesting water and organisms:		
	10^{-4}	3.3 μg/L	
	10^{-5}	0.33 μg/L	
	10^{-6}	0.033 μg/L	
	Ingesting organisms only:		
	10^{-4}	185 μg/L	
	10^{-5}	18.5 μg/L	
	10^{-6}	1.85 μg/L	
NAS	SNARL (chronic)	100 μg/L	NAS 1983
c. Other:			
EPA	RfD (oral)	0.009 mg/kg/day	IRIS 1992
	Carcinogen classification	Group C[b]	IRIS 1992
	q_1^* (oral)	0.6 $(mg/kg/day)^{-1}$	
	Inhalation unit risk	5×10^{-5} $(\mu g/m^3)^{-1}$	
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1993
Arizona	(24-hour average)	110 μg/m^3	
Connecticut	(8-hour average)	400 μg/m^3	
Indiana	(8-hour average)	100 μg/m^3	
Kansas	(annual average)	0.02 μg/m^3	
Louisiana	(annual average)	200 μg/m^3	
Maine		0.0	
Maryland		0.0	
Massachusetts	(24-hour average)	1.08 μg/m^3	
Nevada	(8-hour average)	0.476 μg/m^3	

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

Agency	Description	Information	References
STATE (cont.)			
New York	(1-year average)	66.7 $\mu g/m^3$	
North Carolina	(24-hour average)	0.12 mg/m^3	
North Dakota	(8-hour average)	0.2 mg/m^3	
Oklahoma	(24-hour average)	198 $\mu g/m^3$	
Pennsylvania	(1-year average)	24 $\mu g/m^3$	
Texas	(1-year average)	4 $\mu g/m^3$	
Virginia	(24-hour average)	330 $\mu g/m^3$	
Washington	(24-hour average)	66.6 $\mu g/m^3$	
b. Water:	Drinking water quality standards		FSTRAC 1990
Alabama		7 $\mu g/L$	
Arizona		7 $\mu g/L$	
California		6 $\mu g/L$	
Connecticut		6 $\mu g/L$	
Maine		6 $\mu g/L$	
Massachusetts		7 $\mu g/L$	
Minnesota		6 $\mu g/L$	
New Jersey		2 $\mu g/L$	
Rhode Island		7 $\mu g/L$	
Vermont		6 $\mu g/L$	

[a]Group 3: Not classifable as to human carcinogenicity
[b]Group C: Possible human carcinogen

ACGIH = American Conference of Governmental Industrial Hygientists; BAT = Best Available Technology; C_a = Potential Occupational Carcinogen; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Level; RfD = Reference Dose; SNARL = Suggested No-Adverse Effect Level; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

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9. GLOSSARY

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

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

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

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

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

Carcinogen - A chemical capable of inducing cancer.

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

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

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

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

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

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

9. GLOSSARY

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

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

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

In vivo - Occurring within the living organism.

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

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

Lethal Dose($_{LO}$) (LD_{LO}) - The lowest dose of a chemical introduced by a route other than inhalation that 1s expected to have caused death in humans or animals.

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

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

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

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

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

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

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

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

9. GLOSSARY

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

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

q_1* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* 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).

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

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

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

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

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

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

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

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

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

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

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufftcient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral @SE Figure 2-2) routes.

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

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

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

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

(6). Exposure 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 lS), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

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

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

(10). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into “Less Serious” and “Serious” effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The “Less Serious” respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

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

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

(13). 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 LSE Figure 2-1

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

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

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

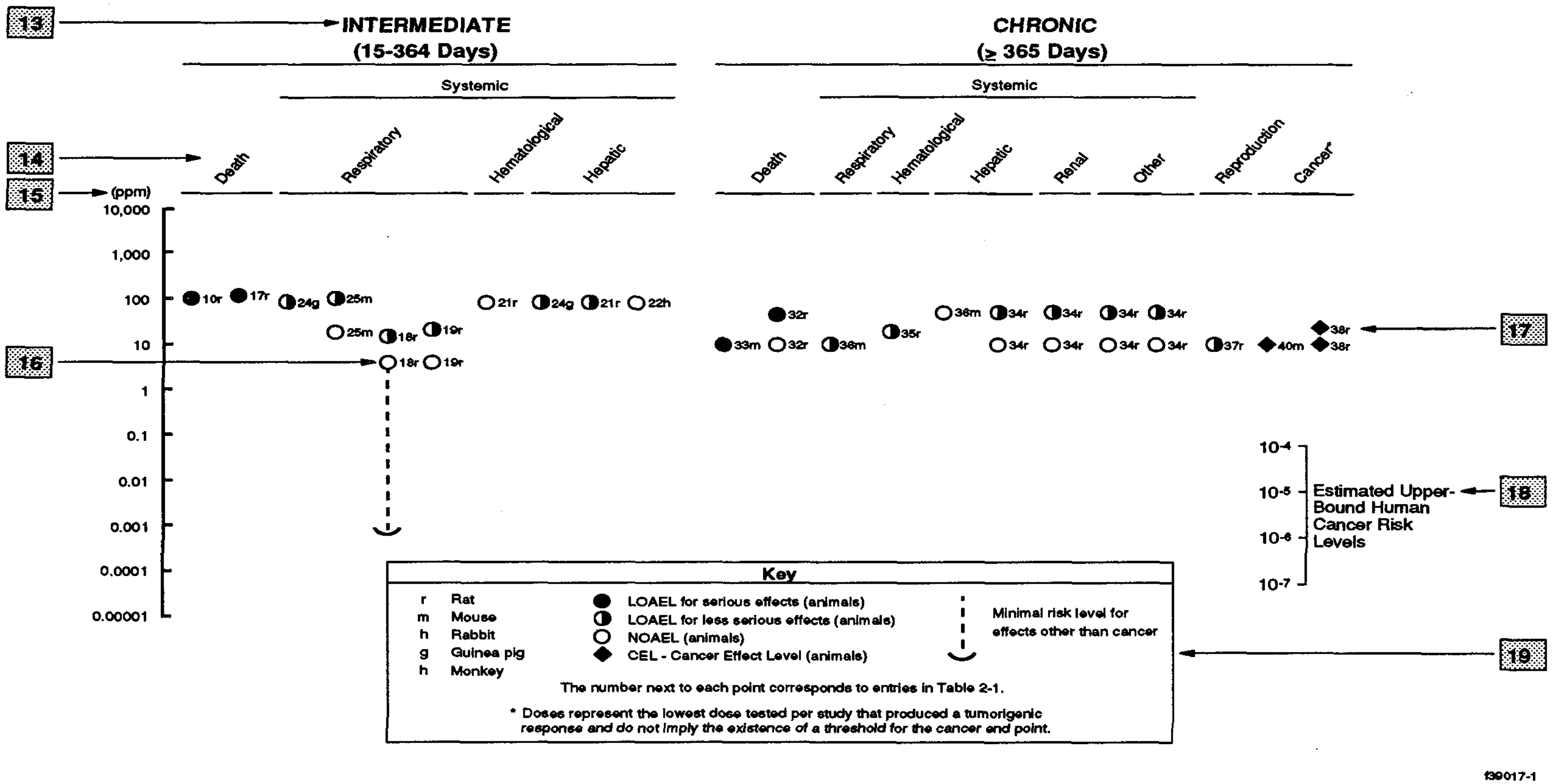
[a] The number corresponds to entries in Figure 2-1.

[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).

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

SAMPLE

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



APPENDIX A

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

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

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

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

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

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

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

Chapter 2 (Section 2.4)

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to 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 substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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

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

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOABL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. Generally an uncertainty factor of 10 is used; however, the MRL Workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

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