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VINYL CHLORIDE

Draft
For Public Comment

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

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DRAFT

**TOXICOLOGICAL PROFILE FOR
VINYL CHLORIDE**

Prepared by:

Clement International Corporation
Under Contract No. 205-88-0608

Prepared for:

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

October 1991

DRAFT FOR PUBLIC COMMENT

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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 which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

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

- (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and
- (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

The ATSDR toxicological profile is intended to characterize succinctly 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, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

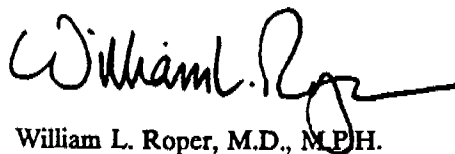
The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Foreword

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
Mail Stop E-29
Atlanta, Georgia 30333

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, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

A handwritten signature in black ink, appearing to read "William L. Roper", with a stylized flourish at the end.

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

CONTENTS

FOREWORD	iii
LIST OF FIGURES	ix
LIST OF TABLES	xi
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT IS VINYL CHLORIDE?	1
1.2 WHAT HAPPENS TO VINYL CHLORIDE WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO VINYL CHLORIDE?	2
1.4 HOW CAN VINYL CHLORIDE ENTER AND LEAVE MY BODY?	3
1.5 HOW CAN VINYL CHLORIDE AFFECT MY HEALTH?	3
1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO VINYL CHLORIDE?	5
1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	5
1.8 WHERE CAN I GET MORE INFORMATION?	6
2. HEALTH EFFECTS	7
2.1 INTRODUCTION	7
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	7
2.2.1 Inhalation Exposure	8
2.2.1.1 Death	8
2.2.1.2 Systemic Effects	8
2.2.1.3 Immunological Effects	26
2.2.1.4 Neurological Effects	27
2.2.1.5 Developmental Effects	28
2.2.1.6 Reproductive Effects	30
2.2.1.7 Genotoxic Effects	31
2.2.1.8 Cancer	33
2.2.2 Oral Exposure	36
2.2.2.1 Death	36
2.2.2.2 Systemic Effects	36
2.2.2.3 Immunological Effects	40
2.2.2.4 Neurological Effects	40
2.2.2.5 Developmental Effects	40
2.2.2.6 Reproductive Effects	40
2.2.2.7 Genotoxic Effects	40
2.2.2.8 Cancer	40
2.2.3 Dermal Exposure	41
2.2.3.1 Death	41
2.2.3.2 Systemic Effects	41
2.2.3.3 Immunological Effects	41
2.2.3.4 Neurological Effects	41
2.2.3.5 Developmental Effects	41
2.2.3.6 Reproductive Effects	41

2.2.3.7	Genotoxic Effects	41
2.2.3.8	Cancer	41
2.3	TOXICOKINETICS	42
2.3.1	Absorption	42
2.3.1.1	Inhalation Exposure	42
2.3.1.2	Oral Exposure	42
2.3.1.3	Dermal Exposure	42
2.3.2	Distribution	43
2.3.2.1	Inhalation Exposure	43
2.3.2.2	Oral Exposure	43
2.3.2.3	Dermal Exposure	44
2.3.3	Metabolism	44
2.3.3.1	Inhalation Exposure	44
2.3.3.2	Oral Exposure	46
2.3.3.3	Dermal Exposure	46
2.3.4	Excretion	47
2.3.4.1	Inhalation Exposure	47
2.3.4.2	Oral Exposure	47
2.3.4.3	Dermal Exposure	48
2.3.4.4	Other Routes of Exposure	48
2.4	RELEVANCE TO PUBLIC HEALTH	48
2.5	BIOMARKERS OF EXPOSURE AND EFFECT	58
2.5.1	Biomarkers Used to Identify or Quantify Exposure to Vinyl Chloride	59
2.5.2	Biomarkers Used to Characterize Effects Caused by Vinyl Chloride	60
2.6	INTERACTIONS WITH OTHER CHEMICALS	61
2.7	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	62
2.8	ADEQUACY OF THE DATABASE	63
2.8.1	Existing Information on Health Effects of Vinyl Chloride	64
2.8.2	Identification of Data Needs	64
2.8.3	On-going Studies	70
3.	CHEMICAL AND PHYSICAL INFORMATION	73
3.1	CHEMICAL IDENTITY	73
3.2	PHYSICAL AND CHEMICAL PROPERTIES	73
4.	PRODUCTION, IMPORT, USE, AND DISPOSAL	77
4.1	PRODUCTION	77
4.2	IMPORT/EXPORT	77
4.3	USE	77
4.4	DISPOSAL	80
5.	POTENTIAL FOR HUMAN EXPOSURE	81
5.1	OVERVIEW	81
5.2.1	Air	81
5.2.2	Water	81
5.2.3	Soil	86
5.3	ENVIRONMENTAL FATE	86
5.3.1	Transport and Partitioning	86

5.3.2	Transformation and Degradation	87
5.3.2.1	Air	87
5.3.2.2	Water	87
5.3.2.3	Soil	88
5.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	88
5.4.1	Air	88
5.4.2	Water	89
5.4.3	Soil	89
5.4.4	Other Environmental Media	89
5.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	90
5.6	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	90
5.7	ADEQUACY OF THE DATABASE	90
5.7.1	Identification of Data Needs	91
5.7.2	On-going Studies	92
6.	ANALYTICAL METHODS	93
6.1	BIOLOGICAL MATERIALS	93
6.2	ENVIRONMENTAL SAMPLES	96
6.3	ADEQUACY OF THE DATABASE	101
6.3.1	Identification of Data Needs	101
6.3.2	On-going Studies	102
7.	REGULATIONS AND ADVISORIES	103
8.	REFERENCES	111
9.	GLOSSARY	147
APPENDICES		
A.	USER'S GUIDE	A-1
B.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS	B-1
C.	PEER REVIEW	C-1

LIST OF FIGURES

2-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation	18
2-2 Levels of Significant Exposure to Vinyl Chloride - Oral	39
2-3 Proposed Metabolic Pathway for Vinyl Chloride	45
2-4 Existing Information on Health Effects of Vinyl Chloride	65
5-1 Frequency of NPL Sites with Vinyl Chloride Contamination	82

LIST OF TABLES

2-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation	9
2-2 Levels of Significant Exposure to Vinyl Chloride - Oral	37
2-3 Genotoxicity of Vinyl Chloride <u>In Vivo</u>	56
2-4 Genotoxicity of Vinyl Chloride <u>In Vitro</u>	57
2-5 On-going Studies on Vinyl Chloride	71
3-1 Chemical Identity of Vinyl Chloride	74
3-2 Physical and Chemical Properties of Vinyl Chloride	75
4-1 Facilities That Manufacture or Process Vinyl Chloride	78
5-1 Releases to the Environment from Facilities That Manufacture or Process Vinyl Chloride . . .	83
6-1 Analytical Methods for Determining Vinyl Chloride in Biological Materials	94
6-2 Analytical Methods for Determining Vinyl Chloride in Environmental Samples	97
7-1 Regulations and Guidelines Applicable to Vinyl Chloride	104

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about vinyl chloride and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Vinyl chloride has been found in at least 245 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for vinyl chloride. As EPA evaluates more sites, the number of sites at which vinyl chloride is found may change. This information is important for you to know because vinyl chloride may cause harmful health effects and because these sites are potential or actual sources of human exposure to vinyl chloride.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

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

1.1 WHAT IS VINYL CHLORIDE?

Vinyl chloride, also known as chloroethene, chloroethylene, ethylene monochloride, or monochloroethylene, is a colorless vapor with a mild, sweet odor. It can exist in liquid form if it is kept under high pressure. Almost all vinyl chloride is man-made. Most of the vinyl chloride produced in the United States is used to make polyvinyl chloride (PVC). PVC is used to make a variety of plastic products including pipes, wire and cable coatings, and packaging materials. Other uses include furniture and automobile upholstery, wall coverings, housewares, and automotive parts. At one time, vinyl chloride also was used as a coolant, a propellant in spray cans, and in some cosmetics. It is no longer used for these purposes. Please refer to Chapter 3 for more information on the chemical and physical properties of vinyl chloride. For more information on the production and use of vinyl chloride, see Chapter 4.

1. PUBLIC HEALTH STATEMENT

1.2 WHAT HAPPENS TO VINYL CHLORIDE WHEN IT ENTERS THE ENVIRONMENT?

Most of the vinyl chloride that enters the environment comes from plastics industries that release it into the air or into waste water. EPA limits the amount industries may release. Vinyl chloride also comes from tobacco smoke. Vinyl chloride is also a breakdown product of other man-made chemicals in the environment. Vinyl chloride has entered the environment at hazardous waste sites as a result of either improper disposal, leakage from storage containers, from spills, or from the breakdown of other chemicals.

Liquid vinyl chloride evaporates easily into the air. Vinyl chloride in water or soil also evaporates rapidly if it is near the surface. Vinyl chloride in the air breaks down in a few days. It does not form other harmful chemicals.

A limited amount of vinyl chloride can dissolve in water. It can enter groundwater and can stay in underground water for many years. It is unlikely that vinyl chloride will build up in plants or animals that you might eat. For more information on what happens to vinyl chloride in the environment, please see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO VINYL CHLORIDE?

The most likely way that you may be exposed to vinyl chloride is by breathing it. Normally, vinyl chloride is not found in urban, suburban, or rural air. However, vinyl chloride has been found in the air near plastics industries, hazardous waste sites, and landfills. In general, the amount of vinyl chloride in the air near these places varies from 0 to 1 part per million parts (ppm) of air. Levels as high as 44 ppm have been found at some hazardous waste sites. Vinyl chloride is in tobacco smoke from cigarettes and cigars.

You may also be exposed to vinyl chloride by drinking water from contaminated wells. However, most drinking water supplies do not contain vinyl chloride. In 1982, vinyl chloride was found in less than 1% of the 945 groundwater supplies tested. The concentrations found in groundwater ranged from 0 to 0.4 ppm. At one time, flow of water through PVC pipes added very low amounts of vinyl chloride to water. For example, in one study of recently installed pipes, the drinking water had 0.001 ppm of vinyl chloride. No current information on the amount of vinyl chloride released from PVC pipes into water is available. In the past, vinyl chloride could get into food that was stored in materials that contained PVC. Now, the United States government regulates food packaging materials and essentially no vinyl chloride enters foods by contact with these products.

1. PUBLIC HEALTH STATEMENT

About 80,000 people work with vinyl chloride at their jobs. This number includes workers who make vinyl chloride and PVC, and who use PVC to make other objects such as pipes. Please refer to Chapter 5 for more information on ways that people are exposed to vinyl chloride.

1.4 HOW CAN VINYL CHLORIDE ENTER AND LEAVE MY BODY?

Vinyl chloride does not enter your body by passing through your skin. However, it can easily enter your body when you breathe air or drink water containing it. This could occur near certain factories or hazardous waste sites. Most of the vinyl chloride that you breathe in or swallow enters your blood rapidly. The vinyl chloride in your blood travels throughout your body. When it reaches your liver, it is changed into several different substances. Most of these new substances travel in your blood. Once they reach your kidneys, they leave your body in your urine. Most of the vinyl chloride is gone from your body a day after you either breathe it in or swallow it. The liver, however, makes some new substances that do not leave your body as rapidly. A few of these substances are more harmful than vinyl chloride because they react with chemicals inside of your body and interfere with the way your body uses or responds to these chemicals. It takes more time for your body to get rid of these changed chemicals, but eventually your body will remove them as well. If you breathe in or swallow more vinyl chloride than your liver can chemically change, you will breathe out the excess vinyl chloride. Chapter 2 contains more information on how vinyl chloride enters and leaves your body.

1.5 HOW CAN VINYL CHLORIDE AFFECT MY HEALTH?

If you breathe high levels of vinyl chloride, you will feel dizzy or sleepy. These effects occur within 5 minutes at about 10,000 ppm of vinyl chloride. You can easily smell vinyl chloride at this concentration. If you breathe very high levels, you may pass out. You can rapidly recover from these effects if you breathe fresh air. Some people get a headache when they breathe fresh air immediately after breathing very high levels of vinyl chloride. People may die if they breathe extremely high levels of vinyl chloride. These levels are much higher than the levels that cause you to pass out. Studies in animals show that extremely high levels of vinyl chloride can damage the liver, lungs, and kidneys. These levels can also damage the heart and prevent blood clotting. The effects of drinking high levels of vinyl chloride are unknown. If you spill liquid vinyl chloride on your skin, it will numb the skin and cause redness and blisters.

Some people who have breathed vinyl chloride over several years have developed changes in the structure of their livers. People are more likely to develop these changes if they breathe high levels of vinyl chloride. Some people who have worked with vinyl chloride have developed nerve damage, and others have developed an immune reaction. The

1. PUBLIC HEALTH STATEMENT

lowest levels that cause liver changes, nerve damage, and the immune reaction in humans are not known. Some people who work at jobs that cause them to be exposed to very high levels of vinyl chloride have problems with the blood flow in their hands. Their fingers turn white and hurt when they go into the cold. It may take a long time to recover when they go into a warm place. In some of these people, changes have appeared on the skin of their hands and forearms. Also, the bones at the tips of their fingers have broken down. Studies suggest that some people may be more sensitive to these effects than others.

Some men who work with vinyl chloride have complained of a lack of sex drive. Results of studies in animals show that long-term exposure may damage the sperm and the testes. Some women who work with vinyl chloride have had irregular menstrual periods. Some have developed high blood pressure during pregnancy. Studies of women who live near vinyl chloride manufacturing plants could not prove that vinyl chloride causes birth defects. Studies in animals show that breathing vinyl chloride may harm the babies of pregnant animals. Animal studies also show that vinyl chloride may cause increased numbers of miscarriages early in pregnancy and decreased weight of the babies. It may also cause delayed skeletal development. The same very high levels of vinyl chloride that caused these effects on the babies also caused adverse effects in the pregnant animals.

Studies of workers who have breathed vinyl chloride over many years showed that it can cause cancer of the liver. Brain cancer, lung cancer, and some cancers of the blood also may be connected with breathing it daily for several years. Studies of long-term exposure in animals show that increases in cancer may occur at very low levels of vinyl chloride in the air. Studies show that animals fed low levels of vinyl chloride each day during their lifetime had an increased risk of getting cancer. These results suggest that breathing air or drinking water containing low levels of vinyl chloride may increase the risk of getting cancer. As a result of these studies, the Department of Health and Human Services has determined that vinyl chloride is a known carcinogen.

The Agency for Toxic Substances and Disease Registry has calculated Environmental Media Evaluation Guides (EMEGs) for vinyl chloride. EMEGs are derived from Minimal Risk Levels (MRLs) which are calculated from human or animal data for vinyl chloride. The MRLs are further described in Chapter 2 and in the footnotes to Tables 2-1 and 2-2. If a person is exposed to vinyl chloride at a level below the EMEG for the period listed below, we do not expect harmful health effects to occur. Because these levels are based only on information currently available, some uncertainty is always associated with them. Also, an EMEG does not imply anything about the presence, absence or level of risk for cancer because the methods for deriving EMEGs do not use any information about cancer. The EMEGs are provided as concentrations in order to

1. PUBLIC HEALTH STATEMENT

Air exposure

- An air EMEG of 0.002 ppm for vinyl chloride was derived from animal data for exposures longer than 14 days but less than one year.

Drinking water exposure

Drinking water EMEGs represent the lower end of a range and are protective for both children and adults.

- A drinking water EMEG of 0.0002 ppm for vinyl chloride was derived from animal data for exposures of one year or more.

Soil exposure

Soil EMEGs represent the lower end of a range and are protective for both children and adults. However, this range is not protective for children (pica) who show increased desire for eating non-food items (such as soil).

- A soil EMEG of 1 ppm for vinyl chloride was derived from animal data for exposures of one year or more.

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

The results of several tests can show if you have been exposed to vinyl chloride. None of these tests are normally available at your doctor's office. Vinyl chloride can be measured in your breath, but the test must be done shortly after exposure. This test is not very helpful for measuring very low levels of the chemical. The amount of the major breakdown product of vinyl chloride, thiodiglycolic acid, in the urine may give some information about exposure. This test must be done shortly after exposure and is not a reliable indicator of the level of exposure. Also, exposure to other chemicals can produce the same breakdown products in your urine. Vinyl chloride may bind to genetic material in your body. The amount of this binding can be measured. This measurement will give information about whether you have been exposed to vinyl chloride. However, scientists do not know if these measurements can tell how much vinyl chloride you have been exposed to. For more information see Chapters 2 and 6.

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

1. PUBLIC HEALTH STATEMENT

The federal government has developed regulatory standards and guidelines to protect individuals from the potential health effects of vinyl chloride in drinking water, food, and air. EPA requires that the amount of vinyl chloride in drinking water should not exceed 0.002 milligrams of vinyl chloride in a liter of water (mg/L) (0.002 ppm). For short-term exposures, EPA requires that drinking water levels should not exceed 2.6 mg/L (2.6 ppm) for 10 days. Adult consumption of drinking water over longer periods should not exceed 0.046 mg/L (0.046 ppm). Children's intake should be limited to less than 0.013 mg/L (0.013 ppm) over long periods.

To limit intake of vinyl chloride in food to levels considered to be safe, the Food and Drug Administration (FDA) regulates the vinyl chloride content of various plastics. These include plastics that carry water and plastics that come into contact with food. Limits range from 5 to 50 ppm, depending on the nature of the plastic and its use.

EPA has named vinyl chloride as a hazardous part of solid waste. If quantities greater than 1 pound are released to the environment, the National Response Center of the federal government must be told immediately.

The Occupational Safety and Health Administration (OSHA) regulates levels of vinyl chloride in the workplace. The maximum allowable amount of vinyl chloride in workroom air during an 8-hour workday in a 40-hour workweek is 1 ppm. The maximum amount allowed in any 15-minute period is 5 ppm. The National Institute for Occupational Safety and Health (NIOSH) classifies vinyl chloride as an occupational carcinogen. Workers exposed to any measurable amount of it must wear special breathing equipment. EPA has determined that factories must limit the amount of vinyl chloride released in air to 10 ppm. For more information, 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

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses 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 vinyl chloride and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for vinyl chloride based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of vinyl chloride are indicated in Figures 2-1 and 2-2. Because cancer effects could occur at lower exposure levels, the figures 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 (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989a), 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.

2. HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.1 Death

A report by Danziger (1960) described the deaths of two vinyl chloride workers. In one case, a worker exposed to high concentrations of vinyl chloride vapor emitted from an open valve was found dead. In another case, a worker responsible for cleaning a polymerization tank was found dead in the tank. Autopsies performed on these men indicated that death was due to asphyxiation. Circumstances surrounding the deaths suggested that the deaths were due to breathing very high levels of vinyl chloride.

Brief exposures of experimental animals such as guinea pigs, mice, and rats to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been shown to be fatal (Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). At these concentrations, deaths occurred within 30-60 minutes.

Decreased longevity was observed at much lower doses of vinyl chloride in intermediate- and chronic-duration studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979a; Hong et al. 1981; Lee et al. 1977a, 1978; Viola et al. 1970). A treatment-related increase in mortality was observed in mice exposed to 500 ppm of vinyl chloride for 6 hours per day, 5 days per week, for 6 months (Adkins et al. 1986). In mice and rats maintained for 12 months following a 6-month, 6-hour-per-day, 5-day-per-week exposure regime, decreased longevity was observed at concentrations as low as 50 ppm (Hong et al. 1981). However, statistical analyses of the data were not available to verify the significance of the decrease. Substantial increases in mortality of mice and rats exposed to 250 ppm vinyl chloride for 12 months were observed by Lee et al. (1977a, 1978). In addition, small increases in mortality of mice and rats during the 12-month exposure period were observed at 50 ppm in these reports. However, statistical analyses indicating the significance of these increases were not presented.

The influence of the age of female animals at the time of exposure to vinyl chloride on survival was examined by Drew et al. (1983). In female hamsters exposed to 200 ppm, two strains of female mice exposed to 50 ppm, and female rats exposed to 100 ppm for 12 months, a higher death rate was observed when 2-month-old animals were exposed than when 8- or 14-month-old animals were exposed. Similar trends were observed when hamsters and mice were exposed to these concentrations for 6 months. These results do not necessarily indicate that young people are more susceptible to the lethal effects of vinyl chloride, since animals that were exposed later in life may have died of age-related causes prior to the expression of the lethal effects. This study was limited in that only one dose of vinyl chloride was tested in each species.

The highest NOAEL values for intermediate-duration studies and all reliable LOAEL values from acute- and intermediate-duration studies that examine the effects of vinyl chloride on death are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each study with a systemic end point in each duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Limited information is available on the acute effects of inhalation of vinyl chloride by humans. The autopsy findings from a man who died after being overcome by vinyl chloride vapor revealed the irritating nature of extremely high-level inhalation exposure. The lungs were found to be intensely hyperemic, and some desquamation of the alveolar epithelium had occurred (Danziger 1960).

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Rat	30 min				300000 (5/5)	Mastromatteo et al. 1960
2	Rat	2 hr				150000	Lester et al. 1963
3	Gn pig	30 min				300000 (1/5)	Mastromatteo et al. 1960
4	Gn pig	up to 8 hr				100000	Patty et al. 1930
5	Mouse	30 min				200000 (2/5)	Mastromatteo et al. 1960
Systemic							
6	Rat	2 hr	Resp	100000	150000 (lung edema)		Lester et al. 1963
7	Rat	1-5 d 6hr/d	Hepatic	50000			Reynolds et al. 1975b
8	Rat	30 min	Resp		100000 (lung congestion)		Mastromatteo et al. 1960
			Hepatic	100000	200000 (liver fatty infiltration)		
			Renal	200000	300000 (kidney congestion)		
9	Rat	1, 5 d 6hr/d	Hepatic	50000			Reynolds et al. 1975a
10	Rat	1, 5 d 6hr/d	Hepatic	50000	100000 (liver vacuolization)		Jaeger et al. 1974

2 HEALTH EFFECTS

5

DRAFT FOR PUBLIC COMMENT

TABLE 2-1 (Continued)

Key to figure*	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
11	Gn pig	30 min	Resp Hemato Hepatic	200000 200000	100000 (lung congestion) 300000 (absence of clotting) 300000 (liver degeneration)		Mastromatteo et al. 1960
12	Mouse	30 min	Resp Hepatic Renal	200000 200000 100000	100000 (lung hyperemia) 300000 (liver congestion) 200000 (kidney degeneration)		Mastromatteo et al. 1960
Neurological							
13	Human	5 min 2x/d		4000	8000 (dizziness)		Lester et al. 1963
14	Rat	1 hr		50000			Hehir et al. 1981
15	Rat	1, 5 d 6hr/d		50000		100000 (anesthesia)	Jaeger et al. 1974
16	Rat	30 min				100000 (narcosis)	Mastromatteo et al. 1960
17	Rat	2 hr			50000 (intoxication)		Lester et al. 1963
18	Gn pig	30 min				100000 (unconscious)	Mastromatteo et al. 1960
19	Gn pig	up to 8 hr		10000		25000 (narcosis)	Patty et al. 1930
20	Mouse	30 min				100000 (narcosis)	Mastromatteo et al. 1960
21	Mouse	1 hr		5000	50000 (ataxia)		Hehir et al. 1981

2. HEALTH EFFECTS

10

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TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		† Reference
					Less serious (ppm)	Serious (ppm)	
Developmental							
22	Rat	10 d 7hr/d Gd6-15			2500 (ureter dilation)		John et al. 1981
23	Rabbit	13 d 7hr/d Gd6-18			500 (delayed ossification)		John et al. 1977
24	Mouse	10 d 7hr/d Gd6-15		50		500 (resorptions)	John et al. 1977
Reproductive							
25	Mouse	5 d 6hr/d		30000			Anderson et al. 1976
Cancer							
26	Mouse	1 hr				5000 (CEL lung)	Behr et al. 1981
INTERMEDIATE EXPOSURE							
Death							
27	Mouse	6 mo 5d/wk 6hr/d		200		500	Adkins et al. 1986
28	Mouse	6 mo 5d/wk 6hr/d				50	Hong et al. 1981

DRAFT FOR PUBLIC COMMENT

HEALTH EFFECTS

11

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
Systemic							1
29	Rat	19 d 8hr/d	Hemato Hepatic Renal	 50000	50000 (decreased white blood cells) 50000 (histopathology)		Lester et al. 1963
30	Rat	10 mo 5d/wk 5hr/d	Hepatic		50 (histopathology)		Wisniewska- Knypl et al. 1980
31	Rat	6 mo 5d/wk 7hr/d	Hemato Hepatic Renal	200 200	100 (increased liver weight)		Torkelson et al 1961
32	Rat	10 wk 5d/wk 1hr/d	Resp	500			Hehir et al. 1981
33	Rat	3 mo 6d/wk 6hr/d	Cardio Hemato Renal	10 100 100	100 (increased heart weight) 3000 (increased spleen weight) 3000 (increased kidney weight)		Bi et al. 1985
34	Rat	6 mo 6d/wk 6hr/d	Cardio Hemato Hepatic		10 (increased heart weight) 10 (increased spleen weight) 10 ^b (increased liver weight)		Bi et al. 1985
35	Rat	92 d 5d/wk 8hr/d	Hemato Hepatic Renal	 20000	20000 (decreased white blood cells) 20000 (histopathology)		Lester et al. 1963

2. HEALTH EFFECTS

12

DRAFT FOR PUBLIC COMMENT

R&S148432

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
36	Rat	10 mo 5d/wk 5hr/d	Hemato	20000	50 (increased spleen weight)		Sokal et al. 1980
			Musc/skel Hepatic		50 (increased smooth endoplasmic reticulum)		
			Renal	50	500 (increased kidney weight)		
			Other		50 (decreased body weight)		
37	Rabbit	6 mo 5d/wk 7hr/d	Hepatic	100	200 (necrosis)		Torkelson et al. 1961
38	Gn pig	6 mo 5d/wk 7hr/d	Hepatic	200			Torkelson et al. 1961
39	Mouse	8 wk 5d/wk 6hr/d	Hemato	1000			Sharma and Gehring 1979
40	Mouse	5-6 mo 5d/wk 5hr/d	Resp		2500 (hypertrophy)		Suzuki 1981, also Suzuki 1978
41	Mouse	1-6 mo 5d/wk 5hr/d	Hepatic		2500 (histopathology)		Schaffner 1979
42	Mouse	20 wk 5d/wk 1hr/d	Resp Hepatic	50 50			Mehtir et al. 1981
43	Dog	6 mo 5d/wk 7hr/d	Hemato Hepatic Renal	200 200 200			Torkelson et al. 1961

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
Immunological							
44	Mouse	8 wk 5d/wk 6hr/d			10 (increased immune response)		Sharma and Gehring 1979
Reproductive							
45	Rat	10 mo 5d/wk 5hr/d		50		500 (decreased spermatogenesis)	Sokal et al. 1980
46	Rat	11 wk 5d/wk 6hr/d		50	250 (reduced male fertility)		Short et al. 1977
47	Rat	3, 6 mo 6d/wk 6hr/d		10	100 (decreased testes weight)		Bi et al. 1985
Cancer							
48	Rat	10 mo 5d/wk 6hr/d				250 (CEL liver)	Hong et al. 1981
49	Rat	6 mo 5d/wk 6hr/d				100 (CEL liver)	Drew et al. 1983
50	Mouse	7-9 mo 5d/wk 6hr/d				50 (CEL liver)	Lee et al. 1978
51	Mouse	6 mo 5d/wk 6hr/d				50 (CEL peritoneum)	Drew et al. 1983

TABLE 2-1 (Continued)

Key to figure*	Species	Exposure duration/frequency	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
52	Mouse	6 mo 5d/wk 6hr/d				50 (CEL lung)	Adkins et al. 1986
53	Mouse	1,3,6 mo 5d/wk 6hr/d				50 (CEL mammary gland)	Hong et al. 1981
54	Mouse	6 mo 5d/wk 6hr/d				50 (CEL peritoneum)	Drew et al. 1983
55	Mouse	4 wk 5d/wk 6hr/d				100 (CEL lung)	Suzuki 1982
56	Hamster	30 wk 5d/wk 4hr/d				500 (CEL liver)	Maltoni et al. 1981
57	Hamster	6 mo 5d/wk 6hr/d				200 (CEL liver)	Drew et al. 1983
CHRONIC EXPOSURE							
Systemic							
58	Rat	12 mo 6d/wk 6hr/d	Hepatic		3000 (increased liver weight)		Bi et al. 1985
			Renal	10	100 (increased kidney weight)		

DRAFT FOR PUBLIC COMMENT

2. HEALTH EFFECTS

15

TABLE 2-1 (Continued)

Key to figure	Species	Exposure duration/frequency	System	NOAEL (mg/m ³)	LOAEL (effect)		Reference
					less serious (mg/m ³)	Serious (mg/m ³)	
Reproductive							
59	Rat	12 mo 6d/wk 6hr/d		10		100 (testes necrosis)	Bi et al. 1985
Cancer							
60	Rat	52 wk 5d/wk 4hr/d				5 (CEL mammary gland)	Maltoni et al. 1981
61	Rat	12, 18, 24 mo 5d/wk 6hr/d				100 (CEL liver)	Drew et al. 1983
62	Rat	12 mo 6d/wk 6hr/d				100 (CEL liver)	Bi et al. 1985
63	Rat	12 mo 5d/wk 6hr/d				250 (CEL liver)	Lee et al. 1978
64	Rat	52 wk 5d/wk 4hr/d				1 (CEL liver)	Maltoni et al. 1981
65	Mouse	12, 18 mo 5d/wk 6hr/d				50 (CEL liver)	Drew et al. 1983
66	Mouse	12 mo 5d/wk 6hr/d				50 (CEL lung)	Lee et al. 1978

TABLE 2-1 (Continued)

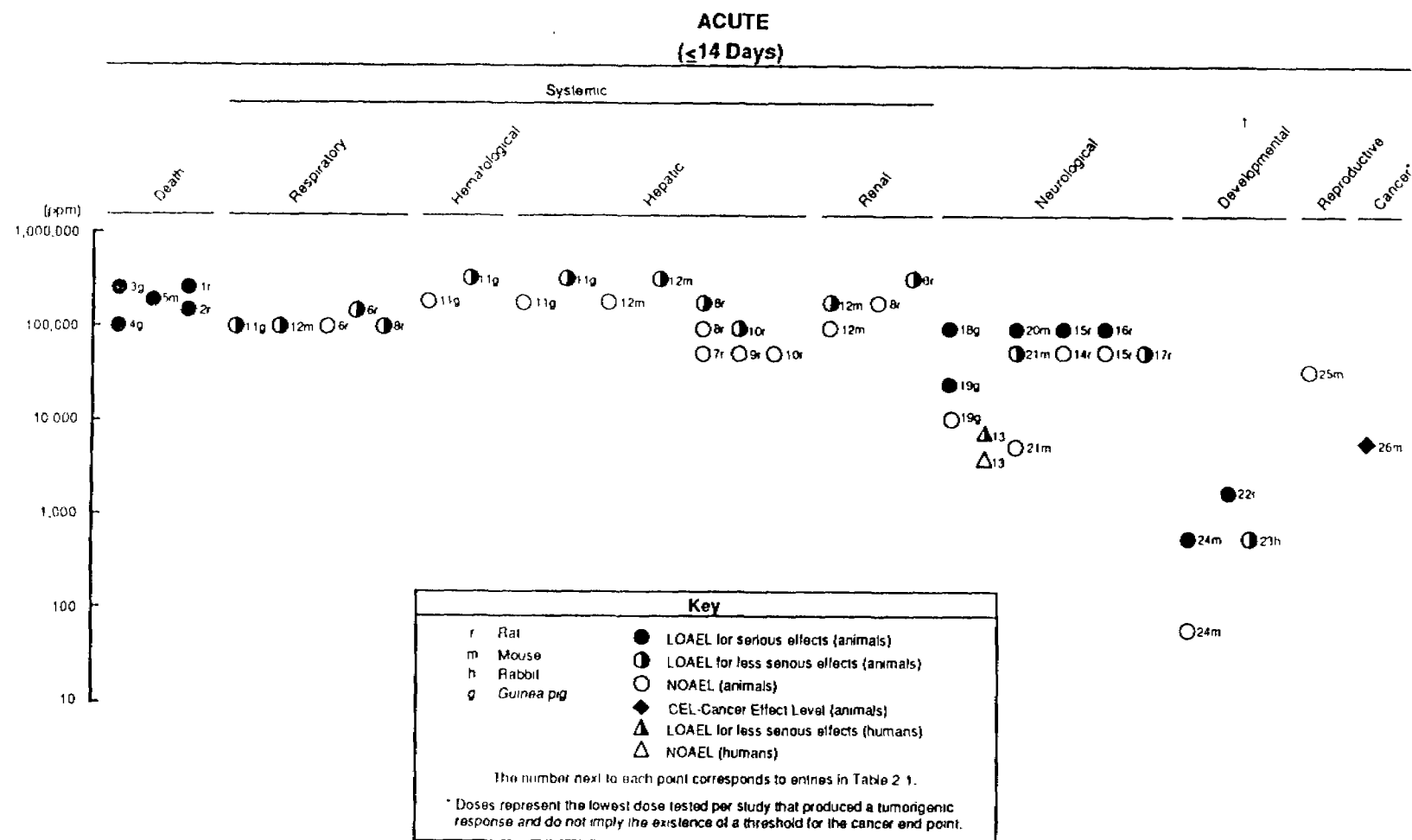
Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (mg/m ³)	LOAEL (effect)		Reference
					Less serious (mg/m ³)	Serious (mg/m ³)	
67	Mouse	12, 18 mo 5d/wk 6hr/d				50 (CEL lung)	Drew et al. 1983
68	Hamster	12, 18, 24 mo 5d/wk 6hr/d				200 (CEL liver)	Drew et al. 1983

^aThe number corresponds to entries in Figure 2-1.

^bUsed to derive an intermediate inhalation Minimal Risk Level (MRL) of 0.002 ppm; dose adjusted from intermittent to continuous dosing (10 ppm x 6 days/7 days x 6 hr/24 hr = 2 ppm), adjusted dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). This intermediate inhalation MRL is presented as a concentration of 0.002 ppm in air as an Environmental Media Evaluation Guide (EMEG) in Section 1.5.

Cardio = cardiovascular; CEL = Cancer Effect Level; d = day(s); Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

FIGURE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation



2. HEALTH EFFECTS

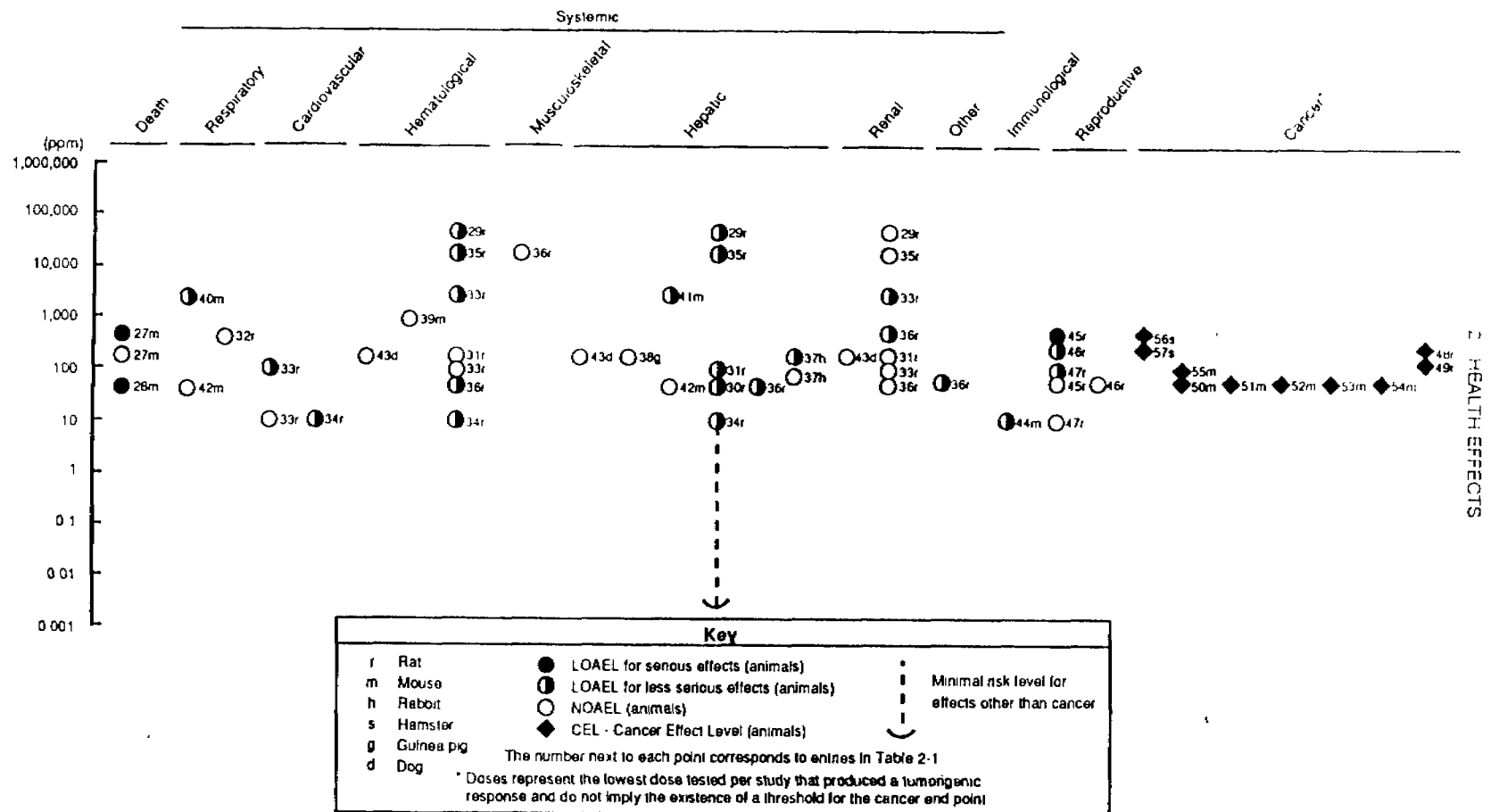
18

DRAFT FOR PUBLIC COMMENT

R&S148438

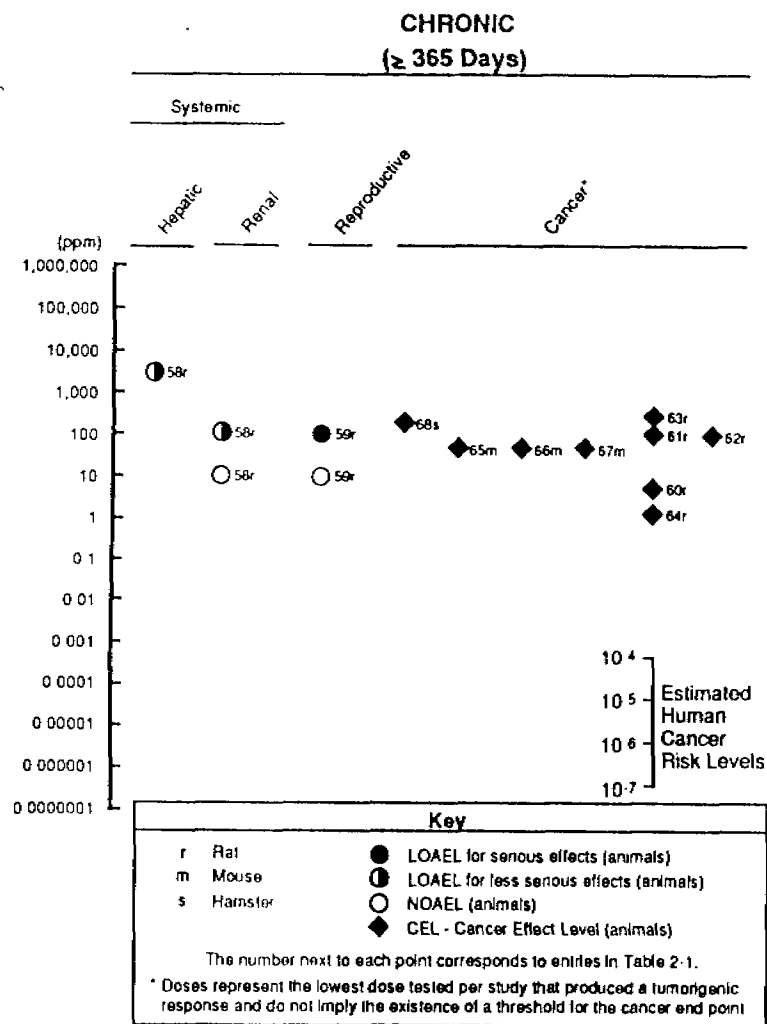
FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)



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FIGURE 2-1 (Continued)



2 HEALTH EFFECTS

Reports regarding respiratory effects in workers who are occupationally exposed to vinyl chloride are contradictory. Whereas a number of epidemiologic studies find no increased incidence of respiratory disease among vinyl chloride workers (Gamble et al. 1976; LaPlanche et al. 1987; Waxweiler et al. 1977), several other epidemiologic surveys and case reports find evidence of pulmonary damage. The adverse respiratory effects reported in these studies include increased incidence of emphysema, decreased respiratory volume and vital capacity, respiratory insufficiency, decreased respiratory oxygen and carbon dioxide transfer, pulmonary fibrosis, and abnormal chest x-rays (Juhe et al. 1974; Lilis et al. 1975, 1976; Lloyd et al. 1984; Suciú et al. 1975; Walker 1976; Wong et al. 1986). Interpretation of many of these results is confounded by the inclusion of smokers among those exposed to vinyl chloride and the concurrent exposure of many vinyl chloride workers to PVC resin dust, which is known to cause respiratory lesions (Mastrangelo et al. 1979).

Brief inhalation of high concentrations of vinyl chloride caused respiratory inflammation in a variety of animals. A 30-minute exposure of guinea pigs, mice, and rats to 100,000 ppm of vinyl chloride produced slight hyperemia in mice and rats and marked pulmonary congestion in guinea pigs. Exposure to higher concentrations (200,000 ppm and 300,000 ppm) caused increased congestion, edema, and, at the highest concentrations, hemorrhages in all three species (Mastromatteo et al. 1960). Edema and congestion of the lungs of rats also were observed following a 2-hour exposure to 150,000 ppm (Lester et al. 1963).

Histopathologic examination of mice exposed to 2,500 ppm vinyl chloride for 5 hours per day, 5 days per week, for 5-6 months revealed proliferation and hypertrophy of bronchiolar epithelium, hyperplasia of alveolar epithelium, hypersecretion of mucin, increased endoplasmic reticulum and free ribosomes in Clara cells, and mobilization of alveolar macrophages (Suzuki 1978, 1980, 1981). These changes were observed irrespective of the recovery period (2 or 37 days) indicating that they were not readily reversible. However, these studies were severely limited by the small number of animals tested and the absence of a statistical analysis.

Chronic exposure of rats to 5,000 ppm for 7 hours per day, 5 days per week, for 12 months produced hyperplasia of olfactory epithelium, increased cellularity of interalveolar septa of the lungs, and an increased incidence of pulmonary hemorrhages (Feron and Kroes 1979). Interstitial pneumonia and two incidences of hemorrhagic lungs were observed in rats exposed to 30,000 ppm of vinyl chloride for 7 hours per day, 5 days per week, for 12 months (Viola et al. 1971). However, the statistical significance of the findings in the studies by Feron and Kroes (1979) and Viola et al. (1971) is unknown.

Cardiovascular Effects. Occupational exposure to vinyl chloride has been associated with the development of Raynaud's phenomenon, a condition in which the fingers blanch and experience numbness and discomfort upon exposure to the cold. This condition has been reported most frequently among workers who cleaned the reactor tanks; a job which reportedly exposed workers to very high levels of vinyl chloride. Although only a small percentage of vinyl chloride workers develop Raynaud's phenomenon (Juhe et al. 1974; LaPlanche et al. 1987; Lilis et al. 1975; Marsteller et al. 1975; Suciú et al. 1963, 1975; Veltman et al. 1975), the incidence is significantly higher than in unexposed personnel (LaPlanche et al. 1987). Investigation of the peripheral circulation of workers afflicted with Raynaud's phenomenon has revealed thickening of the walls of the digital arteries (Harris and Adams 1967; Juhe et al. 1974); narrowing of the arterial lumen, arterial occlusions, tortuosity, and hypervascularity (Juhe et al. 1974; Preston et al. 1976; Veltman et al. 1975; Walker 1976); inflammatory infiltration of the arterioles (Magnavita et al. 1986); deposition of immune products along the vascular endothelium (Ward 1976); vasomotor impairment (Suciú et al. 1963); and impaired capillary microcirculation (Magnavita et al. 1986; Mاريو et al. 1976). Three reports indicate that upon removal from exposure, Raynaud's phenomenon gradually disappears (Freudiger et al. 1988; Suciú et al. 1963, 1975). In

2. HEALTH EFFECTS

one of these reports, improvement was observed within 4 months after the cessation of exposure (Freudiger et al. 1988).

Splenomegaly with evidence of portal hypertension (dilated peritoneal veins and esophageal varices) has been reported by investigators studying the effects of vinyl chloride exposure (Juhe et al. 1974; Lee and Harry 1974; Marsteller et al. 1975). In addition, hypertension among vinyl chloride workers (Suciú et al. 1975; Waxweiler et al. 1977) and significantly increased mortality due to cardiovascular and cerebrovascular disease (Bryen et al. 1976) have been reported.

Investigators studying the anesthetic properties of vinyl chloride in dogs have observed that doses producing anesthesia (100,000 ppm, Oster et al. 1946; 150,000-900,000 ppm, Carr et al. 1949) also caused cardiac arrhythmias. Arrhythmias were characterized by intermittent tachycardia, extraventricular systoles, vagal beats, ventricular fibrillation, and atrioventricular block. However, the statistical significance of these effects was not reported.

Chronic exposure of rats to 5,000 ppm vinyl chloride 7 hours per day, 5 days per week, for 1 year resulted in increases in areas of myodegeneration in the heart and thickening of the walls of arteries (Feron and Kroes 1979). However, the statistical significance of this effect was not reported. Exposure of rats to 30,000 ppm of vinyl chloride for 4 hours per day, 5 days per week, for 1 year also produced thickening of the walls of small arterial vessels. The thickening was characterized by a proliferation of the endothelium. In some vessels, the thickening was severe enough to cause blockage of the lumen (Viola 1970). A study by Bi et al. (1985) demonstrated an increase in the relative heart weight at concentrations of vinyl chloride as low as 10 ppm when administered to male rats for 6 hours per day, 6 days per week, for 6 months.

Gastrointestinal Effects. Approximately 32% of the vinyl chloride workers examined by Lilis et al. (1975) reported a history of "gastritis, ulcers (gastric and duodenal) and upper gastrointestinal bleeding." Because these subjects were not compared to workers who had not been exposed to vinyl chloride, the significance of these findings is unknown. Two studies reported that workers intoxicated by vinyl chloride experienced anorexia (Suciú et al. 1963, 1975). Other symptoms reported by vinyl chloride workers included nausea, abdominal distension, and heartburn.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to vinyl chloride.

Hematological Effects. Blood tests performed at autopsy from two workers whose deaths were believed to be due to exposure to extremely high levels of vinyl chloride, revealed that the blood did not clot (Danziger 1960). Slight-to-severe thrombocytopenia in workers occupationally exposed to vinyl chloride was reported in several studies (Juhe et al. 1974; Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975), but Lilis et al. (1975) found no increased incidence of thrombocytopenia in vinyl chloride workers. One study showed no damage to the bone marrow hematopoietic systems (Juhe et al. 1974). Splenomegaly was reported in a number of these studies (Marsteller et al. 1975; Popper and Thomas 1975; Suciú et al. 1963; Veltman et al. 1975), but Veltman et al. (1975) and Juhe et al. (1974) could find no correlation between the incidence of splenomegaly and thrombocytopenia. Increased levels of a number of plasma proteins (α 1- and α 2-globulin, α 2-macroglobulin, and ceruloplasmin) were reported in studies examining the effects of occupational exposure to vinyl chloride (Harris and Adams 1967; Suciú et al. 1975; Wagnierova et al. 1986, 1988).

A brief (30-minute) exposure of guinea pigs to 300,000 ppm vinyl chloride resulted in a failure of the blood to clot in the animals that died during the exposure (Mastromatteo et al. 1960). Exposure of dogs and rats

2. HEALTH EFFECTS

to 200 ppm, 7 hours per day, 5 days per week, for 6 months had no effect on hematologic values (Torkelson et al. 1961). Also, an 8-week exposure of mice to 1,000 ppm for 6 hours per day, 5 days per week had no effect on erythrocyte or leukocyte counts (Sharma and Gehring 1979). Exposure of rats to either 50,000 ppm for 8 hours per day, for 19 consecutive days or 20,000 ppm for 8 hours per day, 5 days per week, for 92 days resulted in a decrease in white cells (Lester et al. 1963). An increase in the relative spleen weight was observed in rats exposed to 50 ppm for 5 hours per day, 5 days per week, for 10 months (Sokal et al. 1980). Increased relative spleen weight was also reported by Bi et al. (1985) when rats were exposed to 10 ppm for 6 hours per day, 6 days per week, for 6 months. Exposure of rats to 5,000 ppm vinyl chloride for 7 hours per day, 5 days per week, for 1 year caused slightly increased hematopoiesis in the spleen; slightly decreased hemoglobin content, packed cell volume, and erythrocytes; and decreased clotting time (Feron and Kroes 1979; Feron et al. 1979a). The statistical significance of these results was not provided.

Musculoskeletal Effects. Acroosteolysis, or resorption of the terminal phalanges of the finger, was observed in a small percentage of workers occupationally exposed to vinyl chloride (Dinman et al. 1971; Juhe et al. 1974; Lilis et al. 1975; Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). As with Raynaud's phenomenon, acroosteolysis was reported predominantly among polymerization tank cleaners. Bone lesions were most often confined to the terminal phalanges of the fingers, but in a few cases the bones of the toes, sacroiliac joint, arms, legs, and mandible were also involved (Harris and Adams 1967; Juhe et al. 1974; Preston et al. 1976). Development of acroosteolysis was most often preceded by Raynaud's phenomenon (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). In two reports, bone resorption was observed to progress despite discontinuation of exposure (Markowitz et al. 1972; Preston et al. 1976). However, in two other reports, improvement was observed after exposure ceased (Veltman et al. 1975; Wilson et al. 1967). Joint pain was also reported by Lilis et al. (1975).

Although Sokal et al. (1980) found no alterations in the bones of rats exposed to 20,000 ppm for 5 hours per day, 5 days per week, for 10 months, Viola (1970) observed skeletal changes in the bones of the paws of rats exposed to 30,000 ppm for 4 hours per day, 5 days per week, for 12 months. The statistical significance of these effects was not reported.

Hepatic Effects. Throughout the early years of the use of vinyl chloride, workers experienced only a minimal degree of functional hepatic abnormalities. However, when it became apparent in the early 1970s that angiosarcoma of the liver was associated with long-term vinyl chloride exposure, an intensive effort by a number of investigators was initiated to characterize the hepatic effects of vinyl chloride. These studies revealed characteristic hepatic lesions produced by vinyl chloride exposure (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Jones and Smith 1982; Lee and Harry 1974; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; Popper and Thomas 1975; Suciú et al. 1975; Tamburro et al. 1984; Vihko et al. 1984; Waxweiler et al. 1977). The incidence and severity of the effects correlated well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; Waxweiler et al. 1977). A further description of hepatic angiosarcoma may be found in Section 2.2.1.8.

Routine noninvasive techniques revealed hepatomegaly in a limited number of workers (13-37%) (Lilis et al. 1975; Marsteller et al. 1975; Suciú et al. 1963, 1975; Waxweiler et al. 1977). However, when peritoneoscopy was performed or biopsies were obtained from exposed workers, Marsteller et al. (1975) found a much higher prevalence of hepatic abnormalities. Whereas only 37% of the workers studied by Marsteller et al. (1975) had been diagnosed with hepatomegaly, peritoneoscopy revealed a 50% incidence of granular changes in the liver surface and an 86% incidence of capsular fibrosis with increased numbers of capsular vessels. Histopathological examination of the biopsied tissue from these workers revealed an 80% incidence

2. HEALTH EFFECTS

of collagenization of the sinusoidal walls, a 90% incidence of proliferation of cells lining the sinusoids, a 30% incidence of septal fibrosis, and degeneration of hepatocytes (incidence not specified). A number of other investigators observed similar changes in liver tissues obtained from workers exposed to vinyl chloride (Falk et al. 1974; Gedigke et al. 1975; Juhe et al. 1974; Popper and Thomas 1975; Tamburro et al. 1984). Based on these observations, a profile of vinyl chloride-induced liver damage was compiled which includes the following features: hypertrophy and hyperplasia of hepatocytes; activation and hyperplasia of sinusoidal lining cells; fibrosis of portal tracts, septa and intralobular perisinusoidal regions; sinusoidal dilation; and focal areas of hepatocellular degeneration. This pattern of changes was observed to be highly unusual and was similar to the hepatic changes produced by arsenic (Gedigke et al. 1975). In addition, the degenerative changes in hepatocytes appeared to be less severe when biopsy material was obtained from workers who had not been exposed to vinyl chloride recently. However, sinusoidal changes were not influenced by the length of time since the last exposure (Gedigke et al. 1975).

One possible reason that the hepatotoxic effects of vinyl chloride went undetected for many years was the lack of sensitivity of standard biochemical liver function tests to detect the liver injury produced by vinyl chloride (Berk et al. 1975; Marsteller et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). For example, the values obtained in several standard biochemical liver function tests (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltranspeptidase) from workers with biopsy evidence of vinyl chloride-associated liver damage were not significantly higher than those from unexposed controls (Liss et al. 1985). Only serum bile acids and/or indocyanine green clearance correlated with liver injury (Berk et al. 1975; Liss et al. 1985; Tamburro et al. 1984). Furthermore, investigators have shown that levels of chenodeoxycholic acid (a serum bile acid) in asymptomatic vinyl chloride workers were elevated when compared to the 95% interval of values from a healthy reference population (Vihko et al. 1984).

Brief exposure of animals to extremely high concentrations of vinyl chloride has been shown to cause hepatic damage. For example, acute exposure (30 minutes) of guinea pigs, mice, and rats to 300,000 ppm of vinyl chloride caused liver congestion or severe fatty degeneration (Mastromatteo et al. 1960). Exposure to 100,000 ppm for 4 hours caused centrilobular vacuolization and increased serum α -ketoglutarate in rats (Jaeger et al. 1974). However, exposure of rats to 50,000 ppm for 4 or 6 hours produced no observable effects on the liver (Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). In contrast, a single-concentration study in which pregnant rats were continuously exposed to 1,565 ppm for 7-9 days during either the first or second trimester of pregnancy resulted in an increase in the liver to body weight ratio (Ungvary et al. 1978). Interestingly, a single 1-hour exposure of mice to 500, 5,000, or 50,000 ppm of vinyl chloride, followed by an 18-month observation period, resulted in an increased incidence of hepatocellular hypertrophy in these animals at terminal sacrifice (Hehir et al. 1981). The hypertrophy was not dose-dependent; thus, the significance of this effect is uncertain.

In studies with longer durations of exposure, lower concentrations of vinyl chloride have produced hepatic toxicity. Symptoms of hepatotoxicity that have been observed in rats have included degeneration, swelling of hepatocytes with compression of sinusoids, dilation of the rough endoplasmic reticulum, proliferation of smooth endoplasmic reticulum, changes in metabolic enzyme activities, proliferation of reticulocytes, and increased liver to body weight ratio (Bi et al. 1985; Du et al. 1979; Lester et al. 1963; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). For example, exposure of rats to 500 ppm for 7 hours per day, 5 days per week, for 4.5 months resulted in an increase in liver to body weight ratio and granular degeneration (Torkelson et al. 1961). Exposure of rats to 500 ppm for 5 hours per day, 5 days per week, for 10 months caused swelling of hepatocytes and proliferation of reticuloendothelial cells, increased liver weight, and cellular degeneration (Sokal et al. 1980). Also, exposure of rats to 50 ppm for 5 hours per day, 5 days per week, for 10 months produced fatty degeneration and proliferation of the smooth endoplasmic

2. HEALTH EFFECTS

reticulum (Wisniewska-Knypl et al. 1980). An increased liver to body weight ratio was observed in rats exposed to concentrations of vinyl chloride as low as 10 ppm for 6 hours per day, 6 days per week, for 6 months (Bi et al. 1985). Based on this value, an intermediate-duration MRL of 0.002 ppm was calculated as described in the footnote in Table 2-1.

The relative NOAELs for a variety of species following a 6-month exposure to vinyl chloride indicated that mice and rats were the most sensitive (NOAEL = 50 ppm), rabbits were the next most sensitive (NOAEL = 100 ppm), and dogs and guinea pigs were the least sensitive (NOAEL > 200 ppm) (Torkelson et al. 1961).

Popper et al. (1981) compared histopathological findings from sections of liver from mice and rats exposed by Maltoni and LeFemine (1975) with the liver biopsy material obtained from vinyl chloride workers. Hyperplasia and hypertrophy of hepatocytes and/or sinusoidal cells, with areas of sinusoidal dilation, were observed in both humans and rodents. The major difference between the species was the greater degree of fibrosis, seen as reticulin deposition and collagen formation, in the livers of humans. Also, inflammatory cells were present in the livers of humans, but not in rodents.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to vinyl chloride.

Acute exposure of mice and rats to 300,000 ppm of vinyl chloride for 30 minutes resulted in kidney congestion. Also, the kidneys of one mouse out of five exposed to either 200,000 or 300,000 ppm of vinyl chloride for 30 minutes showed degenerative changes (Mastromatteo et al. 1960). Exposure of rats to 50,000 ppm for 8 hours per day for 19 consecutive days or 20,000 ppm for 8 hours per day, 5 days per week, for 92 days caused no adverse effects on the kidneys (Lester et al. 1963). However, exposures of male rats to 3,000 ppm for 6 hours per day, 6 days per week, for 6 months caused the kidney to body weight ratio to increase (Bi et al. 1985). Also, 1 year of exposure to 5,000 ppm for 7 hours per day, 5 days per week caused increased kidney to body weight ratio and tubular nephrosis in rats. Increased blood urea nitrogen and urinary volume were also observed (Feron and Kroes 1979; Feron et al. 1979a). However, the statistical significance of these findings was not provided in the study.

Dermal/Ocular Effects. Local burns on the conjunctiva and cornea were observed in a man who died after exposure to an unknown quantity of vinyl chloride vapor escaping from an open valve (Danziger 1960).

Occupational exposure to vinyl chloride was observed to cause scleroderma-like skin changes on the hands of a small percentage of exposed workers (Juhe et al. 1974; Lilis et al. 1975; Marsteller et al. 1975; Suci et al. 1963, 1975; Veltman et al. 1976; Walker 1976). The skin changes were characterized by a thickening of the skin, decreased elasticity, and slight edema and were almost exclusively observed in workers who also suffered from Raynaud's phenomenon (Freudiger et al. 1988; Juhe et al. 1974; Lilis et al. 1975; Markowitz et al. 1972; Preston et al. 1976; Suci et al. 1975; Veltman et al. 1976; Walker 1976). Skin biopsies revealed increased collagen bundles in the subepidermal layer of the skin (Harris and Adams 1967; Juhe et al. 1974; Markowitz et al. 1972; Veltman et al. 1976). Biochemical analyses by Jayson et al. (1976) demonstrated that a high rate of collagen synthesis was taking place in the affected skin. Most often the skin changes were confined to the hands and wrists, but Jayson et al. (1976) reported scleroderma-like skin changes on the hands, arms, chest, and face of one afflicted worker.

Viola (1970) observed skin changes in rats exposed to 30,000 ppm for 12 months. The skin of the paws of the exposed rats showed areas of hyperkeratosis, thickening of the epidermis, edema, collagen dissociation,

2. HEALTH EFFECTS

and fragmentation of the elastic reticulum. Interpretation of these results is limited by the absence of a statistical analysis and insufficient information on the treatment of control animals.

2.2.1.3 Immunological Effects

A number of studies have examined the immunologic profile of workers occupationally exposed to vinyl chloride. A statistically significant increase in circulating immune complexes in workers exposed to vinyl chloride was observed when compared to levels in unexposed workers (Boddanikowa and Zawilska 1984). The increase in circulating immune complexes was greatest in women and in those with duties involving exposure to relatively high levels of vinyl chloride. Also, elevated immunoglobulins were found in workers exposed to vinyl chloride when compared to levels in unexposed controls (Wagnerova et al. 1986). However, no correlation between the levels of immunoglobulins and the duration of exposure was observed.

Studies of workers that have developed "vinyl chloride disease," a syndrome consisting of Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes, indicate that this disease may have an immunologic basis. Sera obtained from patients with varying degrees of severity of symptoms of vinyl chloride disease demonstrate a close correlation between the disease severity and the extent of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). The most frequent immunologic findings in workers with vinyl chloride disease are an increase in circulating immune complexes or cryoglobulinemia. In workers with the most severe clinical signs, there also is an increased incidence of B-cell proliferation, hyperimmunoglobulinemia, and complement activation (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). Evidence of a structurally altered immunoglobulin G (IgG) has been obtained, and vinyl chloride (or a metabolite) has been proposed to bind to IgG (Grainger et al. 1980). Should such binding occur, the resulting complex may be the antigenic substance that triggers the immune reaction.

Based on the similarity of vinyl chloride disease and systemic sclerosis, which may be a genetically linked autoimmune disease, Black et al. (1983, 1986) examined the human lymphocyte antigen (HLA) phenotypes of patients with vinyl chloride disease. Many autoimmune diseases show statistically significant associations with certain HLA alleles. These authors found that when compared to unexposed controls or asymptomatic controls, workers with vinyl chloride disease had a significantly greater incidence of possessing the HLA-DR5 allele. Furthermore, among those with the disease, the severity of the symptoms was significantly related to the possession of the HLA-DR3 and B8 alleles. These authors concluded that susceptibility was increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it, and progression was favored by HLA-DR3 and B8.

The immunologic effects of vinyl chloride have been examined in mice (Sharma and Gehring 1979). Lymphocytes isolated from the spleens of mice exposed to concentrations as low as 10 ppm vinyl chloride for 4 weeks had increased spontaneous and lectin-stimulated transformation. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride, indicating that a metabolite of vinyl chloride may be responsible for the increase.

The LOAEL value for immunological effects in mice exposed in an intermediate-duration study is recorded in Table 2-1 and plotted in Figure 2-1.

2. HEALTH EFFECTS

2.2.1.4 Neurological Effects

Vinyl chloride was once considered for use as an inhalation anesthetic (ACGIH 1986a). Investigators studying the effects of occupational vinyl chloride exposure frequently report central nervous system symptoms that are consistent with the anesthetic properties of vinyl chloride (Juhe et al. 1974; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suci et al. 1963, 1975; Veltman et al. 1975; Walker 1976; Waxweiler et al. 1977). The most commonly reported central nervous system effects are ataxia or dizziness, drowsiness or fatigue, loss of consciousness, and/or headache. Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability (Suci et al. 1963, 1975), visual and/or hearing disturbances (Juhe et al. 1974; Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975), memory loss (Langauer-Lewowicka et al. 1983; Suci et al. 1963, 1975), and nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suci et al. 1963). Central nervous system tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983); however, reliable estimates of exposure levels producing these effects were not available.

Exposure of volunteers to known levels of vinyl chloride has provided some indication of the levels of vinyl chloride associated with the effects noted above. Volunteers exposed to 25,000 ppm vinyl chloride for 3 minutes, in a single-dose study, reported experiencing dizziness, disorientation, and burning sensations in the feet during exposure (Patty et al. 1930). Recovery from these effects was rapid upon termination of exposure, but the subjects developed headaches. Exposure of volunteers to concentrations of vinyl chloride ranging from 4,000 to 20,000 ppm for 5 minutes was tested by Lester et al. (1963). No effects were noted at 4,000 ppm. However, at 8,000 ppm one of six subjects reported feeling dizzy. The incidence of dizziness increased with concentration. Nausea was experienced at higher concentrations, and recovery from all effects was rapid upon termination of exposure. Headaches developed following exposure to 20,000 ppm.

Indications of an exposure-related peripheral neuropathy have been observed in a number of the occupational studies. A slight peripheral neuropathy was diagnosed in 70% of the vinyl chloride workers examined in a study by Percotini et al. (1986). The peripheral neuropathy was manifested as denervation-related fasciculations and fibrillations and increased duration and amplitude of motor unit potentials (indicating collateral sprouting). Similar effects were observed by Magnavita et al. (1986) in a case study of a vinyl chloride worker. Other peripheral nervous system symptoms have been reported by a number of investigators studying the effects of occupational exposure to vinyl chloride. The most frequent symptom reported was tingling (paresthesia) in the extremities (Juhe et al. 1974; Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suci et al. 1963, 1975; Veltman et al. 1975; Walker 1976). Additional peripheral nervous system symptoms include numbness in the fingers (Juhe et al. 1974; Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suci et al. 1963, 1975), depressed reflexes (Waxweiler et al. 1977), warmth in the extremities (Suci et al. 1963, 1975), and pain in the fingers (Juhe et al. 1974; Sakabe 1975). It is unclear whether some of these symptoms are associated with tissue anoxia due to vascular insufficiency, or whether they represent direct toxic effects of vinyl chloride on peripheral nerves.

Acute exposure of a number of species to high levels of vinyl chloride has provided additional information on the characteristics of the central nervous system effects that are produced. Exposure of guinea pigs to 10,000 ppm for 8 hours (Patty et al. 1930) was observed to be without effects. Increasing the concentration to 25,000 ppm resulted in ataxia, which developed into unconsciousness during the 8-hour exposure period. As the concentration was increased, the development of unconsciousness was more rapid. At 100,000 ppm, Mastromatteo et al. (1960) observed the development of unconsciousness within 30 minutes. Mice experienced similar signs at approximately equivalent exposure levels. At 5,000 ppm, vinyl chloride was

2 HEALTH EFFECTS

without effect during a 1-hour exposure period. Increasing the concentration to 50,000 ppm caused ataxia and twitching (Hehir et al. 1981), and at 100,000 ppm for 30 minutes unconsciousness was produced, preceded by increased motor activity, incoordination, twitching, and tremors (Mastromatteo et al. 1960). Similar effects in rats were observed by Lester et al. (1963), Jaeger et al. (1974), and Mastromatteo et al. (1960). In contrast, in two reports using rats, exposure to 50,000 ppm for either 1 or 6 hours was without effect (Hehir et al. 1981; Jaeger et al. 1974). In addition, tolerance developed to the intoxicating effects of exposure to 50,000 ppm vinyl chloride after five or six 8-hour exposures (Lester et al. 1963).

Chronic exposure of rats to high levels of vinyl chloride has produced damage to nervous tissue. Rats exposed to 30,000 ppm for 4 hours per day, 5 days per week, for 12 months in a single-concentration study were slightly soporific during exposures (Viola 1970; Viola et al. 1971). Following 10 months of exposure, the rats had decreased responses to external stimuli and disturbed equilibrium. Histopathological examination revealed diffuse degeneration of gray and white matter. Cerebellar degeneration in the Purkinje cell layer was pronounced. Also, peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971). Nonneoplastic lesions in the brain were not noted in rats exposed to 5,000 ppm for 7 hours per day, 5 days per week, for 12 months in a single-concentration study by Feron and Kroes (1979).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species from acute- or intermediate-duration studies are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante 1976; Infante et al. 1976a, 1976b; Rosenman et al. 1988; Theriault et al. 1983).

The pregnancy outcome of wives of workers employed at a vinyl chloride polymerization facility was compared to the pregnancy outcome of wives of a control group made up of unexposed rubber workers and PVC fabricators believed to be exposed to "very low" levels of vinyl chloride (Infante et al. 1976a, 1976b; Waxweiler et al. 1977). Pregnancy outcomes were determined based on the responses given by fathers on a questionnaire. Infante et al. (1976a, 1976b) and Waxweiler et al. (1977) reported a significant excess of fetal loss in the group whose husbands had been exposed to vinyl chloride. The greatest difference occurred in wives of men under 30 years of age, where fetal loss was 5.3% for controls and 20.0% for exposed workers. However, this study has been severely criticized based on the conduct of the study and method of statistical analysis used (Hatch et al. 1981; Stallones et al. 1987). Furthermore, Hatch et al. (1981) and Stallones et al. (1987) concluded that the study failed to demonstrate an association of parental exposure to vinyl chloride with increased fetal loss.

Additional work by Infante (1976) and Infante et al. (1976b) examined the occurrence of congenital malformations among populations exposed to emissions from PVC polymerization facilities. A statistically significant increase in birth defects was observed in three cities in which polymerization facilities were located when compared to statewide and countywide averages. The greatest increases were noted in malformations of the central nervous system, upper alimentary tract, and genital organs, and in the incidence of club foot. However, this study has also been criticized based on the conduct and analyses used (Hatch et al. 1981; Stallones et al. 1987). These authors concluded that the study failed to demonstrate an association between

2. HEALTH EFFECTS

exposure to emissions and the prevalence of birth defects. Furthermore, another study that examined the incidence of malformations in one of the cities studied by Infante (1976) concluded that, although the city had statistically increased incidences of congenital malformations, no correlation existed with parental proximity to the polymerization plant or with parental employment at the plant (Edmonds et al. 1975). In fact, more parents of control infants worked at the plant or lived closer to the plant than parents of infants with central nervous system malformations.

Additional studies have also examined the prevalence of congenital malformations in populations exposed to emissions from polymerization facilities (Edmonds et al. 1978; Rosenman et al. 1988; Theriault et al. 1983). The incidence of central nervous system defects in a West Virginia county with a polymerization plant was compared to incidences in other regions in the United States with no known exposure to vinyl chloride (Edmonds et al. 1978). Although the rate of central nervous system defects in the West Virginia county exceeded that in control areas, no correlation was noted between the increased central nervous system defects and parental occupation or potential exposure based on proximity to the plant or prevailing wind patterns.

A significantly greater prevalence of birth defects was found in residents of a town with a polymerization facility than in three matched towns without potential for exposure to vinyl chloride (Theriault et al. 1983). The most commonly reported defects included those of the musculoskeletal, cardiovascular, urogenital, and central nervous systems. The incidences were observed to fluctuate with seasonal changes in emissions. However, no correlations were found between the presence of defects and proximity of the residence to the plant or parental occupation. Also, other industrial emissions could not be eliminated as potential sources of the increased incidence of congenital malformations observed.

No significant increases in birth defects were observed in a community with two polymerization facilities, but odds ratios for central nervous system defects were found to correlate with the amount of emissions from the individual facilities and with the distance of the residences of affected parents from the facilities (Rosenman et al. 1988). However, this study was limited by the small sample size.

Pregnancy outcomes of mothers occupationally exposed to vinyl chloride were compared to those of pregnant workers not exposed to vinyl chloride (Bao et al. 1988). The study authors concluded that exposure to vinyl chloride did not correlate with involuntary infertility, pregnancy outcome, or the incidence of congenital abnormalities.

A number of inhalation studies have examined the effects of vinyl chloride exposure on pregnancy outcome in animals. Results of these studies indicate that vinyl chloride produces developmental effects at concentrations that are also toxic to maternal animals. John et al. (1977, 1981) exposed rats and rabbits to 0, 500, or 2,500 ppm and mice to 0, 50, or 500 ppm throughout the period of organogenesis. Mice were most sensitive to the effects of vinyl chloride. At 500 ppm, maternal toxicity was evidenced by decreased food consumption, decreased body weight gain, and increased mortality. Fetal effects observed at 500 ppm included increased resorptions, decreased litter size and fetal weight, and delayed ossification. The only significant fetal effect observed at 50 ppm was an increase in crown-rump length. The biological significance of this effect is unknown. In rats, 500 ppm caused decreased maternal weight gain and fetal weight, increased crown-rump length, and vertebral lumbar spurs. Increasing the exposure level to 2,500 ppm was not associated with a dose-dependent increase in these effects. The only effects observed at 2,500 ppm were decreased maternal food consumption and, in fetuses, an increased incidence of dilated ureters. In rabbits exposed to 500 ppm, maternal animals had decreased food consumption, and fetal animals had delayed ossification. These effects were not observed in rabbits at 2,500 ppm. However, the number of animals that

2 HEALTH EFFECTS

were tested at 2,500 ppm was much lower than at 500 ppm (5 versus 20), thus no conclusions may be drawn as to the dose-response of these effects.

Exposure of rats to either 0 or 1,565 ppm of vinyl chloride during the first, second, or third trimester of pregnancy was examined (Ungvary et al. 1978). In maternal animals, an increased liver to body weight ratio was observed in those exposed during the first and second trimesters, but no histopathologic alterations were found. A significant increase in resorptions was observed in animals exposed during the first trimester of pregnancy. Two central nervous system malformations (microphthalmia and anophthalmia) were observed in exposed fetuses but not in controls, but the incidence of these malformations did not reach statistical significance. This study is limited in that only a single concentration of vinyl chloride was tested, precluding conclusions as to the dose-response of the effects observed.

The effects of exposure of rats to vinyl chloride throughout gestation were examined by Mirkova et al. (1978) and Sal'nikova and Kotsovskaya (1980). An unspecified number of pregnant rats were exposed to 0, 1.9, or 13.9 ppm for 4 hours per day. Fetuses were examined for abnormalities just prior to the end of gestation, and offspring were examined at 6 months postnatally (Sal'nikova and Kotsovskaya 1980). At 13.9 ppm, a decrease in maternal erythrocyte count and urinary hippuric acid was observed. At 1.9 and 13.9 ppm, fetuses had an increased incidence of hemorrhages and at 13.9 ppm increased edema. However, the affected organs were not specified. Rats examined at 6 months, following in utero exposure to 1.9 ppm, were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidney, spleen; females: lung, liver). In addition to these effects, exposure to 13.9 ppm in utero resulted in an increased pentobarbital sleep time and a decreased ability of the rats to orient themselves.

Continuous exposure of an unspecified number of rats throughout gestation to 2.4 ppm of vinyl chloride resulted in decreased fetal weight and increased early post-implantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects including decreased bile enzyme activity, decreased bile secretion, decreased cholic acid content, and increased hexobarbital sleep time. No histological data on the livers of pups, or information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Also, both this study and the report by Sal'nikova and Kotsovskaya (1980) failed to provide information on the number of animals in each test group.

The highest NOAEL value and all reliable LOAEL values for developmental effects in rats and/or rabbits in acute-duration studies are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

A number of case reports of workers occupationally exposed to vinyl chloride suggest that sexual performance may be affected by vinyl chloride. However, these studies are limited by the lack of quantification of exposure levels and possible concomitant exposures to other chemicals. Sexual impotence was reported by 24% of the workers examined by Suciú et al. (1975). Approximately 20% of the workers examined by Veltman et al. (1975) complained of potency troubles. A loss of libido in 35% and impotence and decreased androgen secretion in 8% of workers exposed, at least once, to very high levels of vinyl chloride were also reported by Walker (1976). Also, in a vinyl chloride worker who died of angiosarcoma of the liver, decreased testicular size was observed (Lee and Harry 1974). However, it is unclear whether this effect was a direct effect of the vinyl chloride exposure or due to wasting secondary to the angiosarcoma.

The sexual function and hormonal levels in 198 males employed in the PVC and acrylic glass industries were examined by Makarov (1984). The report found a significant decrease in sexual function in males exposed

2. HEALTH EFFECTS

to vinyl chloride. However, concomitant exposure to methylmethacrylate cannot be ruled out in this study. Testosterone levels were also substantially decreased. However, the statistical significance of this finding was not reported.

The sexual function, organs, and hormonal levels of 402 females employed in the PVC and acrylic glass industries were also examined by Makarov et al. (1984). When compared with controls, there was an exposure-related decrease in sexual function in females between 41 and 50 years of age and in those who had been exposed to vinyl chloride for 21 or more years. No changes in the incidence of miscarriages or abortions were correlated with exposure. An increase in menstrual activity followed by a hypomenstrual syndrome was reported to occur, but supporting data were not presented. In a study by Bao et al. (1988), increased blood pressure and edema during pregnancy (preeclampsia) and decreased hemoglobin levels were found in female workers exposed to vinyl chloride when compared to unexposed workers.

Although no studies were located that documented the effects of vinyl chloride on reproductive performance when both parental animals were exposed, two dominant lethal studies examined the reproductive performance of exposed males. A brief exposure (5 days, 6 hours per day) of mice to concentrations of vinyl chloride as high as 30,000 ppm had no effect on male fertility or pre- or post-implantation loss (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours per day, 5 days per week, for 11 weeks caused a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility (Short et al. 1977). These results are supported by two studies using rats in which adverse effects of vinyl chloride on the testes were observed (Bi et al. 1985; Sokal et al. 1980). Exposure of rats to 100 ppm for 6 hours per day, 6 days per week, for 12 months caused a significant increase in the incidence of damage to the seminiferous tubules and depletion of spermatocytes (Bi et al. 1985). At the 6-month interim sacrifice, a significant decrease in testicular weight was also observed at 100 ppm. No effect on male reproductive organs was observed in this study at 10 ppm. A significant increase in damage to the spermatogenic epithelium and disorders of spermatogenesis were found with exposure to 500 ppm vinyl chloride for 5 hours per day, 5 days per week, for 10 months (Sokal et al. 1980). No significant decrease in testicular weight was found in rats exposed to 500 ppm for 7 hours per day, 5 days per week, for 4.5 months, or in dogs, rabbits, or guinea pigs exposed to 200 ppm for 7 hours per day, 5 days per week, for 6 months (Torkelson et al. 1960). However, the quality of this study is limited because of the small number of animals tested. Exposures involved up to 10 rats or guinea pigs of each sex, 3 rabbits of each sex, and 1 dog of each sex. No histopathological data on the testes of these animals were presented.

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

2.2.1.7 Genotoxic Effects

Genotoxicity studies of vinyl chloride in humans include a large number of assays for chromosomal aberrations in the cultured lymphocytes of occupationally exposed workers. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon deoxyribonucleic acid (DNA) replication) but also including some chromosomal-type defects such as inversions, rings, and translocations, which affect the entire chromosome. Increased sister chromatid exchanges have also been reported in occupationally exposed workers (Kucerova et al. 1979). One study examined 37 exposed workers and from 16 to 32 unexposed controls twice at intervals of from 2 to 2.5 years (Hansteen et al. 1978). Exposure levels during the time of first sampling were measured at 25 ppm, and there was a statistically significant increase in aberrations among the exposed workers. At the subsequent examination, exposure

2. HEALTH EFFECTS

levels had dropped to 1 ppm, and there were no statistical differences between exposed subjects and controls in the percentage of chromosomal aberrations, indicating that these clastogenic effects are reversible. The study authors suggested that 1 ppm constituted a NOAEL for genotoxic effects in humans.

The reversibility of these clastogenic effects is also suggested by Anderson et al. (1980) who reported that the increase of chromosome aberrations observed in workers exposed to 50 ppm returned to normal within 42 months when the cohort was sampled after exposure levels had been reduced to less than 5 ppm. A positive correlation between frequency of chromosomal aberrations and length of exposure and history of exposure to excursion levels (up to 2,000 ppm) was reported by Purchase et al. (1978), who examined a cohort of 57 vinyl chloride workers, 19 on-site controls, and 5 off-site controls. The exposures for this cohort ranged from 1,000 ppm between 1945 and 1955 and 5 ppm since 1975. These authors also reported an effect on chromosomal aberrations from smoking.

More recent papers on human subjects have focused on specific mechanisms involved in the clastogenic effects of vinyl chloride. A cohort of 67 workers exposed to approximately 5 ppm for an average of 15 years was reported to have a nonrandom distribution of chromatid and bichromatid breaks (Fucic et al. 1990). The most frequently affected areas of the genome were the terminal segments of the A, B, and C group chromosomes, suggesting that vinyl chloride or its metabolites interact more frequently with specific sites along the chromosome than would be expected. The study authors presented no correlation with particular fragile sites (gene sequences more prone to breakage than normal) or oncogene locations known to occur at these terminal segments. The implication is that the carcinogenicity of vinyl chloride could be at least partially explained by its nonrandom interaction with particular genes. These workers were also periodically exposed to 2,000 ppm for short periods. No specific information was given as to the frequency or duration of these events.

The effects of smoking on chromosomal aberrations in vinyl chloride-exposed workers was reexamined by Hrivnak et al. (1990) who found no effect of smoking in 43 workers exposed for an average of 11.2 years to levels of vinyl chloride ranging from 0.8 to 16 ppm. Most cytogenetic studies of the effects of smoking in humans have reported no effect on chromosomal aberrations, although the sister chromatid exchange frequency is usually elevated.

Animal studies of rats and mice exposed via inhalation to vinyl chloride have concentrated on identifying direct effects on the DNA. Increased alkylation of liver DNA and increased cell proliferation were reported by Laib et al. (1989). Both young and old rats were exposed to 600 ppm for 6 hours. The older male rats were sacrificed, and the young rats of both sexes and the adult females received a second 6-hour exposure following a 15-hour interval. The 30 young rats were apparently more susceptible to the effects of vinyl chloride, but only 3 male adults and 2 female adults were used for comparison.

The role of chloroethylene oxide, a metabolite of vinyl chloride, was described by Gwinner et al. (1983). Rats exposed to 2,000 ppm vinyl chloride for 8 hours per day, 5 days per week, for 13 weeks demonstrated hepatocellular ATPase-deficient foci and alkylation of liver DNA. Rats exposed to 2,2'-dichloro-diethylether(bis(chloroethyl)ether) or to chloroethanol did not form these foci, which are considered to be preneoplastic; these compounds do not metabolize to chloroethylene oxide, but rather to the aldehyde, suggesting that the aldehyde is not a mutagen *in vivo*.

The types of adducts of vinyl chloride formed from *in vivo* exposure may depend on the length of exposure, the sensitivity of the method used, and on the animal species. The vinyl chloride-derived nucleoside, N-2,3-ethenoguanosine, has been identified in the liver of vinyl chloride-exposed rats. This nucleoside, when

2. HEALTH EFFECTS

incorporated into DNA, has been shown to be an efficient mutagen that causes base-pair (i.e., purine to purine or pyrimidine to pyrimidine exchange) transitions during transcription (Singer et al. 1987). The identification of the etheno nucleosides has been reported to occur following inhalation exposure to vinyl chloride in Sprague-Dawley and BDVI rats (Bolt et al. 1986; Ciroussel et al. 1990; Eberle et al. 1989). Immature rats exposed *in vivo* formed six times more of this nucleoside, which correlated with the age-related sensitivity to carcinogenesis in these animals (Ciroussel et al. 1990).

Effects of vinyl chloride on DNA are not restricted to the rat. Induction of single-strand breaks in liver DNA of mice after inhalation of vinyl chloride was reported by Walles et al. (1988).

Vinyl chloride has not been shown to be positive for dominant lethal effects in rats exposed to up to 30,000 ppm for 6 hours per day, for 5 days (Anderson et al. 1976; Purchase et al. 1975; Short et al. 1977). The studies showed no evidence of pre- or post-implantation loss among the untreated females mated to exposed males. These results indicate that no germinal mutations were caused by these acute exposures. Table 2-5 lists the key *in vivo* studies of genotoxicity of vinyl chloride.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from the cluster of reports of greater than expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (Bryen et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1986; Wu et al. 1989). Angiosarcoma of the liver is considered to be a very rare type of cancer (25-30 cases per year in the United States) (Heath et al. 1975). However, approximately 30 years after the introduction of vinyl chloride for use in the industrial production of PVC, it became apparent that workers exposed to vinyl chloride had an unusually high incidence of this type of tumor. Investigators identified an increased likelihood of developing hepatic angiosarcoma among those exposed to the highest levels of vinyl chloride and those exposed to vinyl chloride for the longest duration (Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Rinsky et al. 1988; Weber et al. 1981; Wong et al. 1986; Wu et al. 1989). Based on this information, vinyl chloride is considered to be a carcinogen in humans (EPA 1980a; IARC 1979).

Histopathological examination of liver tissue from humans with hepatic angiosarcoma has led to the hypothesis that angiosarcoma develops as a result of hyperplastic changes in sinusoidal cells. Areas of transition to angiosarcoma contained greatly increased numbers of sinusoidal cells with greatly expanded sinusoidal spaces. Also, hepatic cells were replaced by fibrous tissue forming trabeculae. These areas also showed infiltration of angiosarcoma cells. In fully developed angiosarcoma, multiple areas with nodules of angiosarcoma cells were noted, the centers of which exhibited hemorrhagic necrosis (Popper et al. 1981).

Other cancers that have shown a statistically significant increase in mortality among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system. With regard to cancer of the brain and central nervous system, Cooper (1981), Waxweiler et al. (1976), and Wong et al. (1981) reported statistically significant increases; Monson et al. (1975) reported an increase in central nervous system cancer mortality in a proportional mortality study; Bryen et al. (1976) and Tabershaw and Gaffey (1974) reported increases that were not statistically significant; and Fox and Collier (1977), Jones et al. (1988), Thomas et al. (1987), and

2. HEALTH EFFECTS

Wu et al. (1989) found no increase in cancer of the central nervous system among workers occupationally exposed to vinyl chloride.

A significant increase in cancer of the respiratory tract was reported by Belli et al. (1987), Infante et al. (1976), and Waxweiler et al. (1976), and also by Monson et al. (1975) in a proportional mortality study. However, studies by Cooper (1981), Fox and Collier (1977), Jones et al. (1988), Wong et al. (1986), and Wu et al. (1989) did not find a significant increase. Although smoking history was not considered in the studies reporting a statistically significant increase in respiratory cancer, Waxweiler et al. (1976) noted that the types of respiratory tract cancer most frequently recorded were large-cell undifferentiated carcinoma or adenocarcinoma, which are two lung cancer types not usually associated with smoking.

A statistically significant increase in cancers of the lymphatic/hematopoietic system was reported by Rinsky et al. (1988), Smulevich et al. (1988), and Weber et al. (1981). Monson et al. (1975) also reported an increase in their proportional mortality study. However, no statistically significant increase in these types of cancer was reported by Infante et al. (1976), Jones et al. (1988), or Wong et al. (1986).

An increased incidence of malignant melanoma among vinyl chloride workers has been reported (Heldass et al. 1977, 1984), but the significance of this finding has been disputed (Ten Berge 1977).

Few studies directly address the incidence of cancer in women occupationally exposed to vinyl chloride. However, one study found that women employed in the production of PVC had a significantly greater chance of developing leukemia or lymphomas (Smulevich et al. 1988). No such increase was seen in occupationally exposed males. Furthermore, the subgroup of women who were exposed to the highest levels of vinyl chloride had increased incidences of stomach and lung cancer and the highest incidences of leukemia and lymphoma. No significant increase in any type of cancer was observed in exposed males in this report, irrespective of the level of exposure.

Studies in several species support the conclusion that vinyl chloride is carcinogenic. A large series of experiments was performed by Maltoni et al. (1981) using rats (Sprague-Dawley and Wistar), mice, and hamsters. All animals were chamber exposed; controls were chamber exposed to air only. The test material was >99.9% pure. A complete gross and histopathological examination of every animal was performed. However, extremely limited histopathological data were presented and cancer incidences were presented only in summary tables. Also, survival of control animals was poor in some of the experiments, suggesting that animal care was inadequate or that unthrifty animals were used. Furthermore, statistical analyses, where present, appear to be based on a compilation of data from several individual studies. In one group of studies, Maltoni et al. (1981) exposed Sprague-Dawley rats to vinyl chloride for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas at concentrations as low as 5 ppm in females, Zymbal gland carcinomas at 10,000 ppm and above, nephroblastoma at concentrations as low as 100 ppm in males and 250 ppm in females, liver angiosarcoma at concentrations as low as 50 ppm in females and 200 ppm in males, neuroblastoma at 10,000 ppm in females, and forestomach papillomas and acanthoma at 30,000 ppm. Other findings (though not statistically significant) that were considered important, based on historical data from their laboratory indicating the rarity of certain tumors, include angiosarcoma and Zymbal gland carcinoma at 10 and 25 ppm and nephroblastoma at 25 ppm. Maltoni et al. (1981) also reported that decreasing the duration of exposure decreased the incidence of vinyl chloride-related tumors (nephroblastomas, liver angiosarcomas, Zymbal gland carcinomas, and, to some extent, neuroblastomas), but statistics were not presented to support this conclusion.

2. HEALTH EFFECTS

Some variation in the end organs that developed tumors was observed when different species were exposed to vinyl chloride (Maltoni et al. 1981). Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice; Zymbal gland carcinomas, neuroblastomas, and nephroblastomas only in rats; and melanomas, acoustical duct epithelial tumors, lymphomas, and leukemias only in hamsters.

Other inhalation experiments support the carcinogenicity of vinyl chloride. Rats and mice exposed to 0, 50, 250, or 1,000 ppm for 6 hours per day, 5 days per week, for 6 months (Hong et al. 1981) or up to 12 months (Lee et al. 1977a, 1978) had a significantly increased incidence of hemangiosarcoma of the liver at ≥ 250 ppm. An increase in bronchioloalveolar adenoma of the lung and mammary gland tumors (adenocarcinomas, squamous and anaplastic cell carcinomas) were also observed in mice at ≥ 50 ppm after the 12-month exposure, although it is unclear whether the increases in these tumor types are statistically significant (Lee et al. 1977a, 1978). Male rats exposed to concentrations as low as 100 ppm for 6 hours per day, 6 days per week, for 12 months had significantly increased incidences of angiosarcoma of the liver when sacrificed at 18 months (Bi et al. 1985). Rats exposed to 3% vinyl chloride (30,000 ppm) 4 hours per day, 5 days per week, for 12 months had an increased incidence of epidermoid carcinoma of the skin, adenocarcinoma of the lungs, and osteochondroma in the bones (Viola et al. 1971), and rats exposed to 0 or 5,000 ppm for 52 weeks had primary tumors in the brain, lung, Zymbal gland, and nasal cavity (Feron and Kroes 1979). However, these studies (Feron and Kroes 1979; Viola et al. 1971) are limited by the absence of statistical analysis of the data. A concentration-dependent increase in tumor formation (alveologenic adenomas of the lung, angiosarcomas of the liver, and adenosquamous carcinoma of the mammary gland) was observed in mice exposed to 0, 50, 200 or 2,500 ppm vinyl chloride (Keplinger et al. 1975). However, no statistics were presented to support these conclusions. Furthermore, an audit of data by the Manufacturing Chemists Association (MCA 1980) indicated that mishandling of the tissues precluded making statements regarding the relationship of tumors other than angiosarcoma of the liver with vinyl chloride exposure.

In a preliminary study with a limited number of animals, alveogenic lung tumors developed in 26 of 27 mice exposed to 2,500 or 6,000 ppm for 5-6 months (Suzuki 1978). A concentration-related increase in the incidence of alveogenic tumors was observed in a study in which a greater number of mice were exposed to 0-600 ppm for 4 weeks and then observed for up to 41 weeks postexposure (Suzuki 1983). An increase in bronchioloalveolar adenoma was observed in a lifespan study in mice that were exposed to 50 ppm for 100 1-hour exposures, 500 ppm for 10 1-hour exposures, or 5,000 ppm for a single 1-hour exposure (Hehir et al. 1981). The statistical significance of these observations was not presented.

Some data suggest that exposure of animals early in their lives may increase the likelihood of developing tumors or affect the type of tumor that develops. When hamsters, mice, and rats were exposed to vinyl chloride for periods of 6-24 months starting at various times after weaning, the incidence of tumors such as hemangiosarcoma of the liver was greater when animals were exposed for 12 months immediately after weaning than if animals were held for 12 months and then exposed for the next 12 months (Drew et al. 1983). Also, when pregnant rats were exposed from gestation day 12 through 18, the incidence of mammary gland carcinomas, Zymbal gland carcinomas, nephroblastomas, and forestomach epithelial tumors was reported to be greater in transplacentally exposed animals than in maternal animals (Maltoni et al. 1981). No control group was used, however, and no statistics were presented to support the conclusions. Maltoni et al. (1981) also exposed pregnant rats starting on gestation day 12 and continued to expose both maternal animals and offspring for a total of 76 weeks. The incidence of hepatomas was reported to be much higher in offspring than in maternal animals. In contrast, the incidence of neuroblastomas was similar between offspring and

2. HEALTH EFFECTS

parents, and hepatic angiosarcomas had only a slightly higher incidence and slightly shorter latency in offspring than parents. However, no statistics were presented to support these conclusions.

In general, the available evidence from inhalation studies in animals supports the finding in humans; that vinyl chloride is a carcinogen by this route of exposure. The lowest doses tested that produced a tumorigenic response (Cancer Effect Level [CEL]) for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure**2.2.2.1 Death**

No studies were located regarding lethal effects in humans following oral exposure to vinyl chloride.

No studies were located regarding the acute lethal effects of vinyl chloride in animals. However, decreased longevity has been observed in rats as a result of chronic ingestion of vinyl chloride. Significant increases in mortality were observed by Feron et al. (1981) when Wistar rats were allowed to consume vinyl chloride doses as low as 5.6 mg/kg/day in the diet for 4 hours per day over a 2-year period. Also, the effects of consumption of vinyl chloride during a lifespan study in Wistar rats lasting almost 3 years (149 weeks) was examined by Til et al. (1983). These authors found decreased survival at a vinyl chloride dosage of 1.7 mg/kg/day. In both of these studies, vinyl chloride was administered by incorporating PVC resin that was high in vinyl chloride content into the diet. Vaporization of vinyl chloride from the diets was limited by presenting feed containing the vinyl chloride to the rats for only a 4-hour period.

All reliable LOAEL values for death in rats following chronic exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for hematological, hepatic, and dermal/ocular effects in rats following chronic oral exposure are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, or renal effects in humans or animals following oral exposure to vinyl chloride.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to vinyl chloride.

Exposure of rats to 17 mg/kg/day for 2 years caused hypercoagulability of the blood (Feron et al. 1981).

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

Chronic exposure of rats to vinyl chloride in their feed caused an increase in the incidence of basophilic nuclei at 0.018 mg/kg/day for 149 weeks (Til et al. 1983) and resulted in areas of hepatocellular alteration at concentrations as low as 1.8 mg/kg/day in rats exposed for 2 years (Feron et al. 1981). In the study by Feron et al. (1981), areas of necrosis were observed in the liver of female rats exposed to 5.6 mg/kg/day and male rats exposed to 17 mg/kg/day for 2 years.

TABLE 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral

Key to figure*	Species	Route	Exposure duration/frequency	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE								
Death								
1	Rat	(F)	149 wk 4hr/d		0.17		1.7	Til et al. 1983
2	Rat	(F)	2 yr 5d/wk 4hr/d		1.8		5.6	Feron et al. 1981
Systemic								
3	Rat	(F)	149 wk 4hr/d	Hemato Hepatic	1.7	0.018* (cellular alterations)		Til et al. 1983
4	Rat	(F)	2 yr 5d/wk 4hr/d	Hemato Hepatic	5.6	17 (hypercoagulation) 1.8 (cellular alteration)	5.6 (necrosis)	Feron et al. 1981
5	Rat	(GO)	2 yr 1x/d	Derm/oc		30 (increased collagen)		Knight and Gibbons 1987
Cancer								
6	Rat	(GO)	52 wk 5x/wk				0.3 (CEL liver)	Maltoni et al. 1981
7	Rat	(F)	2 yr 5d/wk 4hr/d				1.8 (CEL liver)	Feron et al. 1981

TABLE 2-2 (Continued)

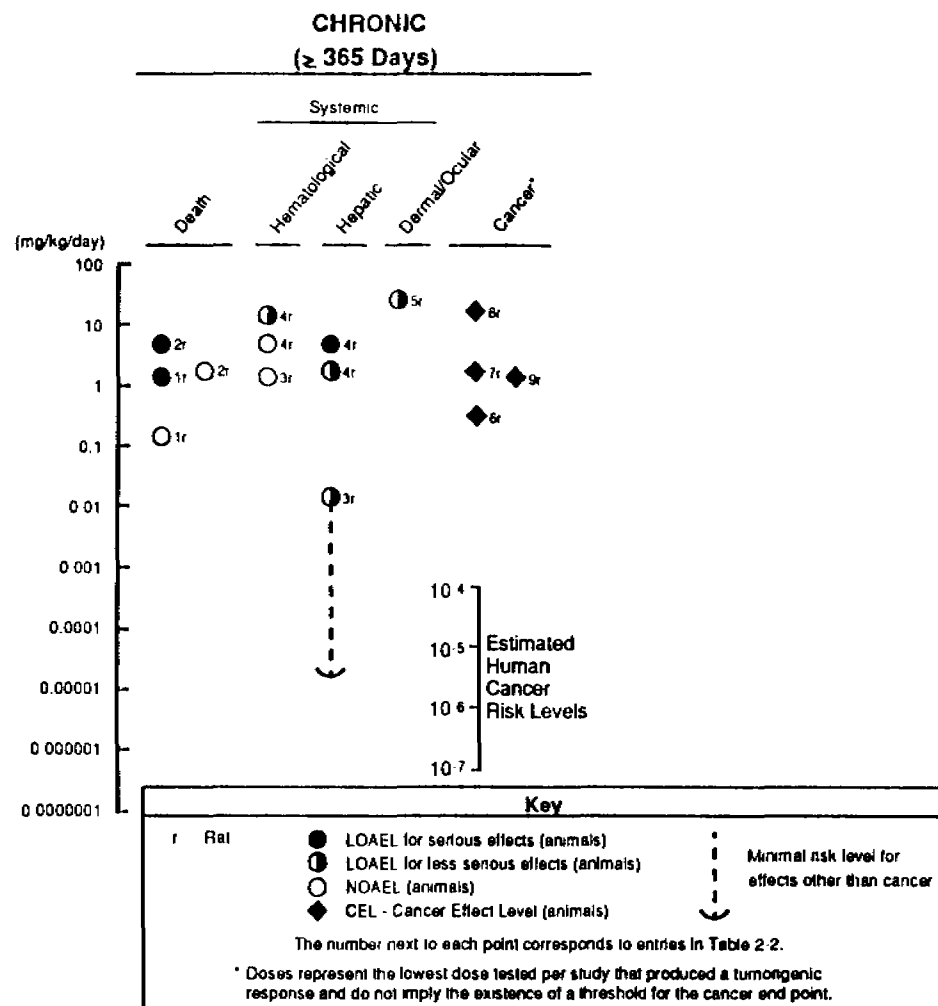
Key to figure ^a	Species	Route	Exposure duration/frequency	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat	(GO)	52 wk 5x/wk				16.65 (CEL liver)	Maltoni et al. 1981
9	Rat	(F)	149 wk 4hr/d				1.7 (CEL liver)	Til et al. 1983

^aThe number corresponds to entries in Figure 2-2.

^bUsed to derive a chronic oral Minimal Risk Level (MRL) of 2×10^{-4} mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL; 10 for extrapolation from animals to humans; and 10 for human variability). This chronic oral MRL has been converted to concentrations of 2×10^{-4} ppm in drinking water and 1 ppm in soil for presentation as Environmental Media Evaluation Guides (EMEGs) in Section 1.5.

CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (GO) = oil gavage; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

FIGURE 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral



2. HEALTH EFFECTS

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to vinyl chloride.

Daily administration of 30 mg/kg of vinyl chloride to rats by gavage for 2 years caused increased thickness, moisture content, and collagen content of the skin. Newly synthesized intermolecular and intramolecular collagen crosslinks were also significantly increased (Knight and Gibbons 1987).

No studies were located regarding the following health effects in humans and/or animals after oral exposure to vinyl chloride:

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to vinyl chloride.

Four studies were located that examined the carcinogenic potential of vinyl chloride in animals when administered by the oral route. In two of these studies, vinyl chloride was added to the diet by incorporating PVC powder containing a high level of the monomer (Feron et al. 1981; Til et al. 1983). To limit volatilization of vinyl chloride from the diet, rats were allowed access to the diet for only 4 hours per day. The actual intake of vinyl chloride in these reports was calculated by taking into consideration both the food consumption and the rate of vinyl chloride evaporation. These studies indicated that higher doses of vinyl chloride produced predominantly angiosarcomas, whereas lower dosages produced predominantly hepatocellular carcinomas. Statistically significant increases in hepatic angiosarcoma of the liver were observed in the 2-year study by Feron et al. (1981) at 5.6 mg/kg/day in males and 17 mg/kg/day in females. In contrast, statistically significant increases in neoplastic nodules of the liver were observed at concentrations as low as 1.8 mg/kg/day in females and 5.6 mg/kg/day in males in the same study (Feron et al. 1981). Also, in the 149-week study by Til et al. (1983), statistically significant increases in hepatocellular carcinoma were observed in males at 1.7 mg/kg/day and hepatic neoplastic nodules were observed in females at 1.7 mg/kg/day. An increased incidence of Zymbal gland tumors was also observed in the study by Feron et al. (1981). Although the increase was not statistically significant, the tumors were considered to be treatment-related based on the historical rarity of this type of tumor.

Two studies were located in which vinyl chloride was administered to Sprague-Dawley rats by gavage for 52 weeks. In one of these studies, a statistically significant increase in the incidence of hepatic angiosarcomas was observed at doses as low as 16.65 mg/kg/day in females and 50 mg/kg/day in males. Zymbal gland tumors at 16.65 and 50 mg/kg/day, even though not statistically significant, were considered to be treatment related because of the rarity of this type of tumor (Maltoni et al. 1981). Lower doses of vinyl chloride were also tested in a similar study in which hepatic angiosarcomas were observed at doses as low as 0.3 mg/kg/day and Zymbal gland tumors at 1 mg/kg/day. Although neither of these findings reached statistical significance, the tumors were considered to be treatment related because of the historically rare observation of these tumor types in the colony (Maltoni et al. 1981).

2. HEALTH EFFECTS

Animal data suggest that dermal absorption of vinyl chloride vapor is not likely to be significant. Dermal absorption in rhesus monkeys was estimated to be 0.031% and 0.023% of the total available vinyl chloride at 800 and 7,000 ppm, respectively (Hefner et al. 1975a). The investigators concluded that, after short-term exposure to high concentrations, dermal absorption was far less significant than inhalation absorption.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding tissue distribution in humans after inhalation exposure to vinyl chloride.

Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread, but storage of vinyl chloride in the body is limited by rapid metabolism and excretion. In rats exposed to ^{14}C -vinyl chloride and pretreated with 6-nitro-1,2,3-benzothiadiazole to block metabolism of vinyl chloride by microsomal cytochrome P-450 oxidation pathways, the highest levels of radiolabel were located in the fat, with lesser amounts in the blood, liver, kidney, muscle, and spleen. When metabolism was not blocked, the highest levels of radiolabeled metabolites were located in the liver and kidney (Buchter et al. 1977). At 10 minutes after a 5-minute exposure of rats to 20,000 ppm ^{14}C -vinyl chloride, radiolabel was detected in the liver, bile duct, digestive tract, and kidney (Duprat et al. 1977). At 3 hours after the exposure described above, radiolabel was also detected in the urinary tract, salivary and lacrimal glands, thymus, and skin. Immediately after a 5-hour exposure to ^{14}C -vinyl chloride at 50 ppm, tissue levels of ^{14}C -activity, expressed as the percentage incorporated per gram of tissue, were highest in the kidney (2.13%) and liver (1.86%), with lower levels in the spleen (0.73%) and brain (0.17%) (Bolt et al. 1976a). Radioactivity in tissue was measured in rats 72 hours after exposure to 10 or 1,000 ppm ^{14}C -vinyl chloride for 6 hours. In order of decreasing concentration for rats exposed to 10 ppm, ^{14}C -labeled compounds (expressed as percentage), present as nonvolatile metabolites, were detected in the liver (0.14), kidney (0.08), skin (0.07), lung (0.07), muscle (0.05), carcass (0.05), plasma (0.05), and fat (0.03). For rats exposed to 1,000 ppm, radiolabel (expressed as percentage) was detected in the liver (0.15), skin (0.12), kidney (0.06), carcass (0.05), lung (0.05), muscle (0.04), fat (not detected), and plasma (not detected) (Watanabe et al. 1976b). There was no difference in the routes or rate of excretion between repeated-dose versus single-dose exposure of rats to 5,000 ppm of ^{14}C -vinyl chloride (Watanabe et al. 1978a). The concentration of radiolabel detected in tissues 72 hours after exposure revealed no statistically significant difference between rats exposed once or repeatedly to vinyl chloride. Percentages of radioactivity detected in tissues are as follows (for single and repeated doses, respectively): liver (0.12)(0.16), kidney (0.06)(0.07), skin (0.05)(0.08), carcass (0.03)(0.04), fat (not detected)(not detected).

Placental transfer of vinyl chloride can occur rapidly in rats. Female rats exposed to approximately 0, 2,000, 7,000, or 13,000 ppm vinyl chloride for 2.5 hours on gestational day 18 showed high concentrations of vinyl chloride in maternal and fetal blood and amniotic fluid. The maternal blood had the highest levels (Ungvary et al. 1978).

2.3.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans after oral exposure to vinyl chloride.

The level of ^{14}C -nonvolatile metabolites was measured in tissues of rats 72 hours after single gavage doses (0.05–100 mg/kg) of ^{14}C -vinyl chloride in corn oil (Watanabe et al. 1976a). The highest levels of

2. HEALTH EFFECTS

radioactivity for each dose level occurred in the liver. These levels were 2-5 times higher than in the other tissues examined (skin, plasma, muscle, lung, fat, and carcass).

2.3.2.3 Dermal-Exposure

No studies were located regarding tissue distribution for humans or animals after dermal exposure to vinyl chloride.

2.3.3 Metabolism**2.3.3.1 Inhalation Exposure**

In the only human data located, metabolism of vinyl chloride was attributed to the cytochrome P-450 monooxygenases in the S-9 fraction from surgically obtained liver specimens. These preparations metabolized vinyl chloride to electrophiles that were mutagenic to *Salmonella typhimurium* TA1530 (Sabadie et al. 1980). When compared with the number of revertants per plate resulting from identically prepared S-9 fractions from female strain BD IV rats, human S-9 fractions induced mutations (and presumably metabolism to a reactive electrophile) to an average 84% of the extent mediated by rat S-9. However, a ninefold individual variation was observed.

Early work on the metabolism of vinyl chloride in animals indicated that metabolism is a dose-dependent, saturable process. Rats were exposed to vinyl chloride in a closed chamber at concentrations of about 50-1,000 ppm for 52.5-356.3 minutes (Hefner et al. 1975b). Additional rats pretreated with ethanol (to inhibit alcohol dehydrogenase activity) or SKF 525-A (to inhibit microsomal oxidase activity) were similarly exposed. Metabolism, estimated by measuring the rate of disappearance of vinyl chloride from the closed system, followed first-order kinetics with a half-life of 86 minutes at less than 100 ppm. At greater than 220 ppm, metabolism was slowed to a half-life of 261 minutes, suggesting saturation of the pathway predominant at less than 100 ppm. Pretreatment with ethanol depressed the rate of metabolism by approximately 83% at less than 100 ppm but by approximately 47% at greater than 1,000 ppm. Pretreatment with SKF 525-A, however, had no effect at less than 100 ppm but depressed metabolism by 19% at greater than 1,000 ppm. The authors postulated three alternative pathways for metabolism, as depicted in Figure 2-3. At low concentrations, sequential oxidation to 2-chloroethanol, 2-chloroacetaldehyde, and 2-chloroacetic acid involving alcohol dehydrogenase (inhibited by pretreatment with ethanol) appeared to be the predominant pathway. Little 2-chloroacetic acid was formed, however, probably because 2-chloroacetaldehyde conjugated rapidly with ubiquitous sulfhydryl groups. When the alcohol dehydrogenase pathway became saturated, 2-chloroethanol could be oxidized by catalase in the presence of hydrogen peroxide (H_2O_2) to a peroxide, which could undergo subsequent dehydration to form 2-chloroacetaldehyde. An alternative pathway involved oxidation by mixed-function oxidase to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranged to form 2-chloroacetaldehyde. These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione S-transferase. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-formyl-methylcysteine, and N-acetyl-S-(2-hydroxyethyl)cysteine (Bolt et al. 1980; Hefner et al. 1975b). Urinary metabolites identified in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al. 1975b; Watanabe et al. 1976b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al. 1975b).

Other animal data expand the hypotheses of Hefner et al. (1975b). Isolated rat liver cells converted ^{14}C -vinyl chloride into nonvolatile metabolites (Hultmark et al. 1979). Using this *in vitro* technique, it was determined

The diagram illustrates the metabolic pathway of vinyl chloride, starting from its chemical structure $\text{ClHC}=\text{CH}_2$ (vinyl chloride). The pathway proceeds through several intermediates and enzymatic steps:

- Vinyl chloride** ($\text{ClHC}=\text{CH}_2$) is converted to **2-chloroethanol** ($\text{ClH}_2\text{C}-\text{CH}_2\text{OH}$) by *mixed function oxidase*.
- Vinyl chloride** is also converted to **2-chloroethylene oxide** ($\text{H}_2\text{C}-\text{CH}(\text{Cl})$ with an epoxide ring) by *mixed function oxidase*.
- 2-chloroethanol** is converted to **2-chloroacetaldehyde** ($\text{ClH}_2\text{C}-\text{C}(\text{H})-\text{CHO}$) by *alcohol dehydrogenase*.
- 2-chloroethanol** is converted to **2-chloroethylhydroperoxide** ($\text{ClH}_2\text{C}-\text{CH}_2\text{OOH}$) by *hydrogen peroxide and catalase*.
- 2-chloroethylene oxide** reacts with *glutathione* to form **G-S-CH₂-CHO** (*S*-formylmethyl glutathione).
- 2-chloroacetaldehyde** reacts with *glutathione* to form **G-S-CH₂-CHO** (*S*-formylmethyl glutathione).
- 2-chloroacetaldehyde** is converted to **2-chloroacetic acid**** ($\text{ClH}_2\text{C}-\text{COOH}$) by *aldehyde dehydrogenase*.
- 2-chloroacetic acid**** reacts with *glutathione* to form **G-S-CH₂-COOH** (*S*-carboxymethyl glutathione).
- G-S-CH₂-CHO** (*S*-formylmethyl glutathione) is converted to **cys-S-CH₂-CHO** (*S*-formylmethyl cysteine**).
- G-S-CH₂-COOH** (*S*-carboxymethyl glutathione) is converted to **cys-S-CH₂-COOH** (*S*-carboxymethyl cysteine).
- cys-S-CH₂-CHO** (*S*-formylmethyl cysteine**) is converted to **cys-S-CH₂-CH₂OH** (*S*-(2-hydroxyethyl)-cysteine).
- cys-S-CH₂-COOH** (*S*-carboxymethyl cysteine) is converted to **cys-S-CH₂-CH₂OH** (*S*-(2-hydroxyethyl)-cysteine) via *transamination* (releasing NH_3 ammonia) and *oxidative decarboxylation* (releasing CO_2 carbon dioxide).
- cys-S-CH₂-CH₂OH** (*S*-(2-hydroxyethyl)-cysteine) is converted to **N-Ac-cys-S-CH₂-CH₂OH** (*N*-acetyl-*S*-(2-hydroxyethyl)cysteine**).
- cys-S-CH₂-COOH** (*S*-carboxymethyl cysteine) is converted to **HOOC-CH₂-S-CH₂-COOH** (*thiodiglycolic acid (thiodiacetic acid)***) via *transamination* (releasing NH_3 ammonia) and *oxidative decarboxylation* (releasing CO_2 carbon dioxide).

**** Excreted in urine**

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2. HEALTH EFFECTS

that metabolism was NADPH-dependent, located in the microsomal fraction of the liver, and probably involved a mixed-function oxidase. Pretreatment with 6-nitro-1,2,3-benzothiadiazole, an inhibitor of some microsomal cytochrome P-450 oxidation pathways, was sufficient to totally block the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). This observation suggests that metabolism of vinyl chloride proceeds primarily through a mixed-function oxidase pathway with likely production of an epoxide intermediate.

Inhalation exposure of high concentrations of vinyl chloride has also been associated with reduction in liver nonprotein sulfhydryl concentration in the rat. These results are consistent with conjugation of the metabolites of vinyl chloride with limited reserves of glutathione and/or cysteine (Bolt et al. 1976b; Hefner et al. 1975b; Jedrychowski et al. 1984; Watanabe et al. 1978a).

Saturation of metabolic pathways was observed in rats and monkeys that were exposed in a closed system ^{14}C -vinyl chloride (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979). In rats, the threshold for saturation was determined to be approximately 250 ppm and a metabolic rate (V_{max}) of 110 mol/hour/kg was estimated (Bolt et al. 1977; Filser and Bolt 1979). In a similar experiment in rhesus monkeys, metabolic saturation was observed to occur at 200 ppm, with a V_{max} of 50 mol/hour/kg (Buchter et al. 1980). The V_{max} of 50 mol/hour/kg that was estimated using rhesus monkeys was suggested as a closer approximation of metabolism in humans than the value of 110 mol/hour/kg estimated for rats by Filser and Bolt (1979).

Several investigators have observed the binding of nonvolatile metabolites of ^{14}C -vinyl chloride to liver macromolecules in vitro and in rats exposed by inhalation (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). In single-exposure experiments at different concentrations, the extent of macromolecular binding increased proportionately to the amount of vinyl chloride metabolized and disproportionately to the exposure concentration (Watanabe et al. 1978a). The extent of macromolecular binding was increased by repeated exposure to vinyl chloride (Watanabe et al. 1978b) and by pretreatment with phenobarbital (Guengerich and Watanabe 1979). Macromolecular binding has been attributed to the reactive intermediate 2-chloroethylene oxide, which has been shown to bind to DNA and ribonucleic acid (RNA), and to its rearrangement product, 2-chloroacetaldehyde, which has been shown to bind to protein molecules (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

2.3.3.2 Oral Exposure

No studies were located regarding metabolism in humans after oral exposure to vinyl chloride.

Urinary metabolites identified from rats ingesting ^{14}C -vinyl chloride are consistent with the metabolic pathways postulated for inhalation exposure, in particular with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde. Metabolites identified include N-acetyl-S-(2-hydroxyethyl)cysteine, 2-chloroacetic acid, and thiodiglycolic acid (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolic saturation appears to occur with a single gavage dose of between 1 and 100 mg/kg/day (Watanabe et al. 1976a).

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to vinyl chloride.

2. HEALTH EFFECTS

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Human data suggest that exhalation of unmetabolized vinyl chloride is not an important pathway of elimination at low exposure concentrations. The mean concentration in expired air for humans exposed for 6 hours to air containing 2.9–23.5 ppm ranged from 0.21 to 1.11 ppm, representing up to 3.6–4.73% of the inhaled concentration (Krajewski et al. 1980).

Animal studies indicate that the importance of exhalation of vinyl chloride as a major route of excretion varies with the exposure concentration. The mode of excretion of vinyl chloride and its metabolites following inhalation exposure of animals to different concentrations reflects the saturation of metabolic pathways at low concentrations. The cumulative excretion of radioactivity over a 72-hour postexposure period was measured in rats exposed to 10–1,000 ppm (Watanabe and Gehring 1976; Watanabe et al. 1976b) or 5,000 ppm (Watanabe et al. 1978b) ^{14}C -vinyl chloride for 6 hours. Radioactivity expired as carbon dioxide or vinyl chloride, excreted in the urine and feces, and retained in the carcass was expressed as a percentage of the total radioactivity recovered. The results suggest that metabolism was nearly complete at 10 ppm, because less than 2% of the recovered radioactivity occurred as unchanged parent compound. The predominant route for excretion of radioactive metabolites was through the urine, accounting for about 70% of the recovered radioactivity. Metabolism became saturated at 1,000 ppm, since unchanged vinyl chloride increased to 12.3% and urinary radioactivity decreased to 56.3%. At 5,000 ppm, more than half the recovered radioactivity appeared as unchanged vinyl chloride in expired air, and urinary excretion accounted for about 27% of the recovered activity. Generally, there was little change in the proportion of recovered radioactivity excreted in the feces or exhaled as carbon dioxide. The percentage of the radioactivity retained in the carcass and tissues appeared to be somewhat decreased at 5,000 ppm compared with 10 and 1,000 ppm, suggesting preferential retention of metabolites rather than unchanged vinyl chloride.

Pulmonary excretion of unaltered vinyl chloride in rats followed first-order kinetics regardless of exposure concentrations, with half-lives of 20.4, 22.4, and 30 minutes following 6-hour exposures at 10, 1,000, and 5,000 ppm, respectively. The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for less than 3% of the total urinary excretion. Half-lives for the rapid (first-order) phase were estimated at 4.6, 4.1, and 4.5 hours, at 10, 1,000, and 5,000 ppm, respectively. Urinary metabolites included N-acetyl-S-(2-hydroxyethyl)cysteine, thioglycolic acid, and possibly S-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). Identification of these metabolites of vinyl chloride in the urine indicates that vinyl chloride is transformed in the body to a reactive metabolite, which is then detoxified by reaction with glutathione (GSH, gamma-glutamylcysteinylglycine). Subsequently the glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite of vinyl chloride is either acetylated or further oxidized and excreted.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vinyl chloride.

Single oral doses of ^{14}C -vinyl chloride (0.05, 0.25, 1.0, 20, 100, and 450 mg/kg) were administered to rats, and the excretion of radioactivity was monitored over a 72-hour period (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a). A striking increase in exhalation of unchanged vinyl chloride and compensatory decreases in urinary and fecal excretion of radioactivity and exhalation of carbon dioxide were

2. HEALTH EFFECTS

observed at greater than 20 mg/kg, suggesting that metabolic saturation had occurred at that dosage. At less than 1.0 mg/kg, the predominant route of elimination was urinary excretion of polar metabolites.

Exhalation of unchanged vinyl chloride was generally complete within 3-4 hours, but excretion of metabolites continued for days (Green and Hathway 1975). Pulmonary excretion of vinyl chloride appeared to be monophasic at less than 1.0 mg/kg, with a half-life of about 55-58 minutes (Watanabe et al. 1976a). At 100 mg/kg, pulmonary excretion of vinyl chloride was biphasic, with half-lives of 14.4 and 40.8 minutes for the rapid and slower phases, respectively. Urinary excretion of radioactivity was biphasic, with the rapid phase accounting for more than 97% of total urinary radioactivity and having half-lives of 4.5-4.6 hours for dosages of 0.05-100 mg/kg.

Metabolites identified in the urine of orally treated rats were consistent with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Green and Hathway 1977; Watanabe et al. 1976a), as postulated for metabolism following inhalation exposure. The major metabolites were identified as thiodiglycolic acid and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (Watanabe et al. 1976a). *N*-Acetyl-*S*-(2-chloroethyl)cysteine and *S*-(2-chloroethyl)cysteine have also been identified (Green and Hathway 1975), but these metabolites are believed to be an artifact of the isolation procedure that was used (Plugge and Safe 1977). Smaller amounts of radiolabeled urea, glutamic acid, and 2-chloroacetic acid were also identified (Green and Hathway 1975).

2.3.4.3 Dermal Exposure

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

2.3.4.4 Other Routes of Exposure

The elimination of radioactivity following intraperitoneal administration of ^{14}C -vinyl chloride to rats resembles the pattern observed following inhalation or oral administration. Following an intraperitoneal dose of 0.25 mg/kg, exhalation of unchanged vinyl chloride, exhalation of carbon dioxide, and urinary and fecal excretion of radioactivity accounted for 43.2%, 11.0%, 43.1%, and 1.8% of the administered dose, respectively (Green and Hathway 1975). At 450 mg/kg, exhaled vinyl chloride increased to 96.2% of the administered dose, carbon dioxide decreased to 0.7%, urinary radioactivity decreased to 2.6%, and fecal radioactivity decreased to 0.1%.

Small doses administered intravenously were eliminated very rapidly and almost entirely by exhalation of unchanged vinyl chloride. Green and Hathway (1975) administered a 0.25-mg/kg intravenous dose of ^{14}C -vinyl chloride to rats and recovered 80% of the dose within 2 minutes and 99% within 1 hour as unchanged compound in expired air.

2.4 RELEVANCE TO PUBLIC HEALTH

The major route of exposure to vinyl chloride by humans living near hazardous waste sites is via inhalation. Vinyl chloride may be present in ambient air near hazardous waste sites as a result of its volatilization from leaks in storage containers, or from contaminated soil or water. Oral exposure to vinyl chloride via ingestion of contaminated water may also occur. Dermal exposure to liquid vinyl chloride is highly unlikely because of its low boiling point (-13.4°C). However, vinyl chloride is generally transported as a liquid in pressurized containers, and puncture of such a container at a hazardous waste site could result in brief exposure of the

2. HEALTH EFFECTS

skin to liquid vinyl chloride. Dermal exposure to gaseous vinyl chloride may also occur, but a study using rats indicated that absorption of vinyl chloride across the skin is very limited (Hefner et al. 1975a).

Additional sources of potential exposure not directly related to living near hazardous waste sites, but which may also apply in such cases, include inhalation of emissions from vinyl chloride production or PVC manufacturing facilities, inhalation of cigarette smoke containing vinyl chloride, ingestion of water contaminated as a result of the leaching of vinyl chloride from PVC pipes, or ingestion of foods contaminated as a result of vinyl chloride leaching from PVC products used in food production or storage. The FDA now regulates the amount of vinyl chloride in PVC products that may be available to leach into foods, thus this mode of exposure is likely to be negligible.

With a vapor density of 2.15, vinyl chloride vapor tends to disperse slowly and flow along the ground, collecting in low spots (Fire 1986). Thus, children playing along the ground will have relatively greater inhalation exposure to vinyl chloride than adults walking upright in the same area.

The effects that have been reported to occur in humans in response to vinyl chloride exposure come almost exclusively from studies of workers exposed by inhalation in the workplace. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, most of the data on humans from these areas concerns effects in males. Also, virtually all of the epidemiological studies are limited by the absence of data on the actual levels to which workers were exposed. However, studies in animals by the inhalation and oral routes provide an indication of the doses of vinyl chloride that may be associated with these effects.

Acute high-level exposure of humans to vinyl chloride is associated with the development of signs of intoxication such as dizziness, drowsiness, and/or headache. Reports from vinyl chloride workers and studies in animals indicate that loss of consciousness may also be associated with exposure to very high levels. Two deaths connected with occupational exposure to vinyl chloride have been reported. Autopsy results from these men as well as autopsy results from animals dying from extremely high-level exposures indicate that levels of vinyl chloride producing death may cause lung and kidney irritation and inhibition of blood clotting. Cardiac arrhythmias and liver degeneration have also been reported in animals as a result of acute exposure to very high levels of vinyl chloride.

Longer-term exposure of humans in occupational settings has been associated with the development of a number of other toxic effects. However, exposure levels in these studies are generally not quantified, and thresholds for the effects have not been identified. Histopathological changes characteristic of vinyl chloride exposure have been reported to take place in the liver. These changes include extensive fibrosis and hypertrophy and hyperplasia of both hepatocytes and sinusoidal cells. These changes in liver structure develop in the absence of overt symptoms of liver toxicity, and standard biochemical measures of liver function have been of little value in detecting them. Reports indicate that peripheral neuropathy may also develop in some workers occupationally exposed to vinyl chloride. Also, toxic effects on male reproductive function may occur. Studies in animals indicate that vinyl chloride may cause fetal resorptions, delayed development, and an increased incidence of the soft tissue anomaly, dilated ureter. When animals were exposed in utero, some changes in liver function were observed during adolescence.

A syndrome referred to as vinyl chloride disease has been observed in a small percentage of vinyl chloride workers, many of whom were employed as polymerization tank cleaners. This job exposed workers to very high levels of vinyl chloride. Vinyl chloride disease is very similar to systemic sclerosis and includes the following symptoms: Raynaud's phenomenon (fingers blanch and experience numbness and discomfort upon

2. HEALTH EFFECTS

exposure to the cold), acroosteolysis (resorption of the terminal bones of the fingers and/or toes), joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes. Studies in animals support these findings. In addition, renal nephrosis and developmental toxicity have been reported to occur in animals exposed to vinyl chloride, but similar results have not been confirmed in humans.

Studies in both humans and animals indicate that vinyl chloride is carcinogenic. Hepatic angiosarcoma has been identified in workers exposed to vinyl chloride by the inhalation route. Also, there are some studies that indicate that cancers of the central nervous system, respiratory tract, and lymphatic and hematopoietic systems may occur in humans following inhalation exposure. Studies in a variety of species exposed by both the inhalation and oral routes show an increased incidence of hepatic angiosarcoma. Therefore, it would be prudent to consider the potential for carcinogenic effects in humans exposed by the oral route as well.

Death. Vinyl chloride, at sufficiently high levels, may be fatal to humans following inhalation exposure. The autopsy report by Danziger (1960) regarding the deaths of two vinyl chloride workers indicated that death was due to asphyxiation but did not estimate the levels to which these workers had been exposed. Inhalation exposure of animals for as brief a period as 30 minutes to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been reported to be lethal to rats, mice, and guinea pigs (Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). The cause of death was attributed to respiratory failure secondary to central nervous system depression in one study (Lester et al. 1963). However, reports of cardiac arrhythmicity at similar levels (Carr et al. 1949; Oster et al. 1946) suggest that cardiac arrest may have contributed to the deaths. The levels of vinyl chloride found to cause death in animals are extremely high and unlikely to exist under most environmental conditions (with the exception of concentrated emissions from a large point source). Due to the limited solubility of vinyl chloride in water, acute ingestion of a lethal dose of vinyl chloride in contaminated water is improbable. Thus, it is unlikely that exposure to low levels of vinyl chloride in the air or water near hazardous waste sites will cause death acutely.

Longer-term, low-level exposures have been associated with decreased survival in a number of animal inhalation exposure studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979b; Hong et al. 1981; Lee et al. 1978; Viola et al. 1970) and oral exposure studies (Feron et al. 1981; Til et al. 1983). Decreased survival of rats was observed at inhalation exposures as low as 50 ppm when exposed 6 hours per day, 5 days per week, for 10 months (Hong et al. 1981) and oral exposures as low as 1.7 mg/kg/day over the course of a lifetime (Til et al. 1983). The decreased survival noted in these studies may be a reflection of increased mortality due to cancer induction by vinyl chloride.

The significance of a shortened lifespan in animals following low-level chronic exposure with regard to potential adverse effects in humans is unknown.

Systemic Effects

Respiratory Effects. Both autopsy reports from workers with vinyl chloride-related deaths (Danziger 1960) and animal studies using extremely high levels of vinyl chloride (100,000 ppm and above) (Lester et al. 1963; Mastromatteo et al. 1960) indicate that such levels of vinyl chloride cause respiratory irritation by the inhalation route. It is unlikely that respiratory irritation will result from exposure to low levels of vinyl chloride in the air near hazardous waste sites.

Studies of workers, who have been occupationally exposed to vinyl chloride, give mixed results regarding the chronic respiratory effects of vinyl chloride. Whereas Gamble et al. (1976), LaPlanche et al. (1987), and Waxweiler et al. (1977) reported no adverse respiratory effects associated with occupational vinyl chloride

2. HEALTH EFFECTS

exposure, other investigators found increased incidences of emphysema, decreased respiratory volume and vital capacity, respiratory insufficiency, decreased respiratory oxygen and carbon dioxide transfer, pulmonary fibrosis, and abnormal chest x-rays (Juhe et al. 1974; Lillis et al. 1975, 1976; Lloyd et al. 1984; Suci et al. 1975; Walker 1976; Wong et al. 1986). Factors that may confound the interpretation of these results include smoking history and exposure to PVC resin dust or to other chemicals.

Histopathologic examination of rats and mice exposed to vinyl chloride for periods of 6 months or a year provide some supportive evidence for respiratory pathology associated with high-level exposure (2,500 and 5,000 ppm)(Feron and Kroes 1979; Suzuki 1978, 1980, 1981). These studies have identified changes such as proliferation and hypertrophy of bronchiolar epithelium, hypersecretion of mucin, hyperplasia of alveolar epithelium, mobilization of alveolar macrophages, increased pulmonary hemorrhages, and interstitial pneumonia.

Cardiovascular Effects. A small percentage of workers exposed to vinyl chloride develop vinyl chloride disease. One of the symptoms of this disease is a condition referred to as Raynaud's phenomenon, in which the fingers blanch and experience numbness and discomfort upon exposure to the cold. Arteriography and biopsy material from afflicted workers indicate that vinyl chloride may cause blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls (Harris and Adams 1967; Juhe et al. 1974; Preston et al. 1976; Veltman et al. 1975; Walker 1976).

Vinyl chloride disease has been reported to be an autoimmune response similar to systemic sclerosis. Mechanisms for the vascular effects have been proposed by Grainger et al. (1980) and Ward (1976), which relate the vascular response to immunologic changes observed in these workers. According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to cause blockage of the small vessels.

Studies in rodents exposed by inhalation to high levels of vinyl chloride, have reproduced these symptoms to some extent. Thickening of arterial vessel walls has been observed in rats exposed to high concentrations of vinyl chloride for a year (Feron and Kroes 1979; Viola 1970). Threshold levels for the production of this effect have not been determined. However, because of the appearance of Raynaud's phenomenon only in workers with exposure to very high levels of vinyl chloride, it is presumed unlikely that persons exposed to low levels of vinyl chloride near hazardous waste sites would be affected.

Limited data are available regarding cardiovascular-related deaths in humans (Bryen et al. 1976); however, cardiac arrhythmias have been produced in dogs exposed by inhalation to extremely high levels of vinyl chloride (Carr et al. 1949; Oster et al. 1946). It is unlikely that persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites will develop cardiac rhythm abnormalities.

Hematological Effects. The blood of both humans and animals that died as a result of acute exposure to extremely high levels of vinyl chloride did not clot (Danziger 1960; Mastromatteo et al. 1960). Also, slight-to-severe thrombocytopenia has been observed in vinyl chloride workers in several but not all studies (Juhe et al. 1974; Lillis et al. 1975; Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975). However, studies in animals using nonlethal concentrations of vinyl chloride have indicated that such levels result in a decreased clotting time. In studies by Feron et al. (1979a) and Feron and Kroes (1979) a decrease was observed in the time necessary for blood to clot in rats exposed to 5,000 ppm for 1 year. A decreased

2. HEALTH EFFECTS

clotting time was also observed in rats fed 17 mg/kg/day for 1 year (Feron et al. 1981). Thus, it is uncertain whether persons exposed to low levels of vinyl chloride near hazardous waste sites would experience abnormal clotting times.

Musculoskeletal Effects. Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. Acroosteolysis, in vinyl chloride workers, was observed to be preceded by Raynaud's phenomenon in most instances (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabc 1975; Veltman et al. 1975; Wilson et al. 1967). It is unclear whether the resorptive bone changes are due to activation of osteoclasts secondary to vascular insufficiency in the finger tips. Because acroosteolysis was observed exclusively in workers with very high levels of exposure, it is unlikely that persons exposed to low levels of vinyl chloride near hazardous waste sites would be affected.

Hepatic Effects. Changes in the liver have been observed in humans exposed to vinyl chloride via inhalation. The characteristic pattern of changes consists of hypertrophy and hyperplasia of hepatocytes and sinusoidal cells; sinusoidal dilation associated with damage to the cells lining the sinusoids and/or sinusoidal occlusion associated with crowding due to cellular hypertrophy and hyperplasia; focal areas of hepatocellular degeneration due to disruption of hepatic circulation; and fibrosis of portal tracts, septa, and intralobular perisinusoidal regions (Falk et al. 1974; Gedigke et al. 1975; Juhe et al. 1974; Marsteller et al. 1975; Popper and Thomas 1975; Popper et al. 1981; Tamburro et al. 1984). These findings are supported by studies in animals (Popper et al. 1981; Sokal et al. 1980; Torkelson et al. 1961). The primary difference between effects observed in animals and humans was the greater degree of fibrosis (reticulin and collagen deposition) in human liver tissue. Structural changes occurred in the livers of humans and animals with little or no change in serum hepatic enzyme activities. Most likely this was because of the limited scope of the necrotic changes. An intermediate-duration inhalation MRL was derived based on hepatic toxicity in male rats observed in a study by Bi et al. (1985).

Hepatotoxicity has also been observed in chronic oral studies. Areas of cellular alteration and necrosis were observed in rats orally exposed to vinyl chloride (Feron et al. 1981; Til et al. 1983). A chronic-duration oral MRL was developed based on hepatotoxic effects in rats observed by Til et al. (1983). Based on the above data it would be prudent to consider that persons exposed to low levels of vinyl chloride in the air or in contaminated water at hazardous waste sites may develop similar hepatic changes.

Acute degenerative changes were also seen in the livers of animals that inhaled extremely high levels of vinyl chloride (Mastromatteo et al. 1960), but it is unlikely for persons briefly exposed to low levels of vinyl chloride near hazardous waste sites to develop similar degenerative changes.

Renal Effects. No evidence of human renal disease has been reported in studies of workers occupationally exposed to vinyl chloride. However, increased severity of tubular nephrosis and increased kidney to body weight ratios were observed in rats exposed to concentrations of vinyl chloride ranging from 100 to 5,000 ppm for periods of up to a year (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a). It is unclear whether the effects observed in rats represent an increase in severity of naturally occurring tubular nephrosis in rats, or whether these effects represent a lesion attributable to toxic effects of vinyl chloride on the kidney. Thus, insufficient data are available to predict whether persons exposed to low levels of vinyl chloride over long periods may develop renal toxicity.

Dermal/Ocular Effects. The third most common characteristic of vinyl chloride disease that was identified in persons with exposure to very high levels of vinyl chloride (polymerization tank cleaners) is thickening of

2. HEALTH EFFECTS

the subepidermal layer of the skin. The changes in the skin may appear as maculae above the joints of the fingers or rope-like bundles on the hands and forearms (Juhe et al. 1974; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1976; Walker 1976). Analysis of biopsied tissue indicates that the thickening is due to increased synthesis and deposition of collagen (Jayson et al. 1976). In most cases, the skin changes are also preceded by Raynaud's phenomenon. Thickening of the skin and increased collagen content have been reproduced to some extent in rats administered high concentrations of vinyl chloride by gavage (Knight and Gibbons 1987). Based on the appearance of this effect predominantly in persons with exposure to very high levels of vinyl chloride, it is unlikely that low-level exposures near hazardous waste sites would cause similar effects.

Immunological Effects. Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers indicating a stimulatory effect of vinyl chloride on the immune system (Bogdanikowa and Zawilska 1984; Wagnerova et al. 1986, 1988).

When workers with vinyl chloride disease were examined, a correlation of the severity of the symptoms of vinyl chloride disease (Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, scleroderma-like skin changes) with the magnitude of the immune response was observed (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). The most frequent immunologic findings in workers with vinyl chloride disease were an increase in circulating immune complexes or cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation.

Because of the similarity of vinyl chloride disease with the proposed autoimmune disease, systemic sclerosis, and the association of many autoimmune diseases with certain inherited genetic characteristics, the human lymphocyte antigen (HLA) phenotypes of vinyl chloride workers both with and without vinyl chloride disease were examined (Black et al. 1983, 1986). The study authors determined that susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLA-DR3 and HLA-B8.

A stimulation of the immune response has been observed in mice exposed to low-to-moderate levels of vinyl chloride via inhalation for several weeks (Sharma and Gehring 1979). Thus, it may be possible for persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites to develop immune stimulation. The threshold for developing an autoimmune response in susceptible persons is unknown.

Neurological Effects. Central nervous system depression is the earliest symptom associated with acute high-level vinyl chloride exposure in humans and animals. Concentrations as low as 8,000 ppm may cause dizziness in humans exposed by inhalation (Lester et al. 1963). Workers exposed to vinyl chloride, before occupational standards were made more rigorous, complained of dizziness, drowsiness, euphoria, nausea, headache, and occasional loss of consciousness (Juhe et al. 1974; Langauer-Lewowicka et al. 1976; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976; Waxweiler et al. 1977). These symptoms were most frequently experienced by those employed in positions with the greatest exposure to vinyl chloride (cleaners of the autoclaves used to synthesize PVC).

A state of unconsciousness was produced in animals acutely exposed via inhalation to concentrations of approximately 100,000 ppm (Hehir et al. 1981; Jaeger et al. 1974; Mastromatteo et al. 1960). It is unlikely that exposure to low levels of vinyl chloride in air or water near hazardous waste sites would cause central nervous system depression.

2. HEALTH EFFECTS

Reports by Magnavita et al. (1986) and Percotini et al. (1986) suggest that peripheral nerve damage may occur in occupationally exposed workers. Chronic inhalation exposure of animals to high levels of vinyl chloride caused nerve damage (Viola et al. 1970, 1971). However, threshold levels for this effect are unknown. Thus, it is unknown whether persons exposed to low levels of vinyl chloride in air or water near hazardous waste sites would experience nerve damage.

Developmental Effects. Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante et al. 1976a, 1976b; Rosenman et al. 1988; Theriault et al. 1983; Waxweiler et al. 1977). In contrast, a number of inhalation studies using pregnant animals have shown developmental toxicity consisting of resorptions, decreased litter size and fetal weight, delayed ossification, and dilated ureters. These effects occurred when animals were exposed during the first trimester of pregnancy and at moderately high levels of vinyl chloride (500-2,500 ppm) (John et al. 1977, 1981; Ungvary et al. 1978). However, these levels also produced maternal toxicity characterized by increased liver weight, decreased food consumption and weight gain, and increased mortality. Adverse postnatal effects have been observed in rats following in utero exposure to low levels of vinyl chloride (Sal'nikova and Kotsovskaya 1980). Therefore, it would be prudent to consider the possibility of developmental effects in environmentally exposed human populations as well.

Reproductive Effects. Studies in humans indicate that male reproductive function may be adversely affected by exposure to vinyl chloride. Decreased androgen levels have been found in workers occupationally exposed to vinyl chloride (Makarov 1984; Walker 1976). Also workers have complained of impotency and decreased libido (Suciú et al. 1975; Veltman et al. 1975; Walker 1976), and a decrease in sexual function was reported by Makarov (1984). These findings are supported by evidence of testicular damage in rats exposed by inhalation (Bi et al. 1985; Sokal et al. 1980).

Fewer studies have reported the effects of vinyl chloride on reproductive function in females. However, a study by Makarov et al. (1984) suggests that menstrual activity may be disturbed in female vinyl chloride workers. Also, reduced hemoglobin levels during pregnancy and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) have been observed by Bao et al. (1988). Studies designed to examine these effects in animals were not located. At present, it is unclear whether adverse reproductive effects could occur in persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites. However, it would be prudent to consider the possibility of reproductive effects in environmentally exposed populations.

Genotoxic Effects. Vinyl chloride is mutagenic in S. typhimurium (Andrews et al. 1976; Bartsch et al. 1975, 1976; de Meester et al. 1980; Elmore et al. 1976; Poncelet et al. 1980; Simmon et al. 1977), but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations (Bartsch et al. 1976). Metabolic activation is necessary for any mutagenic activity in this system (Rannug et al. 1974) or for a maximal response (Simmon et al. 1977). In addition, vinyl chloride in the vapor phase is mutagenic, but not when it is dissolved in water (Poncelet et al. 1980).

Concentrations of vinyl chloride tested in vitro range from 0.275% (Shahin 1976) to 20% (Simmon et al. 1977; Victorin and Stahlberg 1988). Shahin (1976) reported negative results for 0.275% and 0.55% in Saccharomyces cerevisiae. In S. typhimurium, a doubling of revertants has been reported to occur at about 5% vinyl chloride (Victorin and Stahlberg 1988a).

2. HEALTH EFFECTS

There is evidence that in *S. typhimurium*, it is the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde that is responsible for the mutagenicity of vinyl chloride (Jacobsen et al. 1989; McCann et al. 1975; Rannug et al. 1976). Chloroacetaldehyde appears to be less genotoxic in yeast and Chinese hamster ovary cells than 2-chloroethylene oxide (Huberman et al. 1975; Loprieno et al. 1977), and has been shown to inhibit DNA synthesis in avian cells (Kandala et al. 1990). However, 2-chloroacetaldehyde has been shown to react directly with single-stranded DNA, which then caused base changes and subsequent reversion in *Escherichia coli* when the DNA was inserted via phage (Jacobsen et al. 1989). The different effects of the aldehyde and oxide in these studies may reflect differences between the procaryotic and eucaryotic genomes.

Identification of the etheno-derived nucleosides as DNA and RNA adducts following vinyl chloride exposure provides one mechanism for the mutagenicity of this compound (Laib and Bolt 1977). There is evidence that chloroethylene oxide is responsible for the formation of the etheno-DNA adducts, which in turn cause base-pair substitutions (Barbin et al. 1985a; Bolt 1988). These findings support the *in vivo* studies (see Section 2.2.1.7) that indicate that 2-chloroethylene oxide is responsible for DNA alkylation as well as preneoplastic foci in the liver. Key *in vivo* genotoxicity studies are presented in Table 2-3 and *in vitro* genotoxicity studies are presented in Table 2-4.

Cancer. A large number of studies have reported a greater than expected incidence of a rare type of cancer, angiosarcoma of the liver, among workers exposed to vinyl chloride (Bryen et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1986; Wu et al. 1989). Other types of cancer that have shown a statistically significant increase in incidence among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system (Belli et al. 1987; Cooper 1981; Infante et al. 1976; Rinsky et al. 1988; Smulevich et al. 1988; Waxweiler et al. 1977; Weber et al. 1981; Wong et al. 1981).

Because women traditionally have not been employed in PVC-manufacturing positions in the North America and Western Europe, virtually all of the information available from occupational studies in these areas is based on the responses of males to vinyl chloride. One study by Smulevich et al. (1988) reporting on Soviet males and females occupationally exposed to vinyl chloride indicates that females may have higher incidences of stomach and lung cancers, leukemias, and lymphomas than males.

Increased incidences of angiosarcoma of the liver have been found after inhalation of vinyl chloride vapor by a variety of animal species (Maltoni et al. 1981). Although no studies examining the incidence of carcinogenic effects in humans exposed to vinyl chloride by the oral route have been located, vinyl chloride incorporated into the diet of rats has been demonstrated to cause an increased incidence of hepatic angiosarcoma. Based on these findings, the International Agency for Research on Cancer (IARC) has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1, carcinogenic to humans (IARC 1979). EPA also has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its classification scheme as a Group A carcinogen, human carcinogen (EPA 1980a). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An upper bound q_1^* of $2.95 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ was estimated by EPA (1985c) based on the incidence of hepatic angiosarcoma observed in rats in the inhalation study by Maltoni et al. (1981). An upper

TABLE 2-3. Genotoxicity of Vinyl Chloride In Vivo

Species (test system)	End point	Results	Reference
Mouse	Dominant lethal	-	Purchase et al. 1975
Rat	Dominant lethal	-	Anderson et al. 1976
	Chromosomal aberration	+	Short et al. 1977
Human lymphocyte	Chromosomal aberration	+	Anderson and Richardson 1981
	Sister chromatid exchange	-	Hansteen et al. 1978
	Chromosomal aberration	+	Hansteen et al. 1978
		+	Kucerova et al. 1979
		+	Kucerova et al. 1979
		+	Purchase et al. 1978
		+	Ducatman et al. 1975
		+	Anderson et al. 1980
		+	Fucic et al. 1990
		+	Funes-Cravioto et al. 1975
Rat	DNA alkylation	+	Hrivnak et al. 1990
		+	Laib et al. 1989
		+	Gwinner et al. 1983
		+	Singer et al. 1987
		+	Bolt et al. 1986
		+	Ciroussel et al. 1990
Mouse	DNA alkylation	+	Eberle et al. 1989
		+	Osterman-Golkar et al. 1977
Rat		+	Wallis et al. 1988
		+	Green and Hathway 1978

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

TABLE 2-4. Genotoxicity of Vinyl Chloride In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<u>Salmonella typhimurium</u>	Reverse mutation	+	-	Rannug et al. 1974
		+	+	Bartsch et al. 1975, 1976
		+	+	Andrews et al. 1976
		+	+	Simmon et al. 1977
		Not tested	-	Elmore et al. 1976
		+	+	Poncelet et al. 1980
		+	+	de Meester et al. 1980
		+	+	Victorin and Stahlberg 1988a
		+	Not tested	McCann et al. 1975
		+	+	Rannug et al. 1976
<u>Escherichia coli</u>		Not applicable	+	Jacobsen et al. 1989
<u>Saccharomyces cerevisiae</u>		Not tested	-	Shahin 1976
<u>Schizosaccharomyces pombe</u>	Forward mutation	+	-	Loprieno et al. 1977
Chinese hamster ovary cells		Not applicable	+	Huberman et al. 1975
<u>Bacillus subtilis</u>	Rec-repair	Not tested	-	Elmore et al. 1976
Rat liver microsomes	RNA alkylolation	Not applicable	+	Laib and Bolt 1977
QT6 (avian cells)	Inhibition of DNA synthesis	Not applicable	+	Kandala et al. 1990

DNA = deoxyribonucleic acid; RNA = ribonucleic acid; - = negative result; + = positive result

DRAFT FOR PUBLIC COMMENT

2. HEALTH EFFECTS

57

2. HEALTH EFFECTS

bound q_1^* for oral exposure was estimated by EPA (1985b) to be 2.3×10^{-1} (mg/kg/day)⁻¹ based on the combined incidence of liver and lung tumors in rats in the study by Feron et al. (1981). Doses associated with excess cancer risks of 10^{-4} , 10^{-5} , and 10^{-6} by the inhalation and oral routes are plotted in Figures 2-1 and 2-2, respectively.

There are ample data on the genotoxicity of vinyl chloride in both humans and animals. Information on the mechanisms by which this compound may exert its carcinogenic effects have been elucidated from both *in vitro* and *in vivo* studies. Vinyl chloride is metabolized to 2-chloroethylene oxide, which interacts directly with DNA and RNA, producing alkylation products such as 3,N⁴-ethenocytidine, 1,N⁶-ethenoadenosine, 7-N-(2-oxoethyl)-guanosine. This alkylation results in highly efficient base-pair substitution. It appears that the oxide is the ultimate genotoxic intermediate of vinyl chloride, which is consistent with data on the carcinogenicity of the oxirane derivatives of vinyl chloride.

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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic 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 biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to vinyl chloride are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by vinyl chloride 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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2. HEALTH EFFECTS

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Vinyl Chloride

Exposure to vinyl chloride may be monitored to some extent by the identification and quantitation of a number of parameters. For example, following acute exposure to moderate to high levels, vinyl chloride can be measured in expired air. The expiration of vinyl chloride follows first-order kinetics; therefore, this parameter may be directly correlated with exposure levels (Baretta et al. 1969). This measure may provide the most direct evidence of vinyl chloride exposure. However, measurement of exposure by this technique is limited by the rapidity of excretion of vinyl chloride in expired air. The half-life of vinyl chloride in expired air has been determined to be between 20 and 30 minutes following an inhalation exposure and to be approximately 60 minutes following an oral exposure (Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978a, 1978b). Thus, testing must be initiated as soon as possible following termination of exposure. Furthermore, measurement of vinyl chloride in expired air has limited utility for low-level exposures (<50 ppm) because of competition with rapid metabolic processes (Baretta et al. 1969). In addition, it provides no information on the duration of exposure.

Thiodiglycolic acid is a major metabolite of vinyl chloride that is excreted in the urine. Measurement of thiodiglycolic acid in urine has been used to monitor workers occupationally exposed to vinyl chloride (Muller et al. 1979). However, measurement of this metabolite is of limited utility in estimating levels of exposure. The amount of thiodiglycolic acid in the urine will vary according to individual metabolic idiosyncracies. Also, metabolism of vinyl chloride to thiodiglycolic acid is a saturable process. Therefore, when exposure exceeds a certain level, the excretion of vinyl chloride as thiodiglycolic acid will plateau (Watanabe et al. 1976b). Furthermore, the rate of metabolism of vinyl chloride to thiodiglycolic acid may be influenced by the presence of liver disease, ethanol, or certain other substances such as barbiturates (Hefner et al. 1975b)(also see Section 2.6). Similar to the measurement of vinyl chloride in expired air, the measurement of thiodiglycolic acid must take place shortly after exposure, because of the rapidity of its excretion. The half-life for excretion of thiodiglycolic acid following an acute exposure is between 4 and 5 hours (Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b). Finally, excretion of thiodiglycolic acid is not unique to exposure to vinyl chloride. For example, thiodiglycolic acid may be excreted in the urine as the result of exposure to vinylidene chloride, ethylene oxide, or 2,2-dichloroethylether (Norpoth et al. 1986; Petit 1986). Also, infants delivered prematurely have been found to have high levels of urinary thiodiglycolic acid. A correlation was observed between the thiodiglycolic acid levels and the number of weeks prematurely that the infant was born. The origin of this thiodiglycolic acid is unknown, but is not believed to be associated with vinyl chloride exposure (Petit 1986).

The intermediary metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). Two of the DNA adducts that are formed are 1,N⁶-etheno-adenosine and 3,N⁴-ethenocytidine. Monoclonal antibodies for these DNA adducts have been isolated and used in enzyme-linked immunosorbent assay (ELISA) to quantify these ethenoderivatives in biological samples (Eberle et al. 1989; Young and Santella 1988). Measurement of DNA adducts may be useful in estimating vinyl chloride exposure. However, this technique is of limited value for quantifying levels of exposure because formation of these products will be influenced by variability in vinyl chloride metabolism. Also, their persistence in tissues will be influenced by the rate of DNA metabolism and repair. Furthermore, the DNA adducts, for which monoclonal antibodies have been isolated, are formed as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,2-dichloroethane (Bolt et al. 1986; Svensson and Osterman-Golkar 1986). For additional information on the kinetics of vinyl chloride see Section 2.3.

2. HEALTH EFFECTS

Exposure to vinyl chloride may also be estimated to some extent from the diagnosis of physiological effects known to be closely associated with it. For example, a syndrome known as vinyl chloride disease has been identified in workers occupationally exposed to vinyl chloride. This syndrome includes Raynaud's phenomenon, acroosteolysis of the distal phalanges of the fingers, and scleroderma-like changes in the hands and forearms (also see Section 2.2). Although this syndrome resembles systemic sclerosis, a differential diagnosis may be made based on the absence of antinuclear antibodies from the blood of those afflicted with vinyl chloride disease (Black et al. 1983, 1986). The occurrence of vinyl chloride disease in exposed populations is about 3% and susceptibility appears to be genetically related (Black et al. 1983, 1986). Therefore, absence of these symptoms would not eliminate the possibility of exposure, but their presence may be a good indicator of exposure.

Angiosarcoma of the liver has been identified in workers occupationally exposed to vinyl chloride. This type of tumor is extremely rare in the general population (Heath et al. 1975); therefore, its diagnosis may indicate vinyl chloride exposure. However, exposure to arsenicals and Thorotrast® (thorium dioxide; formerly used in arteriography) also causes angiosarcoma of the liver; these substances must be eliminated as causative agents before correlating hepatic angiosarcoma with vinyl chloride exposure (Gedigke et al. 1975; Marsteller et al. 1975).

2.5.2 Biomarkers Used to Characterize Effects Caused by Vinyl Chloride

The realization that angiosarcoma of the liver is associated with vinyl chloride exposure prompted several investigators to try to identify assays that could be used to monitor those individuals considered to be at risk. Standard serum assays designed to detect the presence of hepatic enzymes in the blood were found to be of limited value in monitoring the progression of vinyl chloride-induced hepatic changes (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). This may be because of the relatively slight hepatic damage produced by vinyl chloride and the late development of necrotic areas in the disease process (Popper et al. 1981). In contrast, studies indicate that clearance type assays, which measure liver function, are more sensitive indicators of the hepatic damage resulting from vinyl chloride exposure. Two such assays are the indocyanine clearance test and measurement of serum bile acid levels (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984).

More sophisticated procedures such as computer-assisted tomography, ultrasonography, and $^{99}\text{[Te]}$ liver scanning have been used in patients believed to have vinyl chloride-induced liver damage, but none of these tests is sensitive or specific enough for screening for subclinical asymptomatic hepatic injury (NIOSH 1986). Finally, liver biopsy may provide the most accurate identification of vinyl chloride-associated liver damage (Liss et al. 1985). This is because of the characteristic pattern of hepatic histopathology associated with vinyl chloride-induced damage (Popper et al. 1981). However, liver biopsy is an invasive procedure with attendant risks, and, therefore, may not be justified.

The symptoms and signs associated with vinyl chloride disease (Raynaud's phenomenon, scleroderma-like skin changes, and acroosteolysis) are similar to those observed in systemic sclerosis. Vinyl chloride disease may be differentiated from systemic sclerosis by the absence of antinuclear antibodies in the blood and association of vinyl chloride disease with vinyl chloride exposure (Black et al. 1983, 1986). Raynaud's phenomenon is an early symptom of vinyl chloride disease. However, cyanosis and blanching of fingers with exposure to cold may be the result of a number of other conditions such as connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, or exposure to drugs, chemicals, or vibrating tools (Freudiger et al. 1988). Thus, other potential causes must be eliminated before this syndrome can be used to identify vinyl chloride disease. The symptoms associated with vinyl chloride disease have been attributed to vinyl chloride-

2. HEALTH EFFECTS

induced changes in the microvasculature (Grainger et al. 1980). Capillary abnormalities in the hands may be detected using wide-field capillary microscopy and have been proposed to represent an early manifestation of vinyl chloride's effects (Marioq et al. 1976). Also, immunofluorescent examination of biopsy material from the skin may be used to identify circulating immune complexes and their deposition on the vascular endothelium (Ward 1976).

Chromosomal aberrations found in lymphocytes may be indicative of the genotoxic effects of vinyl chloride (Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990; Funes-Cravioto et al. 1975; Hansteen et al. 1978; Hrivnak et al. 1990; Kucerova et al. 1979; Purchase et al. 1978). However, any of a number of genotoxic substances can cause chromosomal aberrations. Also, de Jong et al. (1988) have found that variability in the control population may obscure the observation of low-level chromosomal aberrations in persons exposed to low levels of vinyl chloride. The DNA adducts produced by the reactive intermediary metabolites of vinyl chloride, 1,N⁶-ethenoadenosine and 3,N⁴-ethenocytidine, may be more specific indicators of vinyl chloride's genotoxic potential.

2.6 INTERACTIONS WITH OTHER CHEMICALS

A number of studies have been performed that examine the effect of agents intended to alter the metabolism of vinyl chloride on its toxicity. For example, the effects of phenobarbital pretreatment on vinyl chloride-induced hepatotoxicity have been examined by Jaeger et al. (1974, 1977), Jedrychowski et al. (1985), and Reynolds et al. (1975a, 1975b). Pretreatment of rats with phenobarbital for 7 days prior to a 4-hour vinyl chloride exposure caused an increase in microsomal cytochrome P-450 activity (Reynolds et al. 1975b) and enhanced hepatotoxicity (Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). In these studies, in the absence of the phenobarbital pretreatment, a single exposure to approximately 50,000 ppm had no detectable adverse effect on the livers of exposed rats. However, following phenobarbital pretreatment, 50,000 ppm of vinyl chloride produced increased serum activity of hepatic enzymes (Jaeger et al. 1977; Jedrychowski et al. 1985), areas of hepatic necrosis (Reynolds et al. 1975a), or both (Jaeger et al. 1974; Reynolds et al. 1975b).

Another agent known to increase mixed function oxidase activity, Aroclor 1254, was also tested for its ability to enhance vinyl chloride-induced hepatotoxicity (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b). Pretreatment of rats with Aroclor 1254 for several days prior to exposure to vinyl chloride resulted in an increase in serum activity of hepatic enzymes (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b) and areas of hepatic necrosis (Conolly et al. 1978; Reynolds et al. 1975b).

Additional support for a role for mixed function oxidases in the enhanced toxicity of vinyl chloride was obtained using SKF525A, a mixed function oxidase inhibitor. If SKF525A was administered following phenobarbital pretreatment and before vinyl chloride exposure, it blocked the ability of phenobarbital pretreatment to enhance vinyl chloride-induced hepatotoxicity (Jaeger et al. 1977).

The role of glutathione conjugation in vinyl chloride-induced toxicity was also examined (Conolly and Jaeger 1979; Jaeger et al. 1977). The investigators hypothesized that depletion of glutathione might enhance the toxicity of vinyl chloride by preventing the excretion of toxic intermediary metabolites. However, diethylmaleate, an agent known to deplete hepatic glutathione levels, had no effect on the toxicity produced by vinyl chloride following pretreatment with either phenobarbital (Jaeger et al. 1977) or Aroclor 1254 (Conolly and Jaeger 1979). Trichloropropene oxide (TCPO), another agent known to deplete hepatic glutathione, caused enhancement of the hepatic toxicity produced by Aroclor 1254 pretreatment and vinyl

2. HEALTH EFFECTS

chloride exposure, but only when the animals had been fasted prior to vinyl chloride exposure (Conolly and Jaeger 1979). The study authors hypothesized that the enhancement of vinyl chloride toxicity was a result of the ability of TCPO to inhibit epoxide hydrolase rather than its ability to deplete glutathione levels.

Although the depletion of cellular glutathione levels did not appear to enhance vinyl chloride toxicity, treatment with cysteine, the rate-limiting precursor in hepatic glutathione synthesis, increased hepatic glutathione levels and provided partial protection against the toxic effects produced by Aroclor 1254 and vinyl chloride (Conolly and Jaeger 1979).

The effects of the interaction of ethanol with vinyl chloride on development were tested by John et al. (1977). In this study, animals were exposed to vinyl chloride in the presence and absence of 15% ethanol in the drinking water during pregnancy. Ethanol caused a decrease in maternal food consumption and maternal weight gain in mice, rats, and rabbits and enhanced incidence of skeletal abnormalities in mice, and to a lesser extent, in rats. Interpretation of these results is clouded by the absence of an ethanol-exposed control group and the current recognition of the adverse effects of ethanol on pregnancy outcome.

In the experiment by Radtke et al. (1981), ethanol-consuming rats exposed to vinyl chloride for a year had an enhanced incidence of hepatic angiosarcomas, hepatomas, and lymphosarcomas, earlier onset of the tumors, and an enhanced death rate. The incidence of vinyl chloride-induced angiosarcomas was potentiated by ethanol, whereas the increased incidences of hepatoma and lymphosarcomas by ethanol were additive in nature. The authors hypothesized that the effects of ethanol on the development of angiosarcomas was due to the ability of ethanol to inhibit the metabolism of vinyl chloride (Hefner et al. 1975b; Hultmark et al. 1979).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vinyl chloride than will most persons exposed to the same level of vinyl chloride in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. 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."

Data suggest that the following subsets of the human population may be unusually susceptible to the toxic effects of vinyl chloride: fetuses; infants; young children; people with liver disease, irregular heart rhythms, impaired peripheral circulation, or systemic sclerosis; people with exposure to organochlorine pesticides; and those consuming ethanol or barbiturates or taking Antabuse for alcoholism. Also, persons who possess the HLA-DR5, HLA-DR3, and B8 alleles may be at increased risk.

Vinyl chloride can cross the placenta and enter the blood of the fetus (Ungvary et al. 1978). Studies by Drew et al. (1983) and by Maltoni et al. (1981) have shown that animals exposed by inhalation prior to adolescence or during pregnancy may have a greater death rate and increased likelihood of developing cancer than adult animals exposed for similar periods. This may relate to the length of the induction period of hepatic angiosarcoma rather than to an increased susceptibility of the young, per se.

2. HEALTH EFFECTS

Vinyl chloride is metabolized in the liver in a multistep process. The intermediary metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been suggested to be responsible for some of the adverse effects produced by vinyl chloride. Thus, activation of the enzyme system responsible for production of these toxic metabolites would be expected to increase the toxicity of vinyl chloride exposures. 2-Chloroethylene oxide is formed by action of the mixed function oxidase system associated with cytochrome P-450. The barbiturate, phenobarbital, and the organochlorine pesticide, Aroclor 1254, increased mixed function oxidase activity and have been shown to greatly increase the hepatotoxicity of vinyl chloride (Conolly and Jaeger et al. 1979; Conolly et al. 1978; Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). Thus, persons taking barbiturates or who might be exposed to organochlorine pesticides that are known to induce microsomal enzymes (such as Aroclor 1254) would be expected to be at increased risk for developing vinyl chloride-induced hepatotoxicity.

An alternative pathway for vinyl chloride metabolism in the liver involves the enzymes, alcohol dehydrogenase and aldehyde dehydrogenase. Vinyl chloride metabolized by these enzymes is not metabolized to 2-chloroethylene oxide, the toxic intermediary metabolite. Persons consuming sufficient amounts of alcohol inhibit this enzyme system (Hefner et al. 1975b; Hultmark et al. 1979). Therefore, these persons have increased levels of the toxic metabolite, 2-chloroethylene oxide. Radike et al. (1981) demonstrated that ethanol-consuming rats exposed to vinyl chloride had an increased incidence of cancer and an earlier death rate than animals exposed to vinyl chloride in the absence of ethanol.

Some persons consume the agent, Antabuse, to curb the desire for alcohol. In its role as a therapeutic agent, Antabuse blocks aldehyde dehydrogenase and causes a build-up of acetaldehyde, which is emetic, in the body when alcohol is consumed. If persons taking Antabuse are exposed to vinyl chloride, the alternative metabolic pathway for vinyl chloride metabolism will be blocked, causing more vinyl chloride to be metabolized to the toxic metabolite, 2-chloroethylene oxide. Thus, these persons may be at increased risk for hepatotoxicity, cancer, and early death.

Very high levels of vinyl chloride have been demonstrated to cause cardiac arrhythmias in dogs (Carr et al. 1949; Oster et al. 1946). Persons with a propensity to develop cardiac arrhythmias due to heart disease or damage may be at an increased risk of having heart beat irregularities when exposed to high concentrations of vinyl chloride.

Vinyl chloride has been shown to cause decreased circulation in the hands and fingers of some persons. Persons with impaired circulation due to some other cause such as connective tissue disorders, systemic sclerosis, hyperviscosity of the blood, or use of vibrating tools, may experience more severe impairment of the circulation.

Work by Black et al. (1983, 1986) has shown that persons with the HLA allele HLA-DR5 may have an increased likelihood of developing vinyl chloride disease, and those with the alleles HLA-DR3 and B8 may have an increased severity of the disease.

2.8 ADEQUACY OF THE DATABASE

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

2. HEALTH EFFECTS

of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vinyl chloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. 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.

2.8.1 Existing Information on Health Effects of Vinyl Chloride

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl chloride are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of vinyl chloride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

Virtually all of the literature regarding health effects in humans comes from studies of workers exposed to vinyl chloride during the production of PVC. Case reports and cohort studies describe some acute health effects and a wide range of long-term health effects. The predominant mode of exposure in these studies is via inhalation. These studies are limited by the lack of reliable data on individual exposure levels. No studies were found regarding the health effects of oral exposure. One case report examined the effects of dermal exposure to liquid vinyl chloride, but exposure by this route is not expected to contribute significantly to producing adverse health effects because of the limited absorption of vinyl chloride through the skin.

A large number of studies examining the health effects of inhaled vinyl chloride by animals were reviewed. As can be seen in Figure 2-4, no information is available on the acute systemic, immunologic, neurologic, developmental, reproductive, or genotoxic effects of exposure of animals by the oral route. No information is available regarding the health effects of exposure by the dermal route, but toxicokinetic studies indicate that this route is not an important means of exposure.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas that contain hazardous waste sites may be exposed to vinyl chloride for brief periods. Exposure most likely would occur by inhalation, but relatively brief oral and dermal exposures are also possible. There are acute inhalation exposure data in humans and animals that indicate that the central nervous system is a major target organ of vinyl chloride toxicity. Symptoms of central nervous system depression ranging from dizziness and drowsiness to loss of consciousness have been observed in humans and animals as a result of brief exposure to very high levels of vinyl chloride. A threshold for central nervous system effects appears to be approximately 8,000 ppm. Extremely high concentrations of vinyl chloride produce death and respiratory irritation in humans and animals by the inhalation route. Based on studies in animals, the threshold for these effects appears to be in the range of 100,000–400,000 ppm. Extremely high concentrations of vinyl chloride produce cardiac arrhythmias in dogs exposed by the inhalation route. No threshold was reported for these effects; acute inhalation studies examining the incidence of cardiac irregularities at a variety of lower doses may be helpful in determining the threshold for this effect. Pharmacokinetic data indicate that similar end points might be expected if sufficiently high doses could be consumed by the oral route. However, the solubility characteristics of vinyl

2. HEALTH EFFECTS

FIGURE 2-4. Existing Information on Health Effects of Vinyl Chloride

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●		●	●	●	●	●	●	●
Oral										
Dermal		●								

HUMAN

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●		●	●						●
Dermal										

ANIMAL

● Existing Studies

2. HEALTH EFFECTS

chloride in aqueous media (1,100–2,763 mg/L at 25°C) (Cowfer and Magistro 1983; EPA 1985b) indicate that achieving concentrations of vinyl chloride in excess of 5,000 ppm may be extremely difficult. Animal studies indicate that an adverse effect on the fetus is the most sensitive end point observed following brief inhalation exposures to vinyl chloride. Concentrations as low as 500 ppm were observed to cause adverse effects on developing fetuses. Studies examining the developmental, neurological, and systemic effects of the highest doses achievable in drinking water would be helpful for determining whether any effects would occur when vinyl chloride-contaminated groundwater or food products are consumed. One report described severe frostbite with second degree burns on the hands of a man resulting from the rapid evaporation of spilled liquid vinyl chloride. Toxicokinetic studies indicate that absorption of vinyl chloride vapor by the dermal route is insignificant; thus, studies examining the effects of acute-duration dermal exposure do not seem warranted.

A report was located regarding hepatic and respiratory effects observed 18 months following a single 1-hour inhalation exposure to vinyl chloride. However, limitations in the study diminished its reliability. Because of the implications of chronic effects from acute exposure, confirmation of these results in another study would be valuable.

Intermediate-Duration Exposure. No studies in humans specifically address intermediate-duration effects by any route. Most epidemiological studies of occupationally exposed persons have concentrated on persons who have been employed over several years. A study with reliable quantification of exposure levels that examined the effects experienced by vinyl chloride workers in their 1st year of exposure would be helpful for predicting the effects that might be observed in populations exposed to hazardous waste sites for similar periods of time. There is a large database describing the effects of intermediate-duration inhalation exposures in animals. Animals exposed to vinyl chloride vapor for more than 2 weeks and less than a year have experienced effects on the liver, kidneys, lungs, and blood. Data were sufficient to determine an intermediate-duration inhalation MRL based on liver effects. However, the MRL was based on a LOAEL and a no-effect level in animals would be more suitable for MRL derivation. Extremely limited information was available regarding oral intermediate-duration effects. One chronic study presented interim sacrifice data that identified relative weight and histopathological changes in the liver. However, only a single-dose group was compared to controls, precluding determination of the dose-response of the effects observed. Thus, no MRL for oral intermediate-duration exposures could be determined. Additional studies examining the effects of oral exposure to vinyl chloride would be helpful for predicting effects that might be observed in humans consuming contaminated drinking water or foods over a similar period of time. As noted above, absorption of vinyl chloride vapor through the skin is not expected to be significant; thus, additional dermal exposure studies do not seem warranted.

Chronic-Duration Exposure and Cancer. A large number of studies of workers exposed to vinyl chloride have identified a wide range of target organs that may be affected by chronic-duration inhalation of vinyl chloride. The target organs include the liver, lungs, blood, immune system, cardiovascular system, skin, bones, nervous system, and the reproductive organs. These studies are severely limited in that individual exposure levels have not been documented. In general, studies in animals provide supportive evidence for these effects and give indications of the exposure levels that may be associated with them.

No information was available regarding chronic-duration oral exposure in humans. However, studies in animals indicate that the liver, blood, and skin are target organs for oral exposure to vinyl chloride. A chronic-duration oral MRL was calculated based on hepatic toxicity. This value was based on a LOAEL. A no-effect level in animals would be more suitable for MRL determination.

2. HEALTH EFFECTS

No information was available regarding effects of chronic-duration dermal exposure in humans or animals, but absorption of vinyl chloride through the skin is not expected to be significant. Thus, dermal exposure studies do not seem warranted.

There is sufficient evidence to indicate that vinyl chloride is carcinogenic to humans and animals exposed via inhalation and in animals exposed via the oral route. The mechanism for carcinogenicity appears to be associated with the formation of reactive intermediates.

Genotoxicity. There are substantial data on both clastogenesis and DNA alkylation in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant. These findings are supported by both animal studies and *in vitro* studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays. There are also data that support the premise that it is the chloroethylene oxide metabolite that is ultimately responsible for the direct action on the DNA, and that the mechanism involves alkylation and subsequent base-pair substitution. There are studies that indicate that the clastogenic effects of vinyl chloride exposure in humans are reversible; additional studies on the fate of the alkylated DNA in humans after an exposure-free interval would be useful for predicting the mechanisms involved in the latency period for carcinogenesis. In addition, further work elucidating the genotoxic role of chloroacetaldehyde would be useful to explain the inconsistent findings of the effects of this metabolite on clastogenesis and the induction of carcinogenesis.

Reproductive Toxicity. Data from a number of epidemiological studies provide suggestive evidence of adverse effects on male and female reproductive function. Sexual impotence and decreased androgen levels were found in men exposed occupationally to vinyl chloride. In women exposed to vinyl chloride, menstrual disturbances and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) were observed. Although no reports of two-generation reproduction studies in animals were located, two studies examining a range of toxic effects in rats indicate that vinyl chloride is toxic to the testes. A two-generation reproduction study in animals would be helpful to assess whether adverse effects on the rate of conception could be correlated with damage to the male reproductive organs or whether disturbances in female menstrual activity could be verified. Also, animal models of preeclampsia could be tested to determine the mechanism by which vinyl chloride might cause this effect. Well-designed and well-conducted epidemiological studies examining such changes would also be helpful. No data are available on the possible reproductive toxicity resulting from oral exposure to vinyl chloride. Oral studies that use drinking water as the vehicle of administration would be particularly useful because contaminated groundwater is a potentially significant source of human exposure.

Developmental Toxicity. The epidemiological studies that have addressed developmental toxicity in offspring of humans who have been exposed to vinyl chloride are controversial. Although some of these purport to show a significant association between birth defects and vinyl chloride exposure, their design and analysis have been severely criticized. At this time, there are insufficient human data to provide a definitive answer to this question. A well-designed and well-conducted epidemiological study examining potential developmental end points would be helpful. There are data showing that vinyl chloride is a developmental toxicant in animals when exposure is by inhalation. Continuous low-level exposure appears to be the most toxic, but the studies that indicated this are flawed. Additional studies examining exposure to low levels of vinyl chloride throughout gestation would be helpful in settling this issue. This issue is particularly important because women living in the vicinity of hazardous waste sites have the potential to be exposed to low levels of vinyl chloride on a continuous basis. Also, studies in animals suggest that offspring exposed *in utero* may experience adverse effects after birth, although these studies are also flawed. Epidemiological studies designed to look at this end point would be helpful. There are no data for oral exposures. Because of this

2. HEALTH EFFECTS

deficiency, oral studies examining a range of developmental end points would be useful in assessing the possibility of these effects in humans.

Immunotoxicity. Studies of workers occupationally exposed to vinyl chloride suggest that the immune system may be activated by vinyl chloride. Some data suggest that reactive intermediates may bind to proteins in the body, sufficiently altering them so that they become antigenic. In some instances, an autoimmune-like syndrome develops. The likelihood of this may be associated with the possession by individuals of specific genetic determinants (HLA alleles). Because of the low incidence of the autoimmune response in humans, the immunotoxicity may be best further studied in one of the strains of mice known to have a propensity for developing autoimmune diseases. Also, additional epidemiological studies examining the immune response of exposed populations may be helpful.

Neurotoxicity. A number of studies in humans and animals demonstrate that vinyl chloride is a central nervous system depressant following brief high-level inhalation exposures. Two studies in animals have also found degenerative effects in central nervous system tissue following chronic inhalation exposure to high levels of vinyl chloride. It is unknown whether these degenerative changes might also occur at lower doses; thus, a study examining the effects of a range of lower doses would be informative. In addition, relatively recent studies present suggestive evidence that vinyl chloride may also produce peripheral nerve damage in humans exposed chronically via inhalation. Animal studies examining histopathological and electrophysiological end points in peripheral nerves would be helpful for assessing what doses may be associated with this effect. Epidemiological studies examining exposed populations for subclinical peripheral nerve damage would be helpful. Oral exposure studies in animals would be beneficial for assessing the likelihood that populations exposed to contaminated water might develop symptoms of neurotoxicity.

Epidemiological and Human Dosimetry Studies. Virtually all of the data on effects in humans following inhalation exposure to vinyl chloride come from epidemiological studies of workers exposed during the production of PVC. These studies are limited by the absence of information on individual exposure levels. Also, in North America and Western Europe, only limited numbers of females have been studied.

For the most part, studies examining the carcinogenic potential of vinyl chloride have been adequate to distinguish an increased incidence of the rare cancer, angiosarcoma. However, many studies have used cohorts that are too small to detect smaller increases in other types of cancer (respiratory, central nervous system, lymphatic, or hematopoietic). Epidemiological studies designed to investigate reproductive and developmental effects of vinyl chloride have not been useful, in part because of a poor choice of statistical analysis, inadequate controls, or failure to take into account other chemical exposures. Additional cohort studies of these end points would be useful for examining these effects in humans.

Clastogenic effects have been used as a dosimeter for exposures to radioactive substances, and work has been done to use this approach for chemical exposures as well. More data on quantified exposures and well-controlled cytogenetic studies would be useful in developing a method for monitoring populations living near hazardous waste sites.

In addition, as noted above, well-designed and well-conducted epidemiological studies examining the incidence of peripheral neuropathies, developmental toxicity (birth defects, miscarriages, delayed prenatal development, postnatal hepatotoxicity), reproductive toxicity (male infertility, menstrual irregularity, preeclampsia in pregnant women), and immune reactivity in exposed populations would also be helpful.

2 HEALTH EFFECTS

Biomarkers of Exposure and Effect. Several potential biomarkers for exposure to vinyl chloride have been identified. Vinyl chloride measured in expired air is an adequate indicator of recent, moderate- to high-level exposure. However, for low-level exposures or exposures that occur over 1-2 hours prior to the time of measurement, this biomarker is not useful. Thiodiglycolic acid, a major urinary metabolite of vinyl chloride, has been used to monitor workers occupationally exposed to vinyl chloride. However, this biomarker is rapidly excreted, and, therefore, the period of its utility is limited. Also, thiodiglycolic acid is not specific for vinyl chloride; it may also be produced as a result of the metabolism of 1,1 dichloroethene, ethylene oxide, or 2,2-dichloroethylether.

The DNA adducts 1,N⁶-ethenoadenosine and 3,N⁴-ethenocytidine, may be used to indicate vinyl chloride exposure, although studies correlating the levels of these adducts with exposure levels are still lacking. These products remain in the body longer than free vinyl chloride or thiodiglycolic acid, thereby increasing the period after exposure that a potential exposure may be detected. However, the presence of these adducts cannot indicate how long it has been since exposure occurred. In addition, these adducts are formed as the result of binding of the intermediary metabolites with nucleic acids, and other compounds producing the same intermediary metabolites will also produce these adducts. For example, these adducts have been identified as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,2-dichloroethane. Studies attempting to identify a metabolite more specific to vinyl chloride may be helpful in developing a biomarker that may be used to facilitate future medical surveillance, which can lead to early detection and possible treatment.

The central nervous system depression associated with brief high-level exposures is easily determined by observation. The hepatic changes that may develop during longer-term exposures are difficult to detect by standard biochemical liver function tests. In contrast, tests of clearance such as the indocyanine clearance test or measurement of serum bile acid levels are more specific and sensitive indicators of vinyl chloride-induced liver damage. Angiosarcoma of the liver is a rare tumor type that has been shown to result from vinyl chloride exposure. However, other agents are known to cause angiosarcoma of the liver, such as arsenic and Thorotrast®. The cyanosis and blanching of the fingers in response to exposure to the cold may be an early indicator for the development of vinyl chloride disease. However, other conditions also known to cause these symptoms include connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, and exposure to drugs, chemicals, or vibrating tools. Finally, measurement of chromosomal aberrations may indicate the genotoxic effects of vinyl chloride. However, these aberrations do not specifically indicate vinyl chloride-induced damage. Also, DNA adducts may signal the potential to develop genotoxic effects. Further work identifying the correlation between the adducts and genotoxic effects would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are few data on humans for all toxicokinetic parameters across all exposure routes. Additional studies examining the toxicokinetics of inhalation and oral exposure in humans would be beneficial. There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of vinyl chloride administered via the oral and inhalation routes, but few describing the toxicokinetics of vinyl chloride administered via the dermal route. One study in rats found an extremely limited absorption of vinyl chloride vapor across the skin. If there is negligible absorption resulting from dermal exposure, then additional studies examining toxicokinetics from dermal exposures are not warranted; another study verifying the limited nature of dermal absorption, however, would be reassuring. Furthermore, the intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. Therefore, information regarding differences in the metabolic pattern according to sex, age, nutritional status, and species and correlations to differences in health effects would also be useful.

2. HEALTH EFFECTS

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion have been studied in animals, but information on toxicokinetics in humans is extremely limited. Human and animal data indicate that similar target organs (liver, central nervous system) for the toxic effects of vinyl chloride exist, suggesting some similarities of kinetics. Limited information is available regarding interspecies differences in kinetics. Most toxicokinetic studies have been conducted using rats, but one study in primates indicates that metabolism may saturate at lower concentrations in primates than rats. This may suggest a lower saturation point in humans also. Additional studies measuring the toxicokinetics in humans could provide valuable data as the roles of individual metabolites in the disease processes associated with vinyl chloride exposure are elucidated.

2.8.3 On-going Studies

On-going studies regarding the health effects of vinyl chloride were reported in the Federal Research in Progress File (FEDRIP 1990) database and SCISearch (1990). Table 2-5 presents a summary of on-going studies that address the health effects of vinyl chloride.

2. HEALTH EFFECTS

TABLE 2-5. On-going Studies on Vinyl Chloride^a

Investigator	Affiliation	Research description	Sponsor
D. Brown	NIOSH, Cincinnati, Ohio	Updating epidemiologic studies on vinyl chloride	NIOSH
M. Humayun	University of Medicine and Dentistry of New Jersey	Mechanisms of mutagenesis by cyclic DNA adducts in rabbits	NCI
H. Jiang	University of Maryland	Effects of vinyl chloride on pregnancy, parturition and fetal development among female workers	NA
B. Singer	University of California, Lawrence Berkeley Lab	Biochemical mechanisms of vinyl chloride carcinogenesis	NCI
J. Taylor	NIEHS	Molecular epidemiology of cancer susceptibility and oncogene activation	NIEHS
R. Thurman	University of North Carolina at Chapel Hill	Mechanisms of hepatotoxicity by environmental pollutants	NIEHS

^aSources: FEDRIP (1990) and SCISearch (1990)

DNA = deoxyribonucleic acid; NA = not available; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Science; NIOSH = National Institute for Occupational Safety and Health

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

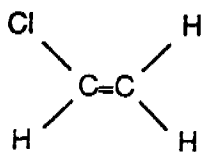
Information regarding the chemical identity of vinyl chloride is located in Table 3-1. This information includes synonyms, chemical formula and structure, and identification numbers.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Vinyl Chloride

Characteristic	Information	Reference
Chemical name	Vinyl chloride	HSDB 1990
Synonym(s)	Chloroethene; chloroethylene; 1-chloroethylene; ethylene monochloride; monochloroethene; monochloroethylene; VC; VCM; vinyl chloride monomer	Fire 1986; HSDB 1990
Registered trade name(s)	No data	
Chemical formula	C_2H_3Cl	HSDB 1990
Chemical structure		
Identification numbers		
CAS registry	75-01-4	HSDB 1990
NIOSH RTECS	KU9625000	HSDB 1990
EPA hazardous waste	U043	HSDB 1990
OHM/TADS	7216947	HSDB 1990
DOT/UN/NA/IMCO shipping	1086	HSDB 1990
HSDB	169	HSDB 1990
NCI	No data	

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Vinyl Chloride

Property	Information	Reference
Molecular weight	62.5	Sax and Lewis 1989
Color	Colorless	Cowfer and Magistro 1983
Physical state	Gas	Cowfer and Magistro 1983
Melting point	-153.8°C	Cowfer and Magistro 1983
Boiling point	-13.4°C	Cowfer and Magistro 1983
Density:		
at -14.2°C	0.969 g/cm ³	Cowfer and Magistro 1983
at 15°C	0.9195 g/cm ³	Sax and Lewis 1989
at 20°C	0.9106 g/cm ³	NIOSH 1986
Vapor density	2.16	Fire 1986
Odor	Sweet	HSDB 1990
Odor threshold:		
Water	3.4 ppm	Amoore and Hautula 1983
Air	3,000 ppm	Amoore and Hautula 1983
Solubility:		
Water at 25°C	2,763 mg/L	EPA 1985b
	1,100 mg/L	Cowfer and Magistro 1983
Organic solvent(s)	Soluble in hydrocarbons, oil, alcohol, chlorinated solvents, and most common organic liquids	Cowfer and Magistro 1983
Partition coefficients:		
Log K _{ow}	1.36	NIOSH 1986
Log K _{oc}	1.99	Lyman et al. 1982
Vapor pressure:		
at 20°C	2,530 mmHg	LARC 1979
at 25°C	2,660 mmHg	Sax and Lewis 1989
Henry's law constant:		
at 10°C	1.2 (atm·m ³)/mol	EPA 1985b
Autoignition temperature	472°C	Cowfer and Magistro 1983
Flashpoint	-77.75°C (open cup)	Cowfer and Magistro 1983
Flammability limits	3.6-33 vol %	NIOSH 1986
Conversion factors		
ppm to mg/m ³ in air	1 ppm = 2.60 mg/m ³	NIOSH 1986
mg/m ³ to ppm in air	1 mg/m ³ = 0.39 ppm	NIOSH 1986
Explosive limits	4-22 vol %	NIOSH 1986

vol = volume

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

In 1988, production of vinyl chloride in the United States was 9.1 billion pounds (CMR 1989), while production in 1986 was 8.4 billion pounds (USITC 1987). The estimated U.S. production level for 1993 is 11.0 billion pounds. Between 1979 and 1988, the vinyl chloride manufacturing industry in the United States grew by 2.1% per year. From the present time to 1993, U.S. vinyl chloride production is expected to increase by 3-4% per year (CMR 1989). The estimated U.S. capacity for vinyl chloride production in 1988 was 9.7 billion pounds, indicating that the U.S. vinyl chloride industry was operating at approximately 94% of its capacity (CMR 1989). In 1989, the estimated U.S. capacity was 10.4 billion pounds (SRI 1990).

Vinyl chloride is currently produced in the United States by 9 companies at 11 facilities, which are as follows (SRI 1990a, 1990b): BF Goodrich Company in LaPorte, Texas; Borden Chemicals and Plastics in Geismar, Louisiana; Dow Chemical in Oyster Creek, Texas and in Plaquemine, Louisiana; Formosa Plastics Corporation in Baton Rouge, Louisiana and in Point Comfort, Texas; Georgia Gulf Corporation in Plaquemine, Louisiana; Occidental Petroleum Corporation in Deer Park, Texas; PPG Industries in Lake Charles, Louisiana; Vista Chemical Company in Lake Charles, Louisiana; and Westlake Monomers Corporation in Calvert City, Kentucky. Table 4-1 summarizes the facilities in the United States that manufacture or process vinyl chloride. This information was obtained from the 1988 Toxic Chemical Release Inventory (TRI88), and it summarizes the reported release data for 1988 (TRI88 1990). Table 4-1 also lists the maximum amounts of vinyl chloride that are present at these sites and the end uses of the vinyl chloride.

The commercial production of vinyl chloride began in the 1930s by reacting hydrogen chloride with acetylene. Currently, vinyl chloride is produced commercially by the chlorination of ethylene through one of two processes, direct chlorination or oxychlorination. Direct chlorination reacts ethylene with chlorine to produce 1,2-dichloroethane. Similarly, oxychlorination produces 1,2-dichloroethane, but this is accomplished by reacting ethylene with dry hydrogen chloride and oxygen. After both processes, the 1,2-dichloroethane is subjected to high pressures (2.5-3.0 megapascals) and temperatures (550-550°C). This causes the 1,2-dichloroethane to undergo pyrolysis, or thermal cracking, which forms the vinyl chloride monomer and hydrogen chloride. The vinyl chloride monomer is then isolated (Cowfer and Magistro 1985). The technical grade product is available in 99.9% purity (HSDB 1990). Recent developments in vinyl chloride production include efforts to minimize by-product formation in 1,2-dichloroethane pyrolysis (Cowfer and Magistro 1985).

4.2 IMPORT/EXPORT

Imports of vinyl chloride were 227 million pounds in 1988 (CMR 1989) and 200 million pounds in 1987 (C&EN 1987). Data describing import trends prior to 1987 were not located. Exports of vinyl chloride were 637 million pounds in 1988 (CMR 1989) and 896 million pounds in 1985 (CMR 1986b). In 1979, vinyl chloride exports were at an all-time high of 1.1 billion pounds (CMR 1981). Since this time, export volumes have been gradually declining (CMR 1981, 1983, 1989).

4.3 USE

Vinyl chloride is an important industrial chemical because of its wide variety of end-use products and the low cost of producing polymers from it. Furthermore, PVC is one of the most efficient construction materials available when analyzed on an energy-equivalent basis (Cowfer and Magistro 1985). Major end-use products include PVC products, such as automotive parts and accessories, furniture, packaging materials, pipes, wall coverings, and wire coatings, and vinyl chloride-vinyl acetate copolymer products, such as films and resins (Cowfer and Magistro 1985; Eveleth et al. 1990).

TABLE 4-1. Facilities That Manufacture or Process Vinyl Chloride*

Facility	Location ^b	Range of maximum amounts on site in pounds	Activities and uses
Kirkhill Rubber Co.	Brea, CA	10,000-99,999	Import; as a formulation component; as a processing aid
Keysor-Century Corp.	Saugus, CA	1,000,000-9,999,999	As a reactant
Union Carbide Corp.	Torrance, CA	100,000-999,999	As a reactant
Georgia Gulf Corp.	Delaware City, DE	1,000,000-9,999,999	As a reactant
C. P. C. Wilmington Assembly Plant	Wilmington, DE	10,000-99,999	As a manufacturing aid
Air Products & Chemicals Inc.	Pace, FL	1,000,000-9,999,999	As a reactant
Union Carbide Corp.	Tucker, GA	100,000-999,999	As a reactant
B. F. Goodrich	Henry, IL	1,000,000-9,999,999	As a reactant; as an article component
Borden Inc. Pkg. & Indst. Products	Illioopolis, IL	10,000,000-49,999,999	As a reactant
Vulcan Chemicals	Wichita, KS	1,000-9,999	As a reactant
Air Products & Chemicals Inc.	Calvert City, KY	1,000,000-9,999,999	As a reactant
Westlake Monomers Corporation	Calvert City, KY	10,000,000-49,999,999	Produce; for sale/distribution
B. F. Goodrich Louisville Plant	Louisville, KY	100,000-999,999	As a reactant
Occidental Chemical Corp.	Addis, LA	1,000,000-9,999,999	As a reactant
Formosa Plastics Corp. Louisiana	Baton Rouge, LA	1,000,000-9,999,999	Produce; for sale/distribution
Borden Chemical & Plastics	Geismar, LA	10,000,000-49,999,999	Produce; for sale/distribution; as a reactant
Union Carbide-Indus. Chemicals	Hahnville, LA	> 1 billion	As a byproduct
B. F. Goodrich Co.	Plaquemine, LA	100,000-999,999	As a reactant
Dow Chemical Co. Plaquemine Louisiana	Plaquemine, LA	10,000,000-49,999,999	Produce; for sale/distribution
Georgia Gulf Corp.	Plaquemine, LA	1,000,000-9,999,999	Produce; for on-site use/processing; for sale/distribution; as a reactant
Certainteed Corp.	Sulphur, LA	1,000,000-9,999,999	As a reactant
PPG Industries Inc.	Westlake, LA	50,000,000-99,999,999	Produce; for sale/distribution; as a byproduct; as an impurity; as a reactant
Vista Chemical Co. Lake Charles Chemical Plant	Westlake, LA	10,000,000-49,999,999	Produce; for sale/distribution
Dow Chemical Co. Michigan Div.	Midland, MI	1,000,000-9,999,999	As a reactant
Rival Manufacturing Co.	Clinton, MO	10,000-99,999	As an article component
Mobay Corp. - Ag. Chem. Div.	Kansas City, MO	100,000-999,999	As a reactant
Variform Inc.	Kearney, MO	1,000,000-9,999,999	Import; for on-site use/processing; as an article component
Vista Polymers	Aberdeen, MS	10,000,000-49,999,999	As a reactant
Colloids Inc. Walsh Div.	Gastonia, NC	10,000-99,999	As a reactant
Occidental Chemical Corp.	Burlington, NJ	1,000,000-9,999,999	As a reactant
Occidental Chemical Corp.	Burlington, NJ	1,000,000-9,999,999	As a reactant
B. F. Goodrich Co.-Vinyl Div.	Pedricktown, NJ	1,000,000-9,999,999	As a reactant
Union Carbide Corp.	Somerset, NJ	10,000-99,999	As a reactant

TABLE 4-1 (Continued)

Facility	Location ^a	Range of maximum amounts on site in pounds	Activities and uses
Eastman Wire & Cable Co.	Winslow, NJ	10,000-99,999	As an article component
Goodyear Tire & Rubber Co.	Niagara Falls, NY	100,000-999,999	As a reactant
General Electric Co. Silicone Products	Waterford, NY	100,000-999,999	As a reactant
National Latex Products Co.	Ashland, OH	1,000-9,999	As a formulation component; as a manufacturing aid
Vygen Corp.	Ashtabula, OH	100,000-999,999	As a reactant
B. F. Goodrich Avon Lake Facilities	Avon Lake, OH	1,000,000-9,999,999	As a reactant
Mapco Plastics Co.	Napoleon, OH	0-99	Import; for on-site use/processing; as a formulation component; as an article component
Vista Polymers Div. Of Vista Chemical Co.	Oklahoma City, OK	1,000,000-9,999,999	As a reactant
Occidental Chemical Corp.	Pottstown, PA	1,000,000-9,999,999	As a reactant
B. F. Goodrich Co. Geon Vinyl Div. Deer Park Plant	Deer Park, TX	1,000,000-9,999,999	As a reactant
Occidental Chemical Corp. Deer Park - VCM	Deer Park, TX	10,000,000-49,999,999	Produce; for sale/distribution
Dow Chemical Co.	Freeport, TX	10,000,000-49,999,999	Produce; for on-site use/processing; as a byproduct; as a reactant; in ancillary or other uses
Shintech Inc.	Freeport, TX	10,000,000-49,999,999	Import; for on-site use/processing; as a reactant
Union Carbide Corp.	Garland, TX	100,000-999,999	As a reactant
B. F. Goodrich Chemical Corporation	La Porte, TX	10,000,000-49,999,999	Produce; for sale/distribution
Occidental Chemical Corp.	Pasadena, TX	1,000,000-9,999,999	As a reactant
Formosa Plastics Corp. Tx	Point Comfort, TX	1,000,000-9,999,999	Produce; import; for on-site use/processing; as a reactant

^aDerived from SRI (1990a, 1990b) and TRI88 (1990)^bPost office state abbreviations used

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

In 1988, the pattern of use for vinyl chloride produced in the United States was as follows: PVC production, 91%; exports, 7%; and other, 2% (CMR 1989). This use pattern indicates that vinyl chloride monomer is almost exclusively used in the United States by the plastics industry.

Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, and in the production of chloroacetaldehyde and methyl chloroform (IARC 1979). In the United States, limited quantities of vinyl chloride were used as an aerosol propellant and as an ingredient of drug and cosmetic products; however, these practices were banned by the EPA in 1974 (IARC 1979; HSDB 1990).

4.4 DISPOSAL

Under the Federal Resource Conservation and Recovery Act (RCRA), those who generate, transport, treat, store, or dispose of vinyl chloride are required to comply with handling and report/record keeping regulations (EPA 1981b). The recommended method of disposal is total destruction by incineration. The temperature of the incinerator must be sufficient to ensure the complete combustion of the vinyl chloride in order to prevent the formation of phosgene. The recommended temperature range for incineration is 450–1,600°C, with residence times of seconds for gases and liquids, and hours for solids (HSDB 1990). If in solution, the vinyl chloride product may need to be adsorbed onto a combustible material prior to incineration. Recommended materials include vermiculite, sawdust, or a sand-soda ash mixture (90/10) covered with wood and paper (OHM/TADS 1985). The vinyl chloride can also be dissolved in a flammable solvent prior to incineration. An acid scrubber should be used in conjunction with the incinerator in order to remove any hydrogen chloride that is produced by the combustion process (HSDB 1990; OHM/TADS 1985).

Aqueous by-product solutions from the production of vinyl chloride are usually steam-stripped to remove volatile organic compounds, neutralized, and then treated in an activated sludge system to remove nonvolatile organic compounds remaining in the waste water (Cowfer and Magistro 1983). A final method of disposal of vinyl chloride is the chemical destruction of small quantities similar to amounts used in experimental laboratories. The recommended technique is to add the vinyl chloride to sodium dichromate in concentrated sulfuric acid, and to allow this solution to react for 1–2 days (HSDB 1990).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Vinyl chloride is used almost exclusively in the United States by the plastics industry for the production of PVC and several copolymers. Anthropogenic sources are responsible for all of the vinyl chloride found in the environment. Most of the vinyl chloride released to the environment is eventually transported to the atmosphere, whereas lesser amounts are transported to groundwater. Vinyl chloride has been detected in the ambient air in the vicinity of vinyl chloride and PVC manufacturing plants and hazardous waste sites. The compound has also leached into groundwater from spills, landfills, and industrial sources. Vinyl chloride has been identified at 245 of the 1,300 NPL hazardous waste sites that have been proposed for inclusion on the NPL (MIS 1990). The frequency of these sites within the United States can be seen in Figure 5.1.

Effluents and emissions from vinyl chloride and PVC manufacturers are responsible for most of vinyl chloride released to the environment. When released to the atmosphere, vinyl chloride is expected to be removed by reaction with photochemically generated hydroxyl radicals (half-life = 1-2 days). Reaction products include hydrochloric acid, formaldehyde, formyl chloride, acetylene, chloroacetaldehyde, chloroacetylchloranil, and chloroethylene. In photochemical smog, the half-life of vinyl chloride is reduced to a few hours. When released to water, volatilization is expected to be the primary fate process. In waters containing photosensitizers, such as humic materials, sensitized photodegradation may also be important. When released to soil, vinyl chloride will either volatilize rapidly from soil surfaces or leach readily through soil, ultimately entering groundwater.

Segments of the general population living in the vicinity of emission sources are exposed to vinyl chloride by inhalation of contaminated air. Average daily intake of vinyl chloride by inhalation for these people ranges from trace amounts to 2,100 $\mu\text{g}/\text{day}$. The average daily intake of vinyl chloride by inhalation is expected to be essentially zero for the remainder of the population. The majority of the general population is not expected to be exposed to vinyl chloride through ingestion of drinking water. The average daily intake of vinyl chloride through diet is predicted to be essentially zero. Workers, particularly in plastic industries, are exposed to vinyl chloride mainly by inhalation, with some absorption through the skin possible. The National Occupational Exposure Survey, conducted by NIOSH from 1981 to 1983, estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride (NOES 1990).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

The major source of vinyl chloride releases to the environment is believed to be emissions and effluents from plastic industries, primarily vinyl chloride and PVC manufacturers. Worldwide emissions of vinyl chloride into the atmosphere during 1982 totalled approximately 400 million pounds (Hartmans et al. 1985). Another emission source includes tobacco smoke which has been found to contain 5.6-28 ng vinyl chloride per cigarette (Hoffman et al. 1976). According to TRI88, an estimated total of at least 1,374,153 pounds of vinyl chloride were released to air in the United States in 1988 from the manufacturing and processing facilities listed in Table 5-1 (SRI 1990a, 1990b; TRI88 1990). The TRI88 data should be used with caution since only certain types of facilities are required to report.

5.2.2 Water

Vinyl chloride released in waste water from the plastics industries is expected to volatilize fairly rapidly (on the order of hours to days) into the atmosphere. Another source of release to groundwater is the anaerobic

5. POTENTIAL FOR HUMAN EXPOSURE

82

 1 TO 4 SITES
 10 TO 14 SITES

5 TO 9 SITES
26 TO 31 SITES

*Derived from MIS 1990

TABLE 5-1. Releases to the Environment from Facilities
That Manufacture or Process Vinyl Chloride^a

Reported amounts released in pounds								
Facility	Location ^b	Air	Underground injection	Water	Land	Total environment ^c	POTW transfer	Off-site waste transfer
Kirkhill Rubber Co.	Brea, CA	13	0	0	0	13	0	0
Keysor-Century Corp.	Saugus, CA	890	0	0	0	890	160	0
Union Carbide Corp.	Torrance, CA	32	0	0	0	32	0	0
Georgia Gulf Corp.	Delaware City, DE	91,453	0	1	0	91,454	0	2,188
C-P-C Wilmington Assembly Plant	Wilmington, DE	13,000	0	0	0	13,000	250	250
Air Products & Chemicals Inc.	Pace, FL	12,000	0	0	250	12,250	0	0
Union Carbide Corp.	Tucker, GA	29	0	0	0	29	0	0
B. F. Goodrich	Henry, IL	33,100	0	0	0	33,100	0	580
Borden Inc. Pkg. & Indst. Products	Illioopolis, IL	89,678	0	390	0	90,068	0	1,155
Vulcan Chemicals	Wichita, KS	115	0	0	0	115	0	0
Air Products & Chemicals Inc.	Calvert City, KY	28,000	0	0	0	28,000	0	0
Westlake Monomers Corp.	Calvert City, KY	85,784	0	16	0	85,800	0	0
B. F. Goodrich Louisville Plant	Louisville, KY	9,200	0	0	0	9,200	14	400
Occidental Chemical Corp.	Addis, LA	31,468	0	0	0	31,468	0	5,001
Formosa Plastics Corp. Louisiana	Baton Rouge, LA	28,192	0	9	0	28,201	0	0
Borden Chemical & Plastics	Geismar, LA	39,068	53	0	0	39,121	0	0
Union Carbide-Indus. Chemicals	Hahnville, LA	37	0	0	0	37	0	0
B. F. Goodrich Co.	Plaquemine, LA	18,900	0	0	0	18,900	0	6
Dow Chemical Co. Plaquemine Louisiana	Plaquemine, LA	7,100	0	0	0	7,100	0	0
Georgia Gulf Corp.	Plaquemine, LA	18,600	0	0	0	18,600	0	0
Certainfeed Corp.	Sulphur, LA	24,500	0	2	0	24,502	0	0
PPG Industries Inc.	Westlake, LA	2,600	0	55	0	2,655	0	23
Vista Chemical Co. Lake Charles Chemical Plant	Westlake, LA	15,500	0	250	0	15,750	0	250
Dow Chemical Co. Michigan Div.	Midland, MI	800	0	0	0	800	0	3
Rival Manufacturing Co.	Clinton, MO	0	0	0	0	0	0	0

5. POTENTIAL FOR HUMAN EXPOSURE

63

DRAFT FOR PUBLIC COMMENT

RL&S148501

TABLE 5-1 (Continued)

Facility	Location ^b	Reported amounts released in pounds						
		Air	Underground injection	Water	Land	Total environment ^c	POTW transfer	Off-site waste transfer
Mobay Corp. - Ag. Chem. Div.	Kansas City, MO	1,280	0	0	0	1,280	0	0
Variform Inc.	Kearney, MO	0	0	0	0	0	0	0
Vista Polymers	Aberdeen, MS	76,562	0	0	0	76,562	0	0
Colloids Inc. Walsh Div.	Gastonia, NC	500	0	0	0	500	0	250
Occidental Chemical Corp.	Burlington, NJ	9,300	0	16	0	9,316	0	70
Occidental Chemical Corp.	Burlington, NJ	27,700	0	3	0	27,703	0	100
B. F. Goodrich Co. Vinyl Div.	Pedricktown, NJ	72,000	0	8	0	72,008	0	100
Union Carbide Corp.	Somerset, NJ	14	0	0	0	14	0	0
Eastman Wire & Cable Co.	Winslow, NJ	0	0	0	0	0	0	0
Goodyear Tire & Rubber Co.	Niagara Falls, NY	89,600	0	0	0	89,600	1,080	780
General Electric Co. Silicone Products	Waterford, NY	272	0	0	0	272	0	0
National Latex Products Co.	Ashland, OH	0	0	0	0	0	0	0
Vygen Corp.	Ashtabula, OH	42,845	0	750	0	43,595	0	0
B. F. Goodrich Avon Lake Facilities	Avon Lake, OH	40,000	0	0	0	40,000	13,000	750
Napco Plastics Co.	Napoleon, OH	0	0	0	0	0	0	0
Vista Polymers Div. Of Vista Chemical Co.	Oklahoma City, OK	65,670	0	0	0	65,670	90	0
Occidental Chemical Corp.	Pottstown, PA	214,810	0	0	1,930	216,740	2,510	0
B. F. Goodrich Co. Geon Vinyl Div. Deer Park Plant	Deer Park, TX	17,400	0	0	0	17,400	0	620,551
Occidental Chemical Corp. Deer Park - VCM	Deer Park, TX	25,000	0	0	0	25,000	0	30
Dow Chemical Co.	Freeport, TX	2,280	0	0	0	2,280	0	0
Shintech Inc.	Freeport, TX	85,550	0	250	0	85,800	0	0
Union Carbide Corp.	Garland, TX	311	0	0	0	311	0	0

5. POTENTIAL FOR HUMAN EXPOSURE

84

DRAFT FOR PUBLIC COMMENT

TABLE 5-1 (Continued)

Facility	Location ^b	Reported amounts released in pounds ¹						
		Air	Underground injection	Water	Land	Total environment ^c	POTW transfer	Off-site waste transfer
Laporte Chemical Corp.	La Porte, TX	3,000	0	0	0	3,000	0	0
Occidental Chemical Corp.	Pasadena, TX	37,000	0	18	0	37,018	0	21,300
Formosa Plastics Corp. TX	Point Comfort, TX	13,000	0	250	0	13,250	0	0
Totals		1374153	53	2018	2180	1378404	17104	653787

¹Derived from SRI (1990a, 1990b) and TRI88 (1990)^bPost office state abbreviations used^cThe sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

5. POTENTIAL FOR HUMAN EXPOSURE

reductive dehalogenation of 1,1,2-trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane to vinyl chloride at hazardous waste sites (Smith and Dragun 1984). Vinyl chloride leaches into groundwater from spills, landfills, and industrial sources (e.g., plastics industry). According to data collected from the analysis of leachates and monitoring wells at sites where groundwater was contaminated by municipal solid waste landfill leachate, vinyl chloride was present in both the leachates and groundwater samples (Sabel and Clark 1984).

Vinyl chloride has been detected in groundwater samples taken at an estimated 3% of the NPL hazardous waste sites included in EPA's Contract Laboratory Program (CLP) at a geometric mean concentration of 0.102 ppm for the positive samples (CLPSD 1989). The compound was not listed in the CLP Statistical Database of chemicals detected in surface water samples collected at NPL sites. Note that information used from the CLP Statistical Database includes data from NPL sites only. According to TRI88, an estimated total of at least 2,018 pounds of vinyl chloride were released to water in the United States in 1988 from the manufacturing and processing facilities listed in Table 5-1 (SRI 1990a, 1990b; TRI88 1990). The TRI88 data should be used with caution since only certain types of facilities are required to report.

5.2.3 Soil

Vinyl chloride can be released into the soil from leachates at hazardous waste sites. Vinyl chloride was not listed in the EPA CLP Statistical Database of chemicals detected in soil samples taken at NPL sites (CLPSD 1989). According to TRI88, an estimated total of at least 2,180 pounds of vinyl chloride were released to land in the United States in 1988 from the manufacturing and processing facilities listed in Table 5-1 (SRI 1990a, 1990b; TRI88 1990). The TRI88 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

Based on a vapor pressure of 2,660 mmHg at 25°C, essentially all vinyl chloride in the atmosphere is expected to exist in vapor form (Eisenreich et al. 1981; Verschueren 1983). Consequently, removal from the atmosphere by dry deposition is not expected to be an important fate process.

The primary removal process for vinyl chloride from natural water systems is volatilization into the atmosphere. Henry's law constant value of $1.2 \text{ atm}\cdot\text{m}^3/\text{mol}$ at 10°C indicates that vinyl chloride should partition rapidly to the atmosphere. The half-life for vinyl chloride volatilization from a typical pond, river, and lake has been estimated to be 43.3, 8.7, and 34.7 hours, respectively. These values are based on an experimentally determined reaeration rate ratio of approximately 2 and assumed oxygen reaeration rates of 0.008, 0.04, and 0.01 per hour for a typical pond, river, and lake, respectively (EPA 1982a). Predicted half-lives should be considered rough estimates since the presence of various salts in natural water systems may affect the volatility of vinyl chloride significantly (Callahan et al. 1979). Many salts have the ability to form complexes with vinyl chloride and can increase its water solubility; therefore, the presence of salts in natural waters may significantly influence the amount of vinyl chloride remaining in the water (Callahan et al. 1979).

The relatively high vapor pressure of vinyl chloride indicates that the compound should volatilize quite rapidly from dry soil surfaces (Verschueren 1983). The effective half-life (due to volatilization) of vinyl chloride placed 10 cm deep in dry soil is predicted to be 12 hours (Jury et al. 1984). Vinyl chloride is soluble in

5. POTENTIAL FOR HUMAN EXPOSURE

water and thus can leach through the soil and travel to groundwater before evaporation can occur (Cowfer and Magistro 1983).

Experimental data regarding adsorption of vinyl chloride to soil were not located. Based on the regression equations given by Lyman et al. (1982), Sabljic (1984), and Kenaga and Goring (1980), the soil organic carbon adsorption coefficient (K_{oc}) for vinyl chloride was estimated to range from 14 to 131. These K_{oc} values suggest a very low sorption tendency, meaning that this compound would be highly mobile in soil. Thus, vinyl chloride has the potential to leach into groundwater.

Vinyl chloride is soluble in most common organic solvents (Cowfer and Magistro 1983). In situations where organic contaminants exist in relatively high concentrations (e.g., landfills, hazardous waste sites), cosolvation of vinyl chloride could have the effect of reducing its volatility, thus causing it to have even greater mobility than indicated by estimated K_{oc} values.

Vinyl chloride's high vapor pressure and low octanol/water partition coefficient ($\log K_{ow} = 1.23$) indicates that it bioaccumulates to a very limited extent (EPA 1982a). The bioconcentration factor (BCF) of an organic chemical can be estimated from the K_{ow} or water solubility. Based on the regression equation given by Veith et al. (1980), the estimated BCF of 5.1 indicates limited bioconcentration in aquatic organisms. Frietag et al. (1985) measured BCFs in algae, fish, and activated sludge. The BCFs for algae, fish, and activated sludge were 40, less than 10, and 1,100, respectively. The very low value for fish, in comparison to the algae and activated sludge, may suggest a detoxification process in higher developed organisms such as fish. Lu et al. (1977) examined the bioaccumulation of ^{14}C -vinyl chloride in a closed model aquatic ecosystem over a 3-day period. The high volatility of vinyl chloride minimized any potential bioaccumulation. Relatively low tissue concentrations found in fish suggested that vinyl chloride is not biomagnified in aquatic food chains to any substantial degree.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Reaction of vinyl chloride vapor with photochemically generated hydroxyl radicals is predicted to be the primary degradation mechanism for this compound in the atmosphere. The half-life for this reaction in the atmosphere ranges from 1.2 to 1.8 days (Cox et al. 1974; Howard 1976; Perry et al. 1977). Products of this reaction are hydrochloric acid, formaldehyde, formyl chloride, carbon monoxide, carbon dioxide, chloroacetaldehyde, acetylene, chloroethylene epoxide, chloroacetylchloranil, and water (Kayiga et al. 1975; Muller and Korte 1977; Woldback and Klaboe 1978). Under conditions of photochemical smog, the half-life of vinyl chloride would be reduced to a few hours (Carassitti et al. 1978). Reaction with ozone and direct photolysis are less important degradation mechanisms of vinyl chloride in the atmosphere (EPA 1985c; Hill et al. 1976; Zhang et al. 1983). Vinyl chloride in the vapor phase does not absorb light of wavelengths above 220 nm; therefore, direct photolysis will not occur in the atmosphere (Hill et al. 1976).

5.3.2.2 Water

The primary removal process for vinyl chloride from surface waters is volatilization into the atmosphere. Vinyl chloride in water does not absorb ultraviolet radiation above 218 nm; therefore, direct photolysis in the aquatic environment is not expected to occur (Hill et al. 1976). Solutions of 10 mg/L (10 ppm) vinyl chloride in pure water were exposed to filtered light (greater than 300 nm) from a mercury lamp (Hill et al. 1976). No photolysis occurred over a 90-hour period. In waters containing photosensitizers, such as

5. POTENTIAL FOR HUMAN EXPOSURE

humic materials, photodegradation may be fairly rapid. If so, in some waters, sensitized photodegradation may also be an important removal mechanism (Hill et al. 1976).

The hydrolytic half-life of vinyl chloride has been estimated to be less than 10 years at 25°C (Hill et al. 1976). Since the volatilization rate of vinyl chloride is much more rapid than the predicted rate of hydrolysis, hydrolysis is not a significant aquatic fate (Callahan et al. 1979; Hill et al. 1976). Vinyl chloride is not oxidized chemically by reaction with photochemically generated molecular oxygen in natural water systems (Hill et al. 1976). Experiments carried out at 20 mg/L vinyl chloride in water saturated with molecular oxygen at elevated temperatures showed that after 12 hours at 85°C, no degradation of vinyl chloride could be detected. At temperatures and oxygen concentrations in natural waters, therefore, vinyl chloride will not be degraded by molecular oxygen at a significant rate (Hill et al. 1976).

The limited amount of existing data indicates that vinyl chloride is resistant to microbial degradation. Hill et al. (1976) found that an isolated microbial culture containing two species of bacteria and three mixed fungal populations was unable to biodegrade vinyl chloride over a 5-week period at concentrations of 20–120 mg/L (20–120 ppm). Helfgott et al. (1977) observed no change in the biochemical oxygen demand in raw sewage seed (used as a microbial inoculum) and raw sewage seed plus vinyl chloride at 20°C over a 25-day period. The authors interpreted this to mean that no biodegradation of vinyl chloride occurred.

5.3.2.3 Soil

The majority of vinyl chloride present on soil surfaces will volatilize to the atmosphere. Vinyl chloride is also mobile in soil and susceptible to leaching (Lyman et al. 1982). The presence of other organic solvents, such as those found at hazardous waste sites, may affect the mobility of the substance in the soil (Cowfer and Magistro 1983). Photodegradation on the surface of soils is expected since sensitized photodegradation in water occurs. Also, based on data in aquatic media, microbial degradation of vinyl chloride is not expected to occur in soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Air in rural/remote and urban/suburban areas of the United States typically contains no detectable amount of vinyl chloride (Grimsrud and Rasmussen 1975a, 1975b; Harkov et al. 1984; Stephens et al. 1986; Wallace et al. 1984). Limited monitoring data indicate that in areas near vinyl chloride and PVC manufacturing facilities, the concentration of vinyl chloride in air typically ranges from trace levels to 105 $\mu\text{g}/\text{m}^3$ (0.041 ppm) (EPA 1979a; Gordon and Meeks 1977), but may exceed 2,600 $\mu\text{g}/\text{m}^3$ (1 ppm) (Fishbein 1979). Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste sites and municipal landfills. Concentrations ranging from below detection limits to 5–8 $\mu\text{g}/\text{m}^3$ (0.002–0.003 ppm) have been measured in the air above some landfills (Baker and Mackay 1985; Stephens et al. 1986). Homes near a hazardous waste site in southern California were found to contain levels as high as 1,040 $\mu\text{g}/\text{m}^3$ (0.4 ppm) (Stephens et al. 1986). Gaseous emissions from 20 Class II (nontoxic) landfills in southern California were analyzed for vinyl chloride (Wood and Porter 1987). Vinyl chloride was found in emissions from 85% of the landfills tested, and it was found in concentrations greater than 1 ppm in more than half of the landfill emissions. The concentration of vinyl chloride measured in this study ranged from 0.24 to 44 ppm. Based on their observations, the authors concluded that the presence of vinyl chloride at these landfills was due to either illegal disposal or *in situ* generation by the degradation of chlorinated solvents by bacteria and other microbes (Wood and Porter 1987).

5. POTENTIAL FOR HUMAN EXPOSURE

5.4.2 Water

Vinyl chloride has been detected at varying concentrations in surface water, groundwater, and drinking water throughout the United States. Concentrations of vinyl chloride in drinking water wells and surface water in New York State were found to be 0.05 and 0.01 ppm, respectively (Burmaster 1982). Monitoring studies in nine states have identified concentrations as high as 9.8 $\mu\text{g/L}$ (0.01 ppm) in surface water and 380 $\mu\text{g/L}$ (0.38 ppm) in groundwater (Coniglio et al. 1980; Dyksen and Hess 1982).

The level of vinyl chloride in groundwater in the United States was determined during the 1982 EPA Groundwater Supply Survey (Westrick et al. 1984). Water supplies from 945 sites throughout the United States were studied. Vinyl chloride was positively identified in only 0.74% of the 945 groundwater supplies (detection limit 0.001 ppm). It was reported that 0.5% of 186 random sample sites and 3.8% of 158 nonrandom sample sites contained detectable levels of vinyl chloride. The maximum concentrations at the random and nonrandom sites were 1.1 $\mu\text{g/L}$ (0.0011 ppm) and 8.4 $\mu\text{g/L}$ (0.0084 ppm), respectively (Westrick et al. 1984). Approximately half of the samples were taken from a random list of water systems, which were subdivided into two sets of systems--those serving fewer than 10,000 people and those serving more than 10,000 people. The nonrandom samples were taken from systems selected by the states, using groundwater sources that were likely to show volatile organic compounds in drinking water (Westrick et al. 1984). Other studies have reported the occurrence of vinyl chloride in groundwater samples collected throughout the United States at levels at or below 380 $\mu\text{g/L}$ (0.38 ppm) (Coniglio et al. 1980; Cotruvo 1985; Goodenkauf and Atkinson 1986; Stuart 1983).

5.4.3 Soil

Monitoring data for vinyl chloride in soil were not located in the available literature.

5.4.4 Other Environmental Media

In the past, vinyl chloride has been detected in various foods as a result of migration from PVC food wrappings and containers (Gilbert et al. 1980). Vinyl chloride has been found in vinegar at levels up to 9.8 ppm, in edible oils at 0.3–18.0 ppm, and in alcoholic beverages at 0.0–8.4 ppm when these foods were packaged and stored in PVC containers (Williams and Miles 1975; Williams 1976). At present, FDA regulates the use of PVC polymers in food packaging materials and the amount of residual monomer in polymers. Results of a modeling study on the migration of vinyl chloride from PVC using liquid chromatography to simulate migration conditions in actual food packaging and storage revealed that, at the very low concentrations of residual vinyl chloride monomer in PVC packaging material, essentially zero migration of vinyl chloride monomer into foods occurs (Kontominas et al. 1985).

Vinyl chloride has leached into drinking water from PVC pipes. One study found that drinking water that ran through PVC pipes contained vinyl chloride at 1.4 $\mu\text{g/L}$ (0.0014 ppm), whereas water that ran through a PVC system 9 years older contained 0.03–0.06 $\mu\text{g/L}$ (3×10^{-5} – 6×10^{-5} ppm) (Dressman and McFarren 1978). The migration of vinyl chloride from rigid PVC water pipes into drinking water was directly proportional to the residual level of vinyl chloride in the pipe itself. Current data addressing the potential for leaching of vinyl chloride monomer from PVC pipes were not located. Under certain test conditions, vinyl chloride monomer in drinking water reacts with chlorine and is converted to chloroacetaldehyde and chloroacetic acid (Ando and Sayato 1984). Information concerning the effect of this reaction on drinking water supplies that are pretreated with chlorine and the extent of this reaction were not stated.

5. POTENTIAL FOR HUMAN EXPOSURE

During an EPA study, detectable levels of vinyl chloride monomer (detection limit 0.05 ppm) were found in indoor air samples taken from two of seven new 1975 model cars. Levels of vinyl chloride in indoor air in the two cars ranged from 0.4 to 1.2 ppm. Ventilation of the car interiors led to the dissipation of vinyl chloride. The cars involved in the study had a high ratio of plastic to interior volume and were expected to provide worst-case concentrations for vinyl chloride in interior car air (Hedley et al. 1976). Because of the limited nature of these data and the fact that this study is somewhat dated, no conclusions can be drawn regarding levels of vinyl chloride monomer in interior air of cars currently being produced.

Vinyl chloride has been detected in tobacco smoke. Cigarette smoke and small cigar smoke have been found to contain 5.6–27 ng vinyl chloride per cigarette (Hoffman et al. 1976).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Inhalation is the most probable route of exposure for the general population. Typical values for the average daily intake of vinyl chloride by inhalation in urban/suburban and rural/remote areas have been estimated to be essentially zero. Assuming that the average adult intake of air is 20 m³/day, the average daily intake of vinyl chloride by people living in the vicinity of emission sources has been estimated to range from trace amounts to 2,100 µg (Gordon and Meeks 1977; EPA 1979a). The majority of drinking water supplies in the United States contain no detectable levels of vinyl chloride (Coniglio et al. 1980; Westrick et al. 1984). Based on this information, it is assumed that the average daily intake of vinyl chloride by ingestion of drinking water for most persons in the United States is essentially zero. Estimates provided by EPA (1985b) indicate that 0.9% of the U.S. population is exposed to levels of vinyl chloride in drinking water greater than or equal to 1.0 µg/L, and 0.3% of the population is exposed to levels greater than 5 µg/L.

The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace. Exposure is believed to occur primarily through inhalation with some absorption through the skin possible (Sittig 1985).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals located near or downwind of production facilities, hazardous waste disposal sites, and landfills may potentially be exposed to higher than background ambient atmospheric levels of vinyl chloride. For specific levels associated with health effects, see Section 2.7. Individuals living near hazardous waste sites and landfills may also be exposed to vinyl chloride in their drinking water. Workers involved in the production or polymerization of vinyl chloride may constitute a group at risk because of the potential for occupational exposure. Smokers may be at increased risk of exposure to higher levels of vinyl chloride as the compound has been detected in tobacco smoke.

5.7 ADEQUACY OF THE DATABASE

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

5. POTENTIAL FOR HUMAN EXPOSURE

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. 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. The physical and chemical properties of vinyl chloride are sufficiently well characterized to permit estimation of its environmental fate.

Production, Import/Export, Use, and Release and Disposal. Vinyl chloride is released primarily to the atmosphere via emissions from vinyl chloride and PVC manufacturing facilities. The risk of exposure to vinyl chloride is highest for workers in the plastics industry and populations living near industrial areas or hazardous waste sites. Current production, use, and manufacturing methods are well described in the literature. More current information on releases and disposal methods might assist in estimating potential exposures to vinyl chloride, particularly for populations living near hazardous waste sites.

Environmental Fate. Vinyl chloride is transported in and partitioned to the air and water and is also partitioned to air from water; it is also partitioned to air from water. Experimental data regarding the partitioning of vinyl chloride to soil are needed. Vinyl chloride is transformed in the atmosphere by photooxidation. It is removed from surface water and groundwater mainly by volatilization and photodegradation. Information regarding the transformation and degradation in soil would be helpful in defining the potential pathways for human exposure.

Bioavailability from Environmental Media. Vinyl chloride can be absorbed following inhalation, oral, and, to a much lesser extent, dermal exposure. These routes of exposure may be of concern to humans because of the potential of vinyl chloride to contaminate air, water, and food. Information regarding the bioavailability from ingestion and dermal contact of contaminated soils would be helpful, particularly for populations living near hazardous waste sites.

Food Chain Bioaccumulation. Vinyl chloride can bioconcentrate to a limited extent in aquatic organisms. Biomagnification of vinyl chloride in terrestrial and aquatic food chains does not appear to be important because of its high volatility and the fact that it is readily metabolized by higher-trophic-level organisms. No data were located regarding biomagnification in terrestrial foodchains.

Exposure Levels in Environmental Media. Vinyl chloride has been detected in air, water, sediment, and food. Intake data for the general population from the various media are available. Data on levels of vinyl chloride in soils are needed. Site-specific data on concentrations of vinyl chloride in air, soil, and water would be helpful in estimating the risk of exposure for populations living in the vicinity of hazardous waste sites. Also, current data on the extent of release (if any) of vinyl chloride from PVC pipes and from car interiors are needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. The metabolites of vinyl chloride have been detected in human tissues and fluids as a result of occupational exposure to the substance. No information on biological monitoring studies for the general population was located. More information on exposure levels for populations living in the vicinity of hazardous waste sites would be helpful.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Registries. No exposure registries for vinyl chloride were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound 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 the exposure to this compound.

5.7.2 On-going Studies

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

Dr. S. Fogel (Cambridge Analytical Association) is examining the feasibility of in situ biodegradation of chlorinated ethenes, specifically vinyl chloride, in contaminated drinking water aquifers. Three microbiological processes have been identified with a high probability of achieving the complete biodegradation of vinyl chloride. The results may enable the design of a specific aquifer restoration plan in which the subsurface environment is modified to create a microbiological barrier across the path of an approaching contaminant plume. Dr. Fogel is also researching biodegradation of chlorinated aliphatic compounds by methane-utilizing bacteria. A bacterium has been isolated that grows by oxidizing methane (a methanotroph) and that can also degrade vinyl chloride. This discovery has significant potential for applications in the field of groundwater and waste water treatment.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring vinyl chloride in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify vinyl chloride. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect vinyl chloride in environmental samples are the methods approved by federal 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

The analytical method used to analyze for the presence of vinyl chloride in biological media is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS), flame ionization detector (FID), or electron capture detector (ECD). Vinyl chloride and/or its metabolite, thiodiglycolic acid, have been detected in breath, urine, blood, and tissues. Breath samples can be preconcentrated by cryogenic trapping. The two methods most commonly used to prepare liquid and solid samples are preconcentration by a purge-and-trap technique or headspace analysis. Preconcentration not only increases the sensitivity but, in certain instances, may decrease the sample separation time prior to quantitation. Details of commonly used analytical methods for several types of biological media are presented in Table 6-1.

Vinyl chloride was determined in exhaled air by preconcentration with a multistage cryogenic trapping system followed by thermal desorption using GC/FID, GC/ECD, and GC/MS (Conkle et al. 1975). Sensitivity is in the low-ppb range. The authors noted that the reproducibility of the subject/sampling system was inconclusive. The quantitative data reflected considerable scatter, apparently indicating the variability of the biological system and the trace nature of the compound. The additional requirement for long-term coupling (30-60 minutes) of the sampling system to the subject probably limits the method to industrial health applications, with relatively robust subjects (Conkle et al. 1975). Barett et al. (1969) monitored exposure to vinyl chloride through breath analysis. The breath samples were collected in pipets with plastic caps lined with six layers of Saran® film identical to that used for the construction of Saran® air sampling bags. Aliquots were drawn from the pipets and injected directly into a gas chromatograph equipped with FID. Detectability of vinyl chloride in the exhaled air by this method becomes limited when air concentrations in the workplace are below 50 ppm.

Vinyl chloride has been measured in rat blood and tissues using headspace GC/FID (Zuccato et al. 1979). In headspace analysis, the gaseous layer above the sample is injected into the gas chromatograph. Sample preparation steps for rat blood and tissues involves extraction in an ethanol-water mixture, incubation, and direct injection into the gas chromatograph. Sample preparation for tissues includes an extra step involving freezing and homogenization before the extraction procedure. Accuracy varied, ranging from about 75% to 92% recovery. The method is sensitive to 5 ng/mL vinyl chloride in blood and 30 ng/g in tissues.

Muller et al. (1979) employed GC/MS as a selective biomonitoring method for the quantitative measurement of thiodiglycolic acid, a urinary metabolite of vinyl chloride. They reported a sensitivity of 50 ng/mL. Precision was generally good. The authors noted that some thiodiglycolic acid has been found in supposedly unexposed subjects. Therefore, exposure to low levels of vinyl chloride could be masked by background metabolic levels within normal limits. This may limit the application of biological monitoring for the measurement of vinyl chloride following low-level exposure (Muller et al. 1979; van Sittert and de Jong 1985).

TABLE 6-1. Analytical Methods for Determining Vinyl Chloride in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference ₁
Breath	Breath collected in pipets lined with Saran® film; direct injection into gas chromatograph	GC/FID	NR	NR	Baretta et al. 1969
Breath	Cytogenic trapping of expired air; thermal desorption into gas chromatograph	GC/FID, GC/ECD, and GC/MS	NR	NR	Conkle et al. 1975
Urine	Acidified and dessicated overnight; add methanol; derivatize with diazomethane; add ion-exchange resin	GC/MS	50 ng/mL	NR	Muller et al. 1979
Urine	Internal standard added to urine; acidification and ethyl acetate extraction; evaporation of solvent; addition of <u>N</u> -trimethylsilyldiethylamine in pyridine (1:1); injection into gas chromatograph	GC/FID, GC/MS	10 mg/L	NR	Draminski and Trojanowska 1981

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood and tissues	Extraction in ethanol-water mixture, incubation, injection into gas chromatograph. Tissue preparation also includes freezing and homogenization before the extraction procedure.	GC/FID	5 ng/mL blood	75-79% blood	Zuccato et al. 1979
			30 ng/g tissue	76-92% tissue	

GC/ECD = gas chromatography/electron capture detector; GC/FID = gas chromatography/flamm ionization detector; GC/MS = gas chromatography/mass spectrometry; NR = not reported

DRAFT FOR PUBLIC COMMENT

6. ANALYTICAL METHODS

In a study by Jedrychowski et al. (1984), urinary excretion of thiodiglycolic acid was determined using GC/FID. The urine was extracted twice with ethyl acetate prior to analysis. No recovery data were given for this method.

6.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to that of biological samples. The most common methods used to detect vinyl chloride in environmental samples are GC/MS, GC/ECD, and GC/FID. Preconcentration of samples is usually done by sorption on solid sorbent for air and by the purge-and-trap method for liquid and solid matrices. Alternatively, headspace above liquid and solid samples may be analyzed without preconcentration. Details of commonly used analytical methods for several types of environmental samples are presented in Table 6-2.

The primary method of analyzing vinyl chloride in air is GC combined with either MS, ECD, or FID. Air samples are usually pumped through a sample collection column with Tenax®-GC, coconut activated charcoal, or spherocarb (a carbon molecular sieve material) as the most common adsorbents. Several authors have noted that Tenax®-GC displays poor retention for vinyl chloride when the compound is present in the very low-ppb range (Bozzelli and Kabbekus 1979; Krost et al. 1982; McMurry and Tarr 1978). Vinyl chloride is thermally desorbed from the collection column and concentrated on a cryogenic trapping column located on the gas chromatograph. Vapors are heat-released from the trapping column directly to the gas chromatograph (Bozzelli and Kabbekus 1979; Krost et al. 1982). Grab samples of air can also be obtained and preconcentrated on a cryogenic column (Rasmussen et al. 1977). The limit of detection for GC/MS and GC/ECD is in the sub-ppb range (Bozzelli and Kabbekus 1979; Harsch et al. 1979; Krost et al. 1982; Rasmussen et al. 1977). Accuracy is generally good (Bozzelli and Kabbekus 1979). With careful technique, precision is adequate, ranging from 5% to 20% (Bozzelli and Kabbekus 1979; McMurray and Tarr 1978).

Trace amounts of vinyl chloride in air and water were detected employing GC/ECD after derivatization to 1,2-dibromochloroethane (Wittisiepe et al. 1990). Air samples were taken by drawing a known volume directly through an ice-cooled adsorption tube. Water samples were purged with an inert gas before being drawn through the adsorption tube. The tubes were eluted with carbon disulfide, and the vinyl chloride was derivatized with bromine water to form 1,2-dibromochloroethane. This derivatization technique is used for enhancement of sensitivity with GC/ECD. The derivative was determined by capillary GC with ECD. The detection limits for air and water samples are 50 ng/m³ and 0.4 ng/L (0.4 parts per trillion), respectively. Results from recovery experiments with dosed water indicated that accuracy was good.

Vinyl chloride can be detected in drinking water, groundwater, waste water, and leachate from solid waste. Analysis of vinyl chloride is done by purge-and-trap or headspace GC. The primary analytical method is separation by GC combined with MS, ECD, FID, Hall's electrolytic conductivity detector (HECD), or another type of halogen specific detector (HSD). In most methods, vinyl chloride is liberated from the liquid matrix by purging with an inert gas and concentrated by trapping on a suitable solid sorbent. Vinyl chloride is thermally desorbed and backflushed onto the column of the gas chromatograph with an inert gas. Detection of vinyl chloride is generally achieved using HECD, HSD, or MS (APHA 1985; EPA 1982d, 1982e; IARC 1978; Reding 1987). The limit of detection is in the sub-ppb range for halogen specific detectors (APHA 1985; EPA 1982d, 1982e) and in the low-ppb range for MS (EPA 1982d). Accuracy is greater than 98% and precision ranges from 11% to 25% for GC/HECD and GC/MS (EPA 1982d).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air	Vinyl chloride in air adsorbed in activated carbon trap and desorbed by carbon disulfide	GC/FID	NR	94% at 0.4-25 ppm	NIOSH 1984
Ambient indoor and outdoor air	Air containing vinyl chloride passed through activated carbon trap and desorbed by dichloromethane or carbon disulfide	GC/FID	5 ppb	NR	IARC 1978
Air	Adsorption on Tenax®-GC, or SKC® Carbon, then thermal desorption	GC/MS	0.33 ppb	NR	Krost et al. 1982
Air	Air prefiltered by Na ₂ S ₂ O ₃ -treated glass fiber filter was passed through spherocarb adsorbent cartridge and thermally desorbed	GC/FID, GC/MS, GC/ECD	0.005 ppb	NR	Harkov et al. 1983, 1984
Automobile exhaust	Exhaust samples contained in aluminized plastic bags	GC/FID	0.02 ppm	NR	Hasanen et al. 1979

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6. ANALYTICAL METHODS

97

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Trapped in cold Tenax®-GC trap; thermal desorption	GC/FID	NR	89.6% at 6 ppb; 100% at 60 ppb	Ives 1975
Air	Sample collected in pressurized canister is passed through a freezeout loop and subsequently heated	GC/ECD	0.01 ppb	NR	Harsch et al. 1979; Rasmussen et al. 1977
Air	Sample collected in polyester-coated plastic bags concentrated by freezeout and subsequently heated	GC/FID	0.4 ppb	NR	McMurry and Tarr 1978
Drinking water	Samples collected in serum reaction bottles; purge and trap technique	GC/HSD, GC/MS	NR	NR	Dressman and McFarren 1978
Drinking water and waste water	Purge and trap in Tenax®-GC; thermal desorption	GC/HSD, GC/MS (EPA Methods 601 and 624)	0.18 ppb (HSD)	102% at 0.8-32.3 ppb	APHA 1985; EPA 1982d
Groundwater, liquid, and solid matrices	Purge at 45°C and trap in Tenax®-GC; thermal desorption	GC/HSD (EPA Method 8010)	0.18 ppb	102% at 0.82-32.3 ppb	EPA 1982c

DRAFT FOR PUBLIC COMMENT

6. ANALYTICAL METHODS

98

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Purge and trap in Tenax®-GC; thermal desorption	GC/Hall detector, GC/PID (EPA Methods 502.2 and 524.2)	0.04 ppb (Hall detector); 0.02 ppb (PID)	100-119% at 5-10 ppb	Reding 1987
Migration of monomer into drinking water from PVC pipes	Small sections put in water in sealed serum vial for a number of days at 20°C; solution directly injected into gas chromatograph	GC/FID	NR	NR	Ando and Sayato 1984
Water	Sample in sealed vial is equilibrated at constant temperature; headspace gas injected into gas chromatograph	GC/FID	<1 ppb	NR	IARC 1978
Landfill gas	Gas from landfill sites sampled by PTFE tubing inside drive-in piezometers was adsorbed in Tenax®-GC or Porapak®, a sorbent; trapped sample desorbed and concentrated in liquid N ₂ -cooled loop and flash desorbed	GC/MS	0.04-0.8 ppm	NR	Young and Parker 1984

DRAFT FOR PUBLIC COMMENT

6 ANALYTICAL METHODS

99

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment and oyster	Homogeneous sample mixed with water and vinyl chloride purged into a closed loop; gas in closed loop injected into gas chromatograph	GC/ECD	2 ng/g (sediment) 4 ng/g (oyster)	NR	Wang et al. 1985
Landfill gas	Sample collected in 2 L evacuated glass bulb; gas directly injected into gas chromatograph	GC/FID	NR	NR	Wood and Porter 1987
Food (orange drink, wine, olive oil)	Sample sealed in vials and equilibrated at 40°C for 2 hours; headspace gas injected into gas chromatograph	GC/FID	NR	NR	Chudy and Crosby 1977
Foodstuffs	Sample sealed in vials and equilibrated at 40°C for a minimum of 2 hours; headspace gas injected into gas chromatograph	GC/FID	1-5 ppb	NR	IARC 1978

EPA = Environmental Protection Agency; GC/ECD = gas chromatography/electron capture detector; GC/FID = gas chromatography/flammable ionization detector; GC/HSD = gas chromatography/halogen specific detector; GC/MS = gas chromatography/mass spectrometry; GC/PID = gas chromatography/photoionization detector; HSD = halogen specific detector; N₂ = nitrogen; Na₂S₂O₃ = sodium thiosulfate; NR = not reported; PFTE = polytetrafluorethylene; PID = photoionization detector; PVC = polyvinyl chloride

6. ANALYTICAL METHODS

Recently, EPA made improvements in methods for measuring volatile organic chemicals. The major change is the use of smaller sample volumes allowed by increased use of capillary gas chromatographic columns. Capillary columns provide better resolution, minimum detection limits, and less column bleed than packed columns (Reding 1987).

Vinyl chloride has been measured in sediment using GC/ECD with sensitivity in the low-ppb range. Accuracy and precision data were not given (Wang et al. 1985). No information on analysis of vinyl chloride in soil was located. GC/HSD of headspace gases is the EPA-recommended method for solid matrices with sensitivity in the sub-ppb range. Accuracy (101.9%) is good and precision (11.4%) is adequate (EPA 1982d). Vinyl chloride levels in food have been determined using GC/FID. Headspace analysis is a common method of preparation of foods with sensitivity in the low-ppb range (IARC 1978).

6.3 ADEQUACY OF THE DATABASE

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

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. 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. Methods are available for measuring vinyl chloride and/or its metabolite, thiodiglycolic acid, in breath, urine, blood, and tissue. These methods are sensitive for measuring levels at which health effects might occur, and for measuring higher background levels that might be found in specific populations known to be exposed to elevated levels of vinyl chloride (e.g., workers in the plastics industry and individuals living in the vicinity of hazardous waste sites). Measurement of urinary thiodiglycolic acid can be used as an indicator of vinyl chloride intake as long as individual variability in metabolism due to such factors as liver disease, use of drugs, and alcohol intake can be accounted for. Exposure to vinyl chloride at concentrations below 1-5 ppm could be masked by background metabolic levels of thiodiglycolic acid within normal limits. Also, the formation of thiodiglycolic acid is not unique to vinyl chloride exposure. The methods are generally reliable, although increased precision for most methods would increase reliability. Background levels for the general population are ill defined. Further research on the relationship between low-level exposure and levels of vinyl chloride in biological media would be helpful in assessing the risks and health effects of chronic, low-level exposure.

Existing methods are sensitive for measuring levels of vinyl chloride and its metabolite, thiodiglycolic acid, in individuals affected by exposure to very high levels of vinyl chloride. Also, methods are available to detect DNA adducts produced by the reaction of vinyl chloride metabolites with DNA. These DNA adducts are specific indicators of vinyl chloride's genotoxic potential. These methods, however, are not sufficiently sensitive to determine the genotoxic effects resulting from low-level exposure. Correlations between levels detected in biological tissues and fluids, and specific observed effects for lower levels of exposure, are not

6. ANALYTICAL METHODS

established. Additional research in this area would allow better assessment of existing methods and would help in defining areas in which improvements are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining vinyl chloride in air and water, the media of most concern for human exposure, are sensitive, reproducible, and reliable for measuring background levels in the environment. Research investigating the relationship between levels measured in air and water and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed. Methods specifically regarding the analysis of vinyl chloride in soils were not located. EPA does, however, have sensitive and reliable methods for determining the concentration of vinyl chloride in soil matrices, which include contaminated soils.

6.3.2 On-going Studies

No on-going studies concerning methods for measuring and determining vinyl chloride in biological and environmental samples were located.

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of vinyl chloride and other volatile organic compounds in blood. These methods use purge and trap methodology and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion range.

R&S148520

7. REGULATIONS AND ADVISORIES

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

ATSDR has derived two MRL values for vinyl chloride. An intermediate-duration inhalation MRL of 0.002 ppm was derived for vinyl chloride based on its ability to cause increased liver weight (Bi et al. 1985). A chronic-duration oral MRL of 2×10^{-5} mg/kg/day was derived for vinyl chloride based on its ability to cause areas of cellular alteration in the liver (Til et al. 1983). No reference dose (RfD) or reference concentration (RfC) exist for vinyl chloride (IRIS 1990).

Vinyl chloride is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987f, 1988c).

The FDA proposed to amend its regulations regarding the vinyl chloride content of polymers used in packaging materials or processing equipment for foods (EPA 1977c; FDA 1986). Depending on the nature of the polymer and its use, proposed vinyl chloride content may range from 5 to 50 ppm.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Vinyl Chloride

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
IARC	Carcinogenic classification	Group 1 ^a	IARC 1987
<u>NATIONAL</u>			
Regulations:			
a. Air:			
OSHA	PEL TWA	1 ppm	EPA 1974a (29 CFR 1910.1017); EPA 1974b
	STEL Peak (15 minutes)	No data 5 ppm	EPA 1974a (29 CFR 1910.1017); EPA 1974b
	Direct employee exposure to vinyl chloride is not allowed	Yes	EPA 1974a (29 CFR 1910.1017); EPA 1974b
	Concentration in exhaust gases from formulation and purification of vinyl chloride shall not exceed ^b :	10 ppm	EPA 1986b (40 CFR 61.63); EPA 1986c
	Reactor opening loss from each reactor not to exceed:	0.02 g/kg of polyvinyl chloride product	EPA 1986b (40 CFR 61.63); EPA 1986c
	In polyvinyl chloride plants using stripping to control emissions		EPA 1986b (40 CFR 61.63); EPA 1986c
	Daily weighted average residual concentration processed each day for polyvinyl chloride dispersion resins may not exceed:	2,000 ppm	EPA 1986b (40 CFR 61.63); EPA 1986c
	Latex resins averaged separately for each type of resin:	400 ppm	EPA 1986b (40 CFR 61.63); EPA 1986c
	Dispersion polyvinyl chloride resins excluding latex:	2 g/kg	EPA 1986b (40 CFR 61.63); EPA 1986c
	Latex resins:	0.4 g/kg	EPA 1986b (40 CFR 61.63); EPA 1986c
b. Water:			
EPA ODW	MCL in drinking water		EPA 1989b (40 CFR 141, 142, 143); EPA 1987d
	Final	0.002 mg/L	
	Proposed	0.001 mg/L	
	Regulated under SDWA of 1986	Yes	FSTRAC 1988
c. Food:			
FDA	Indirect food additive for use only as a component of adhesives	Yes	EPA 1977a (21 CFR 175.105); EPA 1977b
d. Other:			
EPA OERR	Reportable quantity:		EPA 1985a (40 CFR 302); EPA 1986a (40 CFR 117); EPA 1987e
	CERCLA Statutory RQ	1 pound	
	Proposed	10 pounds	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
<u>NATIONAL</u> (Cont.)			
EPA OSW	Designated as a Toxic Pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	EPA 1979c (40 CFR 401.15); EPA 1979b
	Designated as a Hazardous Substances under CERCLA	Yes	EPA 1985a (40 CFR 302); EPA 1987e
	Listing as a Hazardous Waste: Heavy ends from distillation of vinyl chloride monomer production	Yes	EPA 1981b (40 CFR 261.32); EPA 1981c
	Listing as a Hazardous Waste: Discarded commercial chemical products off-specification species, container residues, and spill residues thereof	Yes	EPA 1981a (40 CFR 261.33); EPA 1980b
	Listing as a Hazardous Constituent	Yes	EPA 1988a (40 CFR 261, Appendix VIII); EPA 1988b
	Designated as a Hazardous Air Pollutant under Section 112 of the Clean Air Act	Yes	EPA 1975a (40 CFR 61.01); EPA 1975b
	Groundwater Monitoring Requirement	Yes	EPA 1987b (40 CFR 264, Appendix IX); EPA 1987c
EPA OTS	Toxic Chemical Release Reporting; Community Right-to-Know	Yes	EPA 1988c (40 CFR 372); EPA 1987f
Guidelines:			
a. Air:			
ACGIH	TLV TWA STEL	10 mg/m ³ , 5 ppm No data	ACGIH 1988
EPA	RfC (Inhalation)	No data	IRIS 1990
NIOSH	REL TWA (15 minutes)	2.55 mg/m ³	NIOSH 1985
	IDLH	No data	
	NIOSH recommends that vinyl chloride be treated as an occupational carcinogen	Yes	NIOSH 1985
b. Water:			
EPA ODW	MCLG		EPA 1989b (40 CFR 141.142); EPA 1987d
	Final	Zero	
	Category	I	EPA 1987g
	Health Advisories:		
	1-day (proposed)	2.6 mg/L	
	10-day	2.6 mg/L	
	Longer-term (child)	0.013 mg/L	
	Longer-term (adult)	0.046 mg/L	
	Lifetime	Not recommended	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
<u>NATIONAL (Cont.)</u>			
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health ^c		
	Ingesting water and organisms:		EPA 1980c
	10 ⁻⁵	20 µg/L	
	10 ⁻⁶	2.0 µg/L	
	10 ⁻⁷	0.2 µg/L	
	Ingesting organisms only:		EPA 1980c
	10 ⁻⁵	5.246 µg/L	
	10 ⁻⁶	525 µg/L	
	10 ⁻⁷	52.5 µg/L	
	Drinking water:		EPA 1985b
	10 ⁻⁴	1.5 µg/L	
	10 ⁻⁵	0.15 µg/L	
	10 ⁻⁶	0.015 µg/L	
c. Other:			
EPA	RfD (oral)	No data	IRIS 1990
	Carcinogen classification	A	EPA 1990
	Unit risk (inhalation)	8.4x10 ⁻⁵ (µg/m ³) ⁻¹	EPA 1990
	Unit risk (oral)	5.4x10 ⁻⁵ (µg/L) ⁻¹	EPA 1990
<u>STATE</u>			
Regulations and Guidelines:			
a. Air:	Acceptable Ambient Air Concentrations		NATICH 1990
California-Monterey	(NA)	0.00	
Connecticut	(8 hour)	50.0 µg/m ³	
Florida-Fort Lauderdale	(8 hour)	0.10 mg/m ³	
Kansas-Kansas City	(Annual)	0.244 µg/m ³	
Kansas	(Annual)	3.85 µg/m ³	
Massachusetts	(24 hour)	3.47 µg/m ³	
Massachusetts	(Annual)	0.38 µg/m ³	
Maryland	(NA)	0.0	
Maine	(NA)	0.0	
Michigan	(Annual)	0.4 µg/m ³	
North Carolina	(Annual)	0.00038 mg/m ³	
North Dakota	(NA)	0.0	
Nevada	(8 hour)	0.238 mg/m ³	
New York	(1 year)	0.400 µg/m ³	
Pennsylvania-Philadelphia	(1 year)	2.57 ppb	
Pennsylvania-Philadelphia	(Annual)	2.40 ppb	
South Carolina	(24 hour)	50.0 µg/m ³	
South Dakota	(8 hour)	50.0 µg/m ³	
Texas	(30 minutes)	100.0 µg/m ³	
Texas	(Annual)	10.0 µg/m ³	
Virginia	(24 hour)	130.0 µg/m ³	
Vermont	(Annual)	0.20 µg/m ³	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
<u>STATE</u> (Cont.)			
	Ambient Air Emissions Limitations for Class I areas (24-hour average)		
Kentucky		15 $\mu\text{g}/\text{m}^3$	CELDS 1990
Montana		15 $\mu\text{g}/\text{m}^3$	CELDS 1990
	Designated as a Hazardous Air Pollutant and subject to regulations		EPA 1985d (40 CFR 61.01)
Alabama		Yes	
Arizona		Yes	
Colorado		Yes	
Delaware		Yes	
Florida		Yes	
Georgia		Yes	
Illinois		Yes	
Indiana		Yes	
Iowa		Yes	
Kentucky		Yes	
Louisiana		Yes	
Maryland		Yes	
Mississippi		Yes	
Missouri		Yes	
Montana		Yes	
Nebraska		Yes	
New Mexico		Yes	
North Carolina		Yes	
North Dakota		Yes	
Oklahoma		Yes	
Pennsylvania		Yes	
Tennessee		Yes	
Utah		Yes	
Virginia		Yes	
West Virginia		Yes	
Wisconsin		Yes	
	Permit required to construct and operate an air contamination source project if yearly emissions exceed:		CELDS 1990
Arizona		1 ton	
Connecticut		1 ton	
Missouri		1 ton	
New York		1 ton	
Wisconsin		1 ton	
	Prevention of Significant Deterioration Adopted air pollution control standards found in EPA 1978 (40 CFR 52.21)		
South Carolina		Yes	CELDS 1990

DRAFT FOR PUBLIC COMMENT

R8S148525

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
<u>STATE (Cont.)</u>			
	Sources exempt from air monitoring requirements if net emissions increase is:		CELDS 1990
Delaware	(24 hour)	15 $\mu\text{g}/\text{m}^3$	
Louisiana	(24 hour)	15 $\mu\text{g}/\text{m}^3$	
Oregon	(24 hour)	15 $\mu\text{g}/\text{m}^3$	
Wisconsin	(24 hour)	15 $\mu\text{g}/\text{m}^3$	
Wisconsin	Hazardous Air Contaminants without Acceptable Ambient Concentrations requiring application of Lowest Achievable Emission Rates	300 pounds/year	WAC 1988
Wisconsin	Exemption from requirement of Construction or Modification and New Operation Permits for Air Pollution Sources if emissions do not exceed:	1 ton/year	CELDS 1990
b. Water:			
	Drinking water quality guidelines and standards		FSTRAC 1988
Arizona		1 $\mu\text{g}/\text{L}$	
California		2 $\mu\text{g}/\text{L}$	
Florida		1 $\mu\text{g}/\text{L}$	
Kansas		1 $\mu\text{g}/\text{L}$	
Massachusetts		1 $\mu\text{g}/\text{L}$	
Maine		2 $\mu\text{g}/\text{L}$	
Minnesota		0.15 $\mu\text{g}/\text{L}$	
New Jersey		2 $\mu\text{g}/\text{L}$	
New Mexico		1 $\mu\text{g}/\text{L}$	
New York		5 $\mu\text{g}/\text{L}$	
Rhode Island		0 $\mu\text{g}/\text{L}$	
Vermont		1 $\mu\text{g}/\text{L}$	
Oklahoma	MAL in drinking water	0.002 mg/L	CELDS 1990
	MCL in drinking water		CELDS 1990
Alabama		0.002 mg/L	
Colorado		0.002 mg/L	
Georgia		0.002 mg/L	
Massachusetts		0.002 mg/L	
Missouri		0.002 mg/L	
New York		0.002 mg/L	
North Carolina		0.002 mg/L	
North Dakota		0.002 mg/L	
Ohio		0.002 mg/L	
Puerto Rico		10 ppb	
Rhode Island ^d		0.002 mg/L	
South Dakota		0.002 mg/L	
Tennessee		0.002 mg/L	
Texas		0.002 mg/L	
Utah		0.002 mg/L	
Wisconsin		0.0002 mg/L	
Wisconsin	MCLG	Zero	CELDS 1990

7 REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
<u>STATE</u> (Cont.)			
New York	Effluent standards: maximum allowable concentrations into saturated or unsaturated zones	5.0 µg/L	CELDS 1990
	Allowable concentration limits for Class GA waters	5.0 µg/L	CELDS 1990
Utah	Ground Water Quality Standards	0.002 mg/L	CELDS 1990
Wisconsin	Public Health Groundwater Quality Standards:		
	Enforcement Standard	0.015 µg/L	WAC 1985
	Preventative Action Limit	0.0015 µg/L	WAC 1985
	Human Cancer Criteria		DNR 1987
	Public Water Supply		
	Warm water sport fish communities	0.15 µg/L	
	Cold water communities	0.15 µg/L	
	Great Lakes communities	0.15 µg/L	
	Non-Water Supply		
	Warm water sport fish communities	10 µg/L	
	Cold water communities	3.7 µg/L	
	Warm water forage and limited forage fish communities and limited aquatic life	30 µg/L	
c. Other:			
Kentucky	Defined as hazardous waste	Yes	NREPC 1988 (401 KAR 31:040)

^aGroup 1: Carcinogenic to Humans

^bApplies to reactors, strippers, mixing, weighing and holding containers, and monomer recovery systems

^cBecause of its carcinogenic potential, the EPA-recommended concentration for vinyl chloride in ambient water is zero. However, because attainment of this level may not be possible, levels which correspond to upper bound incremental lifetime cancer risks of 10^{-5} , 10^{-6} , and 10^{-7} are estimated.

^dAnalysis for vinyl chloride is required only for groundwater systems that have detected one or more of the following: tetrachloroethylene, trichloroethylene, 1,2-dichloroethane, 1,1,1-trichloroethane, cis 1,2-dichloroethylene, trans 1,2-dichloroethylene, or 1,1-dichloroethylene.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; MAL = Maximum Allowable Level; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NA = not applicable; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfC = Reference Concentration; RfD = Reference Dose; RQ = Reportable Quantity; SDWA = Safe Drinking Water Act; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average

8. REFERENCES

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

9. GLOSSARY

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₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

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

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- 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.

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

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

q₁* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q₁* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

9. GLOSSARY

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 (TD₅₀) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

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

APPENDIX A

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 endpoint 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 10,000,000. 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 with 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 sufficient 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 (LSE 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.

APPENDIX A

- (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 18), 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 0.0006 ppm (see footnote "c").
- (9). 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.
- (10). Reference The complete reference citation is given in Chapter 8 of the profile.
- (11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or 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.
- (12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0006 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.

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 0.0006 ppm (see footnote "c" 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 (q₁).
- (19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

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

CHRONIC EXPOSURE							
							11
	Cancer						
38	Rat	18 mo 5d/wk 7hr/d				20 ^b (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 ^b (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 ^b (CEL, lung tumors, hemangiosarcomas)	NTP 1982

*The number corresponds to entries in Figure 2-1.

^bPresented in Section 1.4.

^cUsed to derive an intermediate inhalation minimal risk level (MRL) of 4×10^{-3} mg/m³; concentration was converted to an equivalent concentration in humans; concentration was adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability). This MRL is converted into 6×10^{-4} ppm and is presented in Section 1.4

CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; LC₅₀ = lethal concentration, 50% kill; mo = month; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

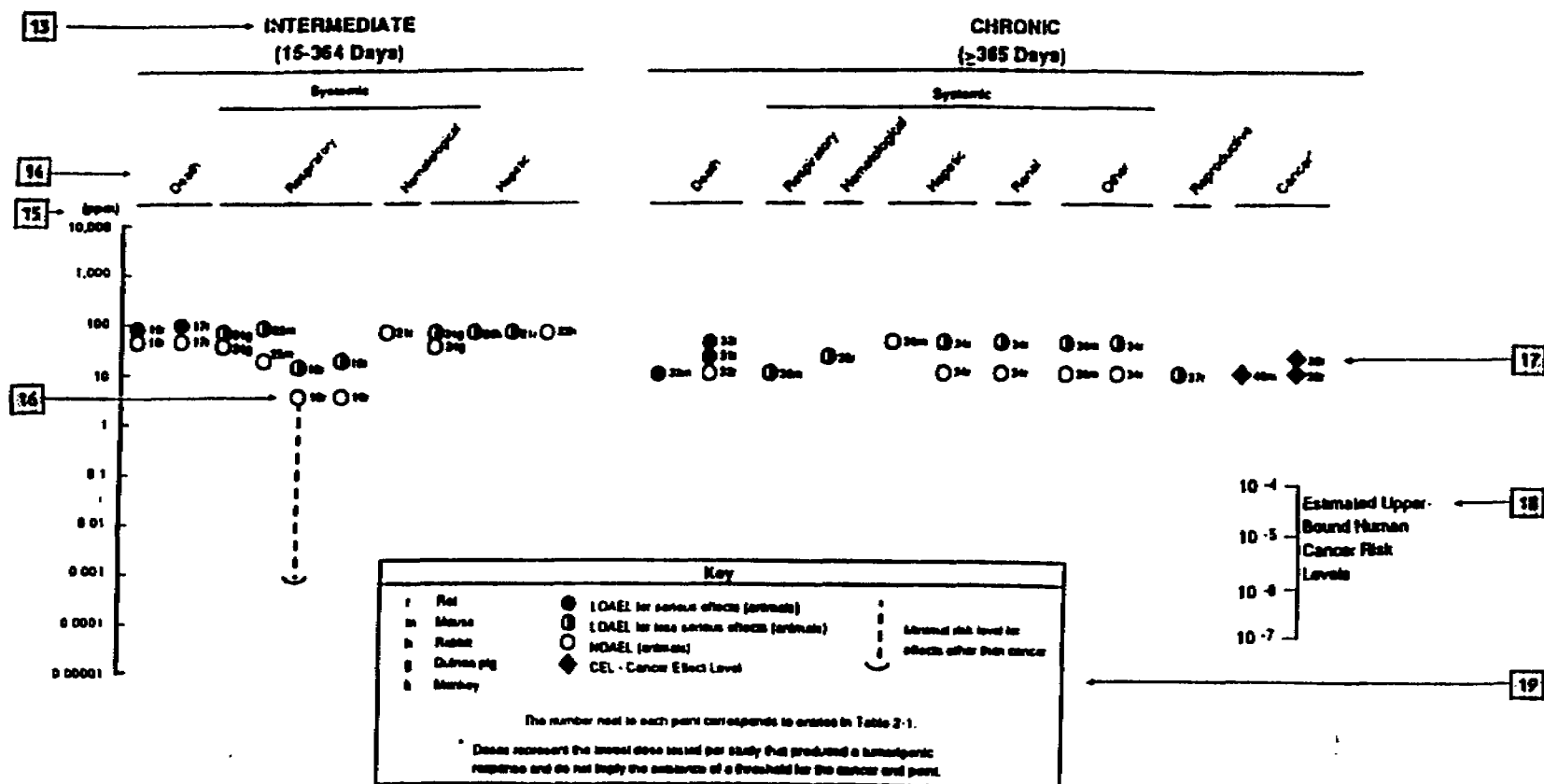
APPENDIX A

A-4

...DRAFT FOR PUBLIC COMMENT...

SAMPLE

...DRAFT FOR PUBLIC COMMENT...



APPENDIX A

A-5

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

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

APPENDIX A

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 LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the 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
ft	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
K _d	adsorption ratio
kg	kilogram
kg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter

APPENDIX B

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

LC		STEL	short term exposure limit
LC _{Lo}		STORET	STORAGE and RETRIEVAL
LC ₅₀		TLV	threshold limit value
LD _{Lo}		TSCA	Toxic Substances Control Act
LD ₅₀		TRI	Toxics Release Inventory
LOAEL		TWA	time-weighted average
LSE		U.S.	United States
m		UF	uncertainty factor
mg		yr	year
min		WHO	World Health Organization
mL		wk	week
mm			
mmHg		>	greater than
mmol		≥	greater than or equal to
mo		=	equal to
mppcf		<	less than
MRL		≤	less than or equal to
MS		%	percent
NIEHS		α	alpha
NIOSH		β	beta
NIOSHTIC	f	δ	delta
ng		γ	gamma
nm		μm	micron
NHANES		μg	microgram
nmol			
NOAEL			
NOES			
NOHS			
NPL			
NRC			
NTIS			
NTP			
OSHA			
PEL			
pg			
pmol			
PHS			
PMR			
ppb			
ppm			
ppt			
REL			
RfD			
RTECS			
sec			
SCE			
SIC			
SMR			

APPENDIX C

PEER REVIEW

A peer review panel was assembled for vinyl chloride. The panel consisted of the following members: Dr. Finis Cavender, Associate Professor, Abilene Christian University, Abilene, Texas; Dr. Richard Monson, Director, Occupational Health Program, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and Dr. Martha Radike, Research Associate Professor, Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, Ohio. These experts collectively have knowledge of vinyl chloride'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.

VINYL CHLORIDE MANUFACTURING RECORDS

<u>YEARLY</u>	<u>PRODUCTION</u>	<u>HIGHEST MONTH</u>
1969	301,459,981	Dec. 48,139,506
1970	591,154,586	May 63,601,276
1971	628,847,720	Dec. 63,369,912
1972	697,260,942	Dec. 64,543,760
1973	708,175,890	Mar. 70,099,570
1974	618,917,641	Jun. 62,953,750
1975	446,219,718	Jul. 50,048,333
1976	674,107,628	Aug. 67,347,768
1977	577,355,204	Jun. 64,114,291
1978	657,621,139	Apr. 69,621,334
1979	741,582,777	May 67,923,259
1980	485,319,456	Mar. 72,171,801
1981	581,826,838	May 61,576,905
1982	683,402,313	Dec. 71,981,288
1983	732,432,388	Jul. 73,019,734
1984	766,161,810	May 75,846,502
1985	781,685,138	Dec. 76,008,176
1986	867,294,116	Mar. 75,887,686
1987	859,699,332	Dec. 76,296,559
1988	841,483,490	Jul. 75,973,775
1989	860,022,150	Oct. 76,881,505
1990	906,270,312	Mar. 81,766,760
1991	825,379,072	Dec. 84,038,708
1992	957,051,711	Oct. 87,841,398

RECORD YEAR - 1992 - 957,051,711

RECORD MONTH - Oct. '92 - 87,841,398

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LAD - Vinyl 2

	VCM PRODUCTION								
	1977	1978	1979	1980	1981	1982	1983	1984	
1		40,727,000	48,274,700	60,414,100	39,363,100	36,928,800	62,746,000	53,497,000	1
2		24,442,800	60,665,400	73,555,800	23,190,200	61,275,000	62,592,900	65,382,500	2
3		61,776,100	67,833,100	35,570,900	58,039,900	73,761,000	59,173,700	70,867,800	3
4		59,792,300	75,060,300 [*]	60,078,300	51,601,500	61,311,900	59,709,100	68,354,400	4
5		74,844,700 [*]	54,481,200	54,259,300	72,569,300	61,777,000	56,133,100	72,304,500	5
6		56,761,000	80,989,800 [*]	43,377,900	72,180,900	61,863,500	69,454,000	55,987,300	6
7		52,214,500	69,276,500	28,017,800	53,828,800	10,159,300	66,587,500	69,156,500	7
8		57,428,300	55,945,000	63,655,100	46,788,200	20,152,400	49,998,000	22,238,100	8
9		66,328,200	62,594,200	55,307,700	39,270,200	59,787,600	61,917,000	37,234,000	9
10	7,805,900	65,183,400	80,362,100	54,081,200	31,840,400	60,111,200	56,195,800	55,451,100	10
11	41,168,700	64,099,900	68,153,000	58,234,500	30,870,100	69,931,700	67,213,300	75,788,500	11
12	39,541,900	62,174,400	71,173,100	61,383,400	29,172,400	67,789,300	62,014,400	73,162,900	12
YTD	88,516,500	685,772,600	794,808,400 ^{**}	647,936,000	548,714,800	644,848,700	733,736,800	710,424,500	YTD

* RECORD MONTH!

** RECORD YEAR!!

VCM PRODUCED		CUMULATIVE							
	1985	1986	1987	1988	1989	1990	1991	1992	
1	71,015,500	76,090,700	80,079,700	87,712,400	98,338,120	70,913,230	98,922,848	109,977,767	1
2	74,038,700	56,343,300	75,888,400	85,467,520	97,620,992	99,206,043	77,153,440	81,470,123	2
3	69,713,700	84,496,300	64,866,600	86,612,592	108,891,808	100,925,432	82,053,808	102,048,656	3
4	71,966,600	63,965,900	91,603,000	86,244,096	84,388,384	95,423,250	58,435,856	115,427,822	4
5	72,666,900	79,635,000	85,457,100	57,873,488	109,510,416	40,211,784	76,431,117	127,515,520	5
6	65,104,600	73,949,700	83,900,600	76,020,960	85,391,181	100,441,346	85,060,041	118,663,056	6
7	49,530,700	76,705,600	89,390,700	92,229,568	104,340,038	117,796,195	111,173,093	108,810,814	7
8	55,830,500	68,096,900	87,564,200	94,214,752	104,220,093	100,154,293	113,449,536	82,545,968	8
9	71,422,500	76,205,250	85,279,500	101,163,392	84,068,019	88,871,008	91,391,116	0	9
10	74,044,200	78,626,100	85,125,400	106,880,896	80,401,004	66,548,576	118,307,729	96,207,160	10
11	71,084,400	71,634,376	87,416,300	108,266,608	98,566,178	78,935,920	117,150,272	120,724,368	11
12	67,384,200	83,937,792	89,174,100	110,124,573	94,590,769	113,358,896	115,740,232	121,000,201	12
YTD	813,097,400	857,676,917	1,005,797,100	1,092,850,845	1,150,327,602	1,112,785,939	1,148,639,604	1,187,462,860	YTD

Record year

Record quarter

Record quarter