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2. Equitable Environmental Health, Inc. Supplementary epidemiological study of vinyl chloride workers. Report prepared for the Manufacturing Chemists Association, September 1976.

3. Tabershaw/Cooper Associates, Inc. Epidemiological study of vinyl chloride workers. Submitted to the Manufacturing Chemists Association, May 3 1974.

CMA 009823

Toxicological Profile for

VINYL CHLORIDE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

Comment Period Ends:

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TOXICOLOGICAL PROFILE FOR VINYL CHLORIDE

Date Published — January 1988

Prepared by:

Technical Resources, Inc.
under Contract No. 68-03-3268

Revised by:

Syracuse Research Corporation
under Contract No. 68-03-3521

for

Agency for Toxic Substances and Disease Registry (ATSDR)
U.S. Public Health Service

in collaboration with

U.S. Environmental Protection Agency (EPA)

Published by:

Oak Ridge National Laboratory
under
DOE Interagency Agreement No. 1425-1425-A1

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FOREWORD

The Superfund Amendments and Reauthorization Act 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 (also known as SARA) 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 list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic 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 guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is 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 statement is material that presents 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. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program 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 front 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 comment that will make the toxicological profile series of the greatest use.

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, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

James O. Mason

James O. Mason, M.D., Dr. P.H.
Assistant Surgeon General
Administrator, ATSDR

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS VINYL CHLORIDE?

Vinyl chloride is a colorless gas with a mild, sweet odor. Most of the vinyl chloride produced in the United States is used to make polyvinyl chloride (PVC), a material used to manufacture a variety of plastic and vinyl products including pipes, wire and cable coatings, packaging materials, furniture and automobile upholstery, wall coverings, housewares, and automotive parts. Much smaller amounts of vinyl chloride are used as a refrigerant gas and in the manufacture of other chlorinated compounds. The major sources of release of vinyl chloride to the environment are atmospheric emissions and wastewater discharges from the plastics industries (primarily vinyl chloride and PVC manufacturers). Most of the vinyl chloride released to the environment eventually ends up in air.

1.2 HOW MIGHT I BE EXPOSED TO VINYL CHLORIDE?

Humans are exposed to vinyl chloride from environmental and occupational sources. The low levels of vinyl chloride found in the environment (often called background levels) are usually more than a thousand times lower than levels found in occupational locations. Background levels in the environment are usually expressed in terms of parts of vinyl chloride present in a billion parts of air or water (ppb). Background levels found in the air we breathe result from the discharge of exhaust gasses from factories that manufacture or process vinyl chloride, or evaporation from areas where chemical wastes are stored. Highest background levels have been measured in air near vinyl chloride factories or over chemical waste storage areas. Air inside new cars may contain levels of vinyl chloride higher than expected background levels, because vinyl chloride may seep into the air from the new plastic parts.

Background levels in drinking water come from factories that release wastes into rivers and lakes, from seepage into water in areas where chemical wastes are stored, or from contact with polyvinyl chloride pipes. In the past, concentrations exceeding expected background levels were present in foods packaged in plastic that contained vinyl chloride.

Occupational sources, such as what might be experienced in vinyl chloride manufacturing or processing factories, may result in exposure to levels in the air much higher than those from environmental sources. Levels in the air in occupational locations are usually expressed in terms of parts of vinyl chloride per million parts of air (ppm).

1.3 HOW DOES VINYL CHLORIDE GET INTO MY BODY?

The most likely route for vinyl chloride to enter the body is by breathing contaminated air containing the vapor. This route of exposure may be important for persons employed in vinyl chloride manufacturing or processing, but may also be of concern for those living in a community where vinyl chloride plants are located, or those living near hazardous waste disposal sites. Vinyl chloride can also enter the body by eating food or drinking water containing the compound. Insignificant amounts of vinyl chloride can enter foods that are packaged in plastic made from polyvinyl chloride and insignificant amounts can enter drinking water transported in polyvinyl chloride pipes. In addition, vinyl chloride may be present in drinking water contaminated with hazardous waste. Levels of vinyl chloride present in drinking water and packaged foods and beverages are far below those expected to have an effect on health. Absorption of vinyl chloride through the skin is not likely to be important.

1.4 HOW CAN VINYL CHLORIDE AFFECT MY HEALTH?

Short-term exposures to very high levels in contaminated air can cause dizziness, giddiness, stumbling and incoordination, headache, unconsciousness, and death. Long-term exposure to lower concentrations, for example, in factories where vinyl chloride was made or processed, has caused "vinyl chloride disease," which is characterized by severe damage to the liver, effects on the lungs, poor circulation in the fingers, changes in the bones at the end of the fingers, thickening of the skin, and changes in the blood. Increased risk of cancer of the liver, brain, lungs, and possibly other organs, and increased risk of miscarriage have been associated with breathing air in factories containing vinyl chloride.

Health effects have not been associated with the very low levels of vinyl chloride measured in drinking water or foods.

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

Vinyl chloride can be detected in urine and body tissues, but the tests are not a reliable indicator of exposure. Measuring the amount of the predominant breakdown product of vinyl chloride in the urine may give some indication of recent exposure; however, people differ in the quantity of excretion of this breakdown product. This method, therefore, is not a reliable indicator of either the level or the duration of exposure, particularly at low exposure levels. The laboratory tests commonly used by doctors to evaluate liver damage and liver function generally are not reliable for monitoring liver damage from vinyl chloride exposure.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The graphs on the following pages show the relationship between exposure to vinyl chloride and known health effects. In the first set of graphs labeled "Health effects from breathing vinyl chloride" (Fig. 1.1), exposure is expressed in parts of vinyl chloride per million parts

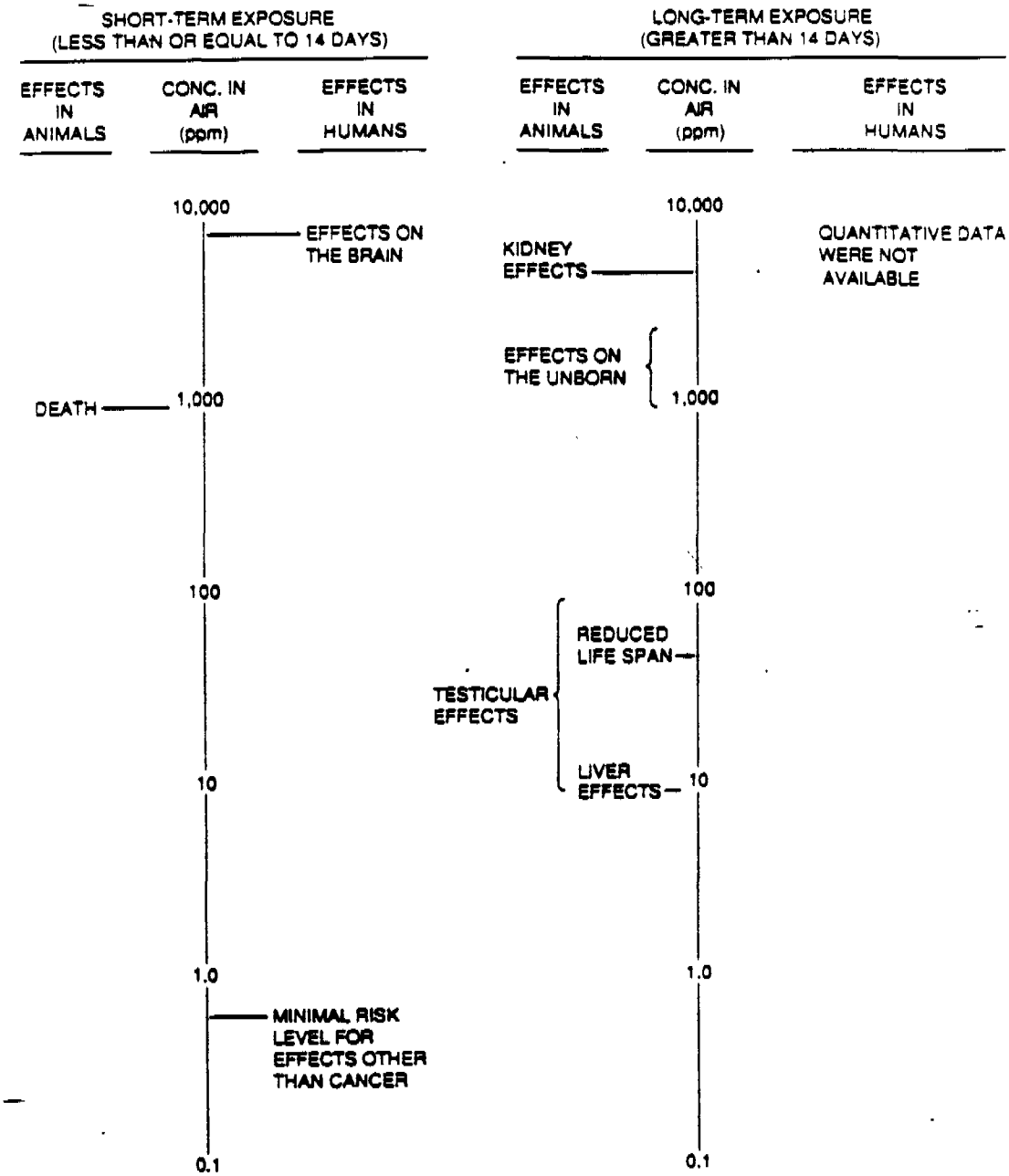


Fig. 1.1. Health effects from breathing vinyl chloride.

of air (ppm). In the second set of graphs, the same relationship is shown for the known "Health effects from ingesting vinyl chloride" (Fig. 1.2). Exposures are expressed in milligrams of vinyl chloride per kilogram of body weight per day (mg/kg/day). In both graphs, effects in animals are shown on the left, effects in humans on the right.

The first column, labeled "Short-term exposure," refers to effects associated with exposure durations of 14 days or less. The column labeled "Long-term exposure" refers to exposures lasting longer than 14 days. The levels marked on the graphs as "Minimal risk for effects other than cancer" are estimates based on data obtained from laboratory animals, and hence are subject to the uncertainties involved in using animal data to predict effects in humans. This data extrapolation is necessary, however, because quantitative exposure data were not available for humans.

1.6.1 Toxic Effects Other Than Cancer

For breathing vinyl chloride, animal data were sufficient to estimate that short-term exposure to 0.7 ppm would result in minimal risk from effects other than cancer. The data did not provide sufficient information to estimate with confidence a level that would be safe for long-term exposure.

For ingesting vinyl chloride, minimal risk of effects other than cancer is expected for lifetime "doses" of 0.0013 mg/kg/day, based on data from laboratory animals.

1.6.2 Cancer

From available data in animals, the Environmental Protection Agency (EPA) has estimated that breathing air containing 1 ppm vinyl chloride every day, all day, for 70 years, increases, at the most, risk of 1100 persons in a population of 10,000 (or 1,100,000 persons in a population of 10,000,000) developing cancer. Consuming 1.0 µg/kg/day vinyl chloride from food and water every day for 70 years increases, at the most, risk of 23 persons in a population of 10,000 (or 23,000 persons in a population of 10,000,000) developing cancer. It should be noted that these risk values are plausible upper-limit estimates. Actual risk levels are unlikely to be higher and may be lower.

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

The Occupational Safety and Health Administration (OSHA) regulations state that a worker must not be exposed to a concentration of vinyl chloride in air that exceeds 1 ppm over any 8-hour work period, and that the concentration must not exceed 5 ppm for more than 15 minutes. The National Institute for Occupational Safety and Health (NIOSH) recommends that workers exposed to any measurable amount of vinyl chloride wear an air-supplied respirator. EPA has determined that factories must limit air emission of vinyl chloride to 10 ppm.

Pursuant to the Safe Drinking Water Act, EPA established that community drinking water systems that regularly serve the same 25 persons for at least 8 months of the year must limit vinyl chloride in

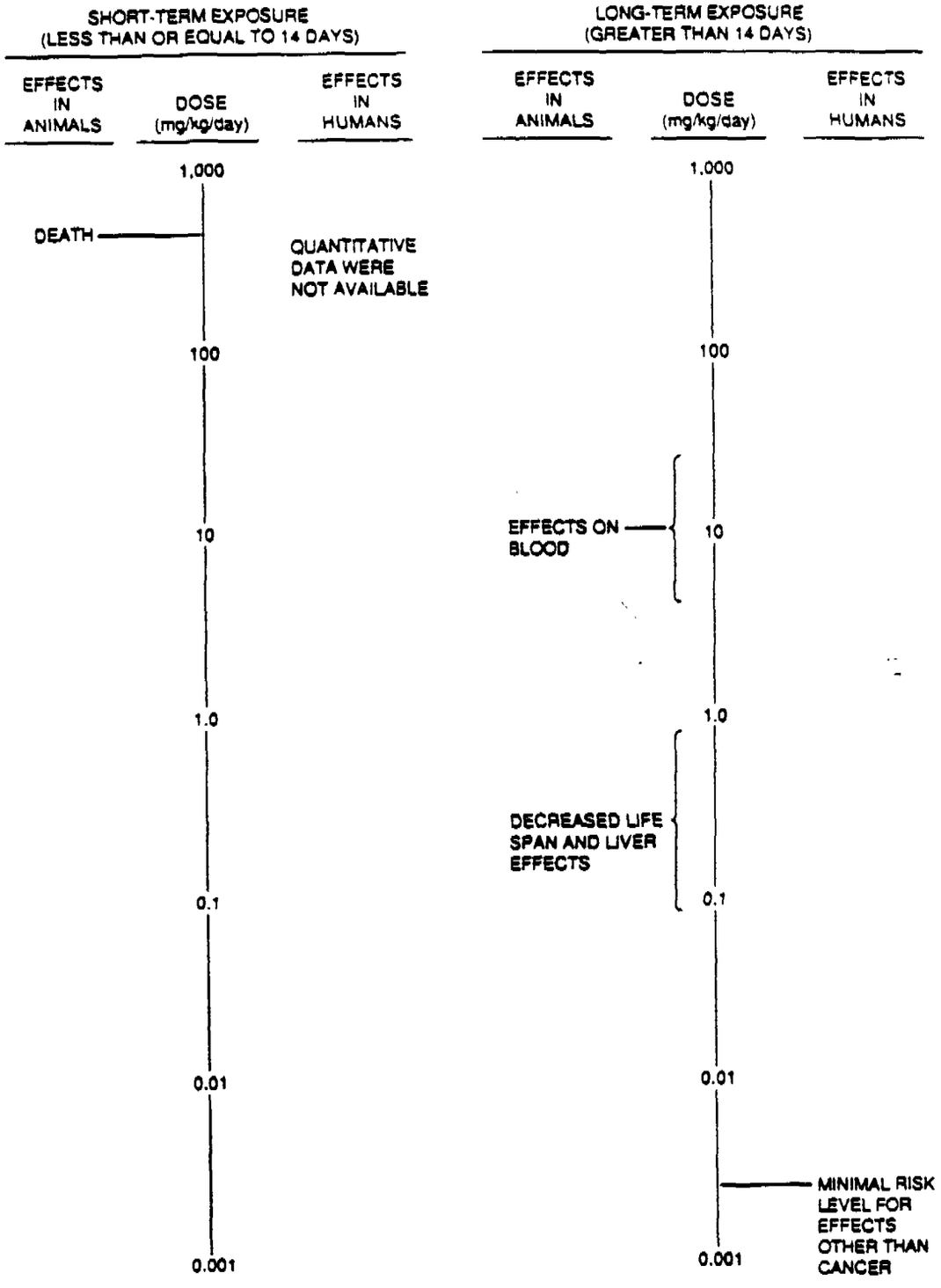


Fig. 1.2. Health effects from ingesting vinyl chloride.

the drinking water to 0.002 mg/L, starting January 9, 1989. In order to limit ingestion of vinyl chloride in food, the Food and Drug Administration (FDA) recently amended its regulations regarding the vinyl chloride content of various plastics used for food packaging. Limits range from 5 to 50 ppm, depending on the nature of the plastic and its use.

In order to exercise control over the handling of vinyl chloride, EPA has designated the chemical as a hazardous constituent of solid waste. If quantities greater than 1 pound are released to the environment, the National Response Center must be notified immediately.

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to vinyl chloride. The purpose of this section is to present levels of significant exposure for vinyl chloride based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of vinyl chloride and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of vinyl chloride that have been monitored in human fluids and tissues and information about levels of vinyl chloride found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graph may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies on exposure to vinyl chloride in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest wh re there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda to provide this information.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental vs actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these minimal risk levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} to 10^{-7}) reported by EPA. In addition, the actual dose (level of exposure) associated with the tumor incidence is plotted.

2.2.1 Key Studies and Graphical Presentations

Dose-response-duration data for the toxicity and carcinogenicity of vinyl chloride are displayed in two types of graphs. These data are derived from the key studies described in the following sections. The "thermometer" graphs in Figs. 2.1 and 2.2 plot exposure levels vs NOAELs and LOAELs for various effects and durations of inhalation and oral exposures, respectively. The graphs of levels of significant exposure in Figs. 2.3 and 2.4 plot end-point-specific NOAELs and LOAELs and minimal levels of risk for acute (<14 days), intermediate (15-364 days), and chronic (≥365 days) duration for inhalation and oral exposures, respectively.

2.2.1.1 Inhalation exposure

Lethality and decreased longevity. Acute occupational exposure to high unspecified concentrations of vinyl chloride has caused death in humans (ACGIH 1986a). Guinea pigs exposed to 100,000 ppm died within 30 minutes as a result of central nervous system (CNS) depression (Patty

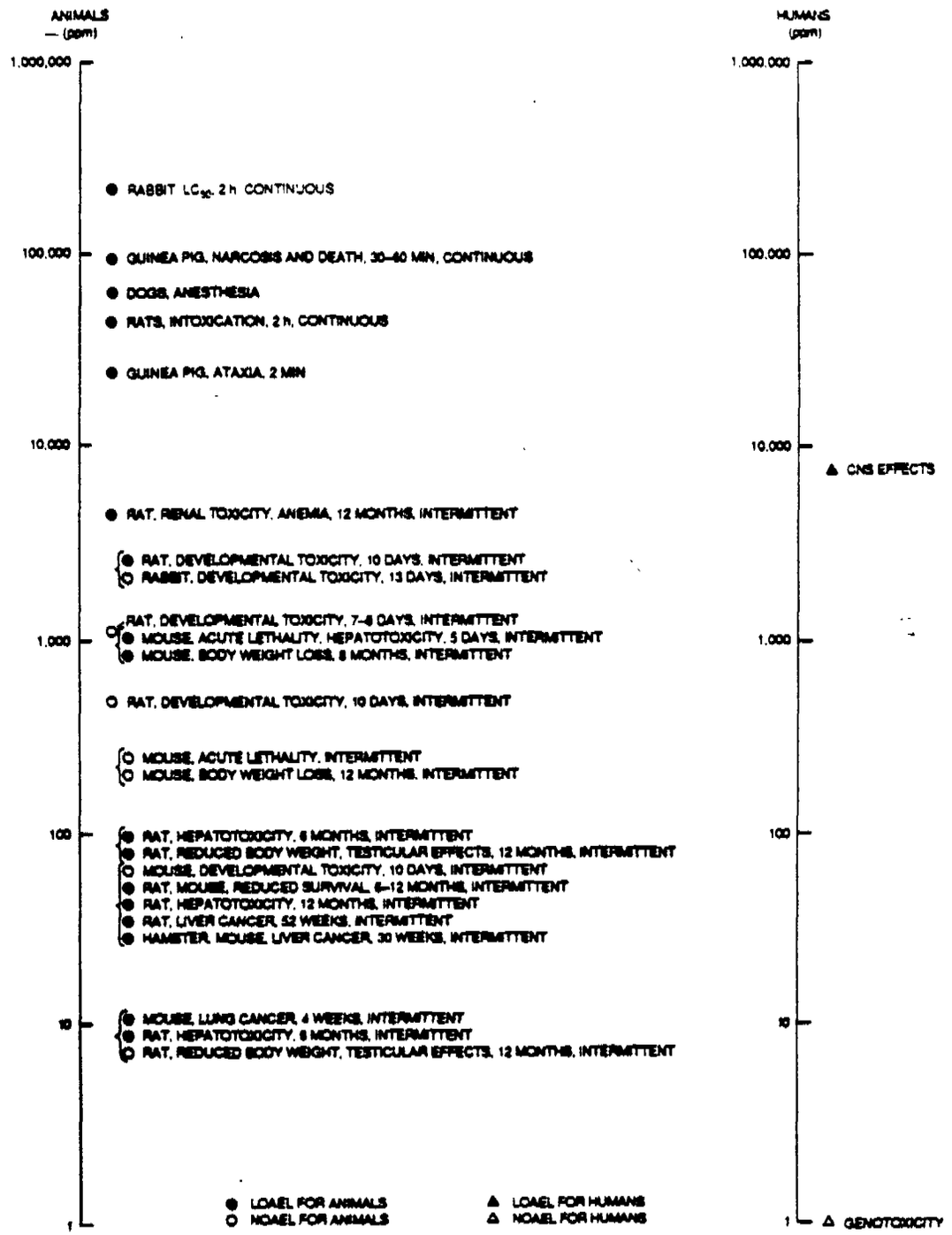


Fig. 2.1. Effects of vinyl chloride—inhalation exposure.

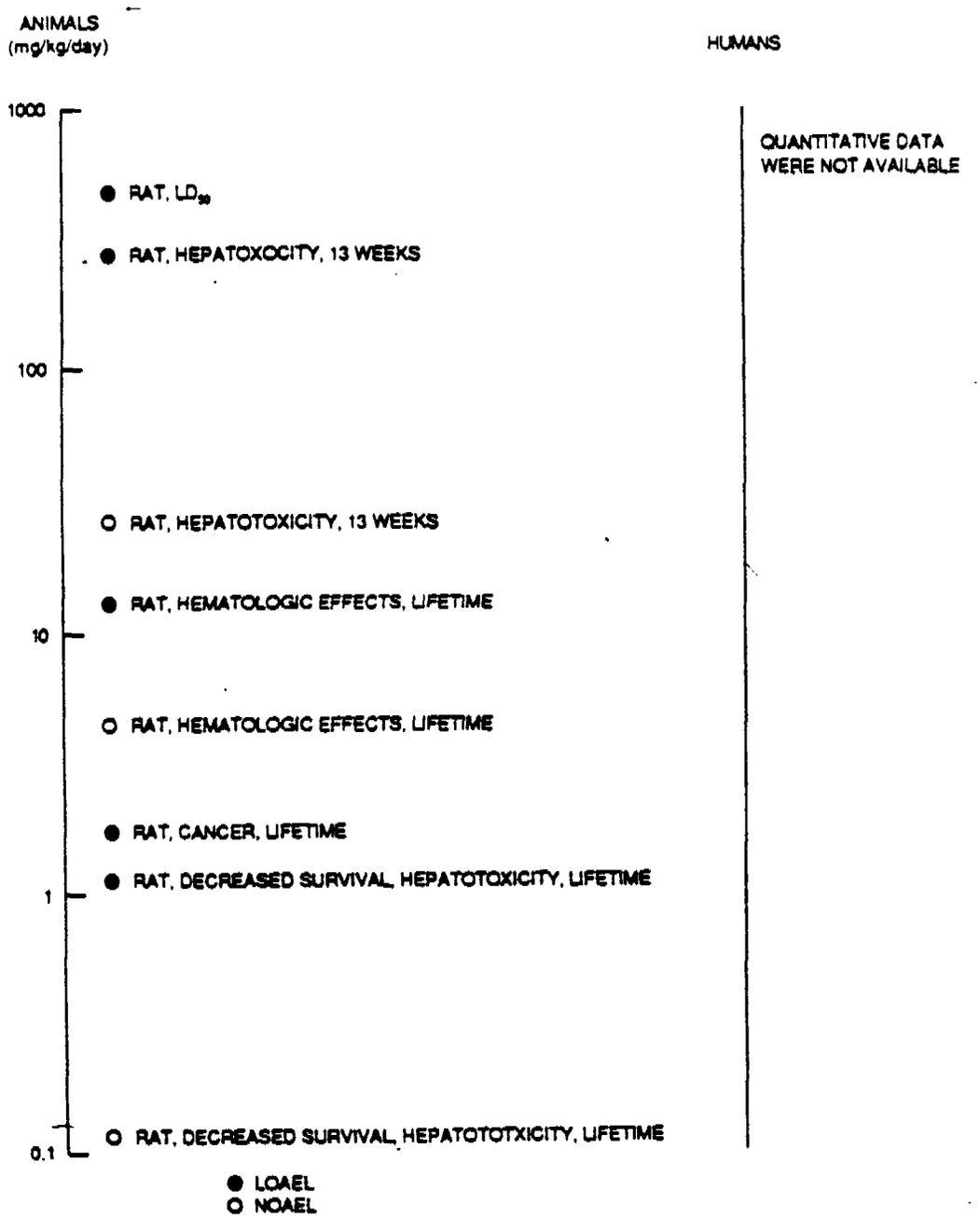


Fig. 2.2. Effects of vinyl chloride—oral exposure.

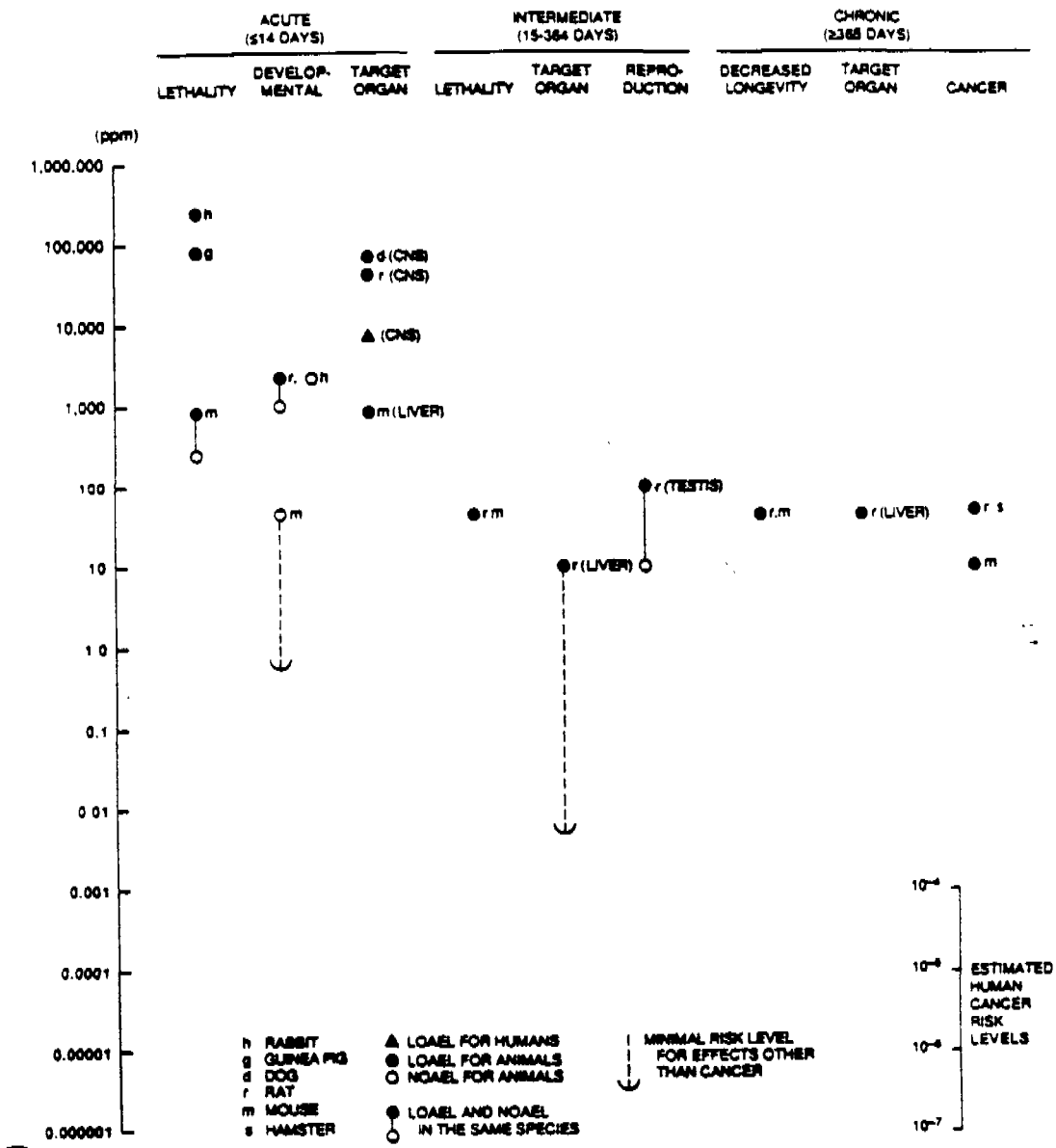


Fig. 2.3. Levels of significant exposure for vinyl chloride—inhalation.

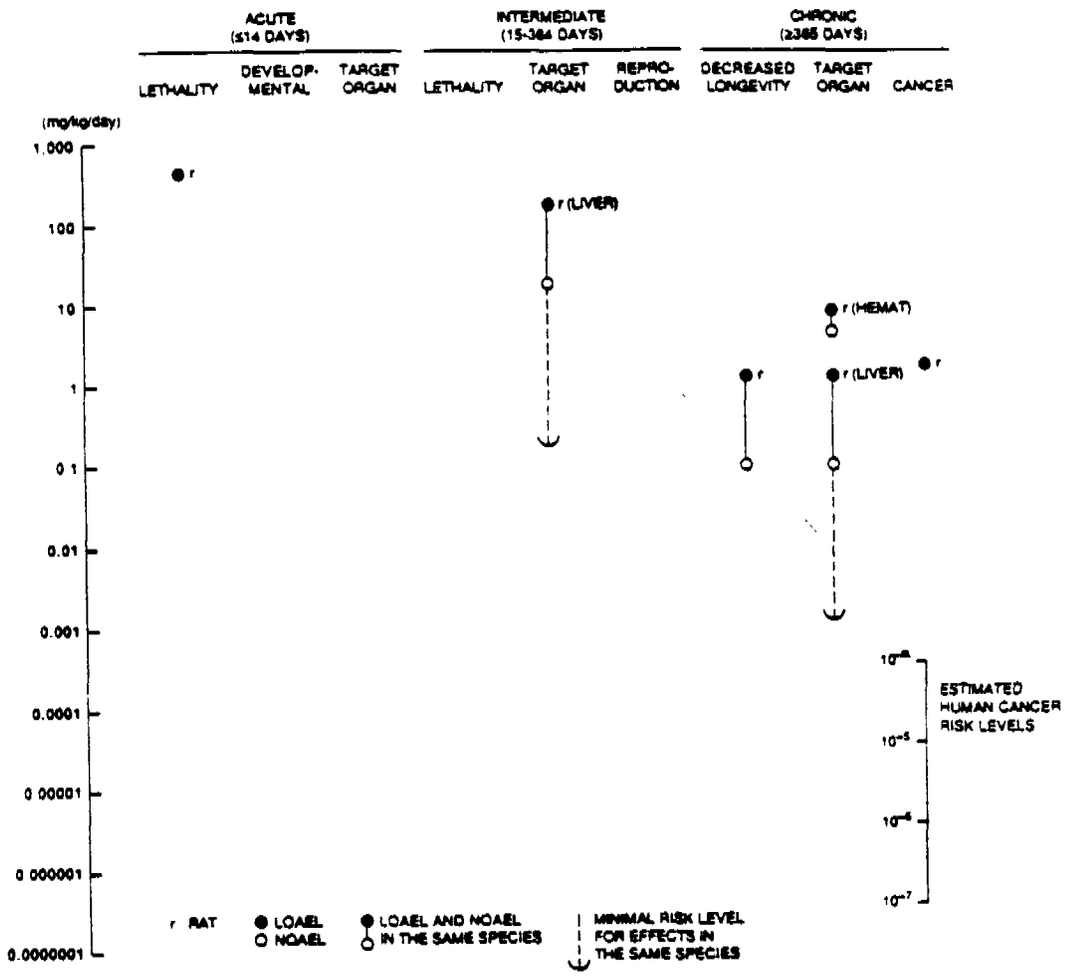


Fig. 2.4. Levels of significant exposure for vinyl chloride—oral.

et al. 1930). Levels plotted as LOAELs on the graphs in Figs. 2.1 and 2.3 include a 2-h LC_{50} of 230,800 ppm in rabbits (EPA 1985a), a level of 100,000 ppm that was lethal in guinea pigs after 30 to 60 min (Patty et al. 1930), a level of 1000 ppm that decreased survival in mice exposed intermittently for 5 days (Lee et al. 1977a), and a level of 50 ppm that decreased survival in rats and mice exposed intermittently for 6 to 12 months (Lee et al. 1977a, Hong et al. 1981).

Systemic/target organ toxicity. Humans occupationally exposed to high levels of vinyl chloride have suffered from a syndrome called vinyl chloride disease, which displays manifold signs of toxicity involving the liver, CNS, and peripheral circulation and nerves. Exposures have not been quantified, however, and thresholds for this syndrome have not been identified. Important target organs in animals are the liver and CNS. CNS effects generally follow acute exposure to high levels (see Figs. 2.1 and 2.3), such as 8000 ppm associated with CNS effects in humans (Lester et al. 1963), 70,000 ppm associated with anesthesia in dogs (Oster et al. 1947), and 50,000 ppm associated with intoxication in rats (Lester et al. 1963). CNS effects involving occupational exposure have been reported, but exposures have not been quantified (Dinceva et al. 1985, Perticoni et al. 1986, Halama et al. 1985).

The liver appears to be the most sensitive organ in humans and animals. Acute hepatotoxicity was observed in mice dying after intermittent exposure to 1000 ppm for 5 to 9 days (Lee et al. 1977a) (see Figs. 2.1 and 2.3). In rats, exposures of intermediate (6 months) duration to 10 ppm were a LOAEL for liver effects (Bi et al. 1985) (see Figs. 2.1 and 2.3). A chronic LOAEL for liver effects in rats was observed at 50 ppm in a chronic (12 months) experiment (Lee et al. 1977a) (see Figs. 2.1 and 2.3). However, since this was the lowest concentration tested, a chronic NAOEL could not be determined. After 12-month exposure, 100 ppm was a LOAEL and 10 ppm was a NOAEL for reduced terminal body weights in rats (Bi et al. 1985) (Fig. 2.1). Minimal risk levels are not estimated in Fig. 2.3 based on liver toxicity at the acute level of 1000 ppm, because this level was a frank effect level, and a NOAEL or LOAEL was not identified. A minimal risk level of 0.005 ppm for intermediate exposure is based on the LOAEL for liver effects observed in rats exposed intermittently to 10 ppm for 6 months (Bi et al. 1985). Data were not sufficient to estimate a minimal risk level for chronic exposure.

Developmental toxicity. In humans, increased incidence of fetal loss (Infante et al. 1976, Waxweiler et al. 1977) has been associated with occupational exposure to vinyl chloride, but exposures have not been quantified. Animal data identify a NOAEL for developmental toxicity in rabbits exposed intermittently to 2500 ppm on days 6 to 18 of gestation (John et al. 1977). The same study identifies intermittent exposure of mice at 50 ppm on days 6 to 15 of gestation as a NOAEL and similar exposure of rats at 2500 ppm as a LOAEL. A NOAEL for rats of 1500 ppm exposed intermittently on 10 days of gestation was identified from a study by Ungvary et al. (1978). The animal data are depicted in Figs. 2.1 and 2.3.

A minimal risk level of 0.7 ppm is estimated for acute exposure based on the NOAEL of 50 ppm for developmental toxicity in mice (John

et al. 1977). This NOAEL is comfortably below the NOAEL of 250 ppm for lethality in mice and below the frank effect level of 1000 ppm for hepatotoxicity in the acute phase of the Lee et al. (1977a) study.

Two studies indicating subtle effects at unusually low exposure levels (Mirkova et al. 1978, Sal'nikova and Kitsovskaya 1980) were insufficiently reported and judged to be inadequate for critical evaluation.

Reproductive toxicity. Two occupational studies associated effects on sexual and endocrinological function in men and women and on gynecological health in women with exposure to vinyl chloride (Makarov 1984, Makarov et al. 1984). Although exposure levels were estimated, the reports were inadequately reported for critical evaluation, and the data from these studies are not plotted on the graphs. Animal data are limited to a 1-year study in rats in which intermittent exposure to 100 ppm was a LOAEL for testicular effects and 10 ppm was a NOAEL (see Figs. 2.1 and 2.3).

Genotoxicity. Several studies reviewed in Sect. 4.3.5.1 on genotoxicity in humans demonstrate that vinyl chloride causes chromosomal aberrations in lymphocytes in occupationally exposed workers. The key study (Hansteen et al. 1978) identified a NOAEL of 1 ppm for this effect. Positive results were obtained in microorganisms in nonhuman systems, in the recessive lethal test in *Drosophila* and in other mammalian test systems (see Section 4.3.5.2 on genotoxicity in animals).

Carcinogenicity. Several epidemiology studies, many of which have been reviewed by EPA (1985b), associated occupational exposure to vinyl chloride with cancers of the liver, brain, lung, and possibly other sites. Concentrations of vinyl chloride in the workroom air were not measured. In the key studies used by EPA (1985b) to derive an inhalation potency factor (Maltoni et al. 1980, 1981), rats were exposed intermittently to 1 to 30,000 ppm for 52 weeks, and mice and hamsters were exposed to 50 to 30,000 ppm for 30 weeks followed by an observation period. Estimation of carcinogenic potency was based on the incidence of liver angiosarcomas in rats. A statistically significant increase in tumor incidence was observed in all three species at ≥50 ppm. Several other inhalation studies, reviewed in Sect. 4.3.6, Carcinogenicity, support the carcinogenicity of inhalation exposure to vinyl chloride. Studies by Suzuki (1981, 1983) appear to define intermittent exposure of mice to 10 ppm as a low level associated with increased incidence of lung cancer, although statistical analyses were not performed. Mice were exposed for 4 weeks followed by a 41-week observation period. The concentration of 50 ppm associated with cancer in rats and hamsters and the concentration of 10 ppm associated with lung cancer in mice are depicted in Figs. 2.1 and 2.3.

From the incidence of liver angiosarcomas in rats of both sexes in the Maltoni et al. (1980, 1981) experiments, and based upon the absorbed doses of vinyl chloride, a q_1^* of 2.95×10^{-1} $(mg/kg/day)^{-1}$ was estimated by EPA (1985b). Assuming humans breathe 20 m^3/day, absorb 50% of inhaled vinyl chloride, and weigh 70 kg each, estimated concentrations associated with cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and

10^{-7} are 9×10^{-4}, 9×10^{-5}, 9×10^{-6}, and 9×10^{-7} ppm, respectively (see Fig. 2.3).

2.2.1.2 Oral exposure

Lethality and decreased longevity. Oral lethality data are limited to an LD_{50} in rats of 500 mg/kg (Sax 1984), and an effect level of 1.3 mg/kg/day and a NOAEL of 0.13 mg/kg/day in a lifetime dietary study in rats (Dow Chemical Company 1984, Til et al. 1983) (see Figs. 2.2 and 2.4).

Systemic/target organ toxicity. Oral toxicity data were not located for humans. The liver appears to be the critical target organs for animals orally exposed to vinyl chloride. In a 13-week gavage study in rats, 300 mg/kg/day was a LOAEL and 30 mg/kg/day was a NOAEL for hepatotoxicity (Feron et al. 1975), (see Figs. 2.2 and 2.4). A minimal risk level of 0.30 mg/kg/day is estimated for intermittent oral exposure based on the NOAEL of 30 mg/kg/day (see Fig. 2.4). In a lifetime dietary study in rats (Dow Chemical Company 1984, Til et al. 1983), a LOAEL of 1.3 mg/kg/day and a NOAEL of 0.13 mg/kg/day for hepatotoxicity were identified (see Figs. 2.2 and 2.4). A minimal risk level for chronic oral exposure is estimated from the NOAEL of 0.13 mg/kg/day for hepatotoxicity because this dose is also a NOAEL for decreased longevity. The minimal risk level is -0.0013 mg/kg/day (see Fig. 2.4). Other effects observed in a lifetime dietary study in rats by Feron et al. (1981) include mild hematological changes at ≥14.1 mg/kg/day, but not at 5.0 mg/kg/day. These data are depicted in Fig. 2.2, but have no bearing on critical evaluation.

Developmental toxicity. Data were not located regarding developmental toxicity in orally exposed humans or animals.

Reproductive toxicity. Data were not located regarding reproductive toxicity in orally exposed humans or animals.

Genotoxicity. See Sect. 2.2.1.1 on genotoxicity associated with inhalation exposure.

Carcinogenicity. Data were not located regarding cancer in orally exposed humans. In the key lifetime dietary study in rats (Feron et al. 1981) used by EPA (1985a, 1987a) to derive a potency estimate for oral exposure, rats were fed diets that provided vinyl chloride at doses of 1.8, 5.6, or 17.0 mg/kg/day for lifetime. An increased incidence of neoplastic nodules of the liver and/or hepatocellular carcinoma, statistically significant, was observed at ≥1.8 mg/kg/day in females and at ≥5.6 mg/kg/day in males. The lower dose is depicted in Fig. 2.4 as the lowest dose in animals associated with cancer. EPA (1985a, 1987a) estimated cancer potency at 2.3 $(mg/kg/day)^{-1}$ based on the combined incidence of liver and lung tumors in both sexes of rats. Doses associated with excess cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} are plotted in Fig. 2.4.

2.2.1.3 Dermal exposure

Pertinent data regarding toxicity in humans or animals dermally exposed to vinyl chloride were not located in the available literature.

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

Biological monitoring for exposure to vinyl chloride has had limited success. In an early study, Baretta et al. (1969) attempted to correlate postexposure concentrations of vinyl chloride in exhaled air with exposure levels. Although there was a very close relationship between exposure levels ≥50 ppm and levels in expired air, the method does not appear to be useful at exposure concentrations <50 ppm. Methods have been devised to quantify vinyl chloride in urine (van Sittert and de Jong 1985) and tissue (Zuccato et al. 1979), but metabolism occurs so quickly that quantification of levels of unchanged compound in urine is not likely to reflect exposure levels, particularly at low concentrations.

More recently, biological monitoring has focused on correlating urinary levels of thiodiglycolic acid, the major urinary metabolite of vinyl chloride (Green and Hathway 1977), with exposure levels in the air (Heger et al. 1982). The results, presented in Fig. 2.5, suggest a reasonable correlation between exposure concentration and urinary output of thiodiglycolic acid. In reviewing these data, however, Tarkowski (1984) noted that a great deal of individual variation occurred, and the correlation was not strong enough to render this method reliable at exposure concentrations of <5 ppm. Tarkowski (1984) concluded that no reliable method exists for biological monitoring of exposure to vinyl chloride.

As indicated in Sect. 4.3.2.1, *Hepatotoxicity*, liver disease is probably the most common adverse effect associated with exposure to vinyl chloride. Generally, routinely performed biochemical screening and liver function screening tests have not been useful in monitoring the presence, severity, or progress of vinyl chloride disease (Lee et al. 1977b, Lilis et al. 1975). More recently, Doss et al. (1984) measured total urinary porphyrins and secondary urinary coproporphyrin in several patients with liver disease resulting from exposure to vinyl chloride. These investigators observed a correlation between slightly to moderately elevated total urinary porphyrin and the early stages of toxic liver disease. Particularly noted was a marked elevation in urinary coproporphyrin. In cases of chronic liver disease, total urinary porphyrin was markedly elevated to 3 to 6 times the upper normal limit, but coproporphyrin appeared to be elevated relatively less than was observed for acute toxicity. The investigators observed that elevated urinary coproporphyrin is a common clinical pathological finding in vinyl-chloride-related liver disease and may be useful in monitoring chronic exposure and progress of the clinical case.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

Levels of vinyl chloride in environmental media are typically low and, generally, are not likely to result in significant human exposure. The most important medium for human exposure is air. Atmospheric levels in most places are usually below the level of detection (Stephens et al. 1986; Grimsrud and Rasmussen 1975a,b; Harkov et al. 1984; Wallace et al. 1984; EPA 1985b). Levels from trace to 105 $\mu g/m^3$ (0.4 ppm) have been

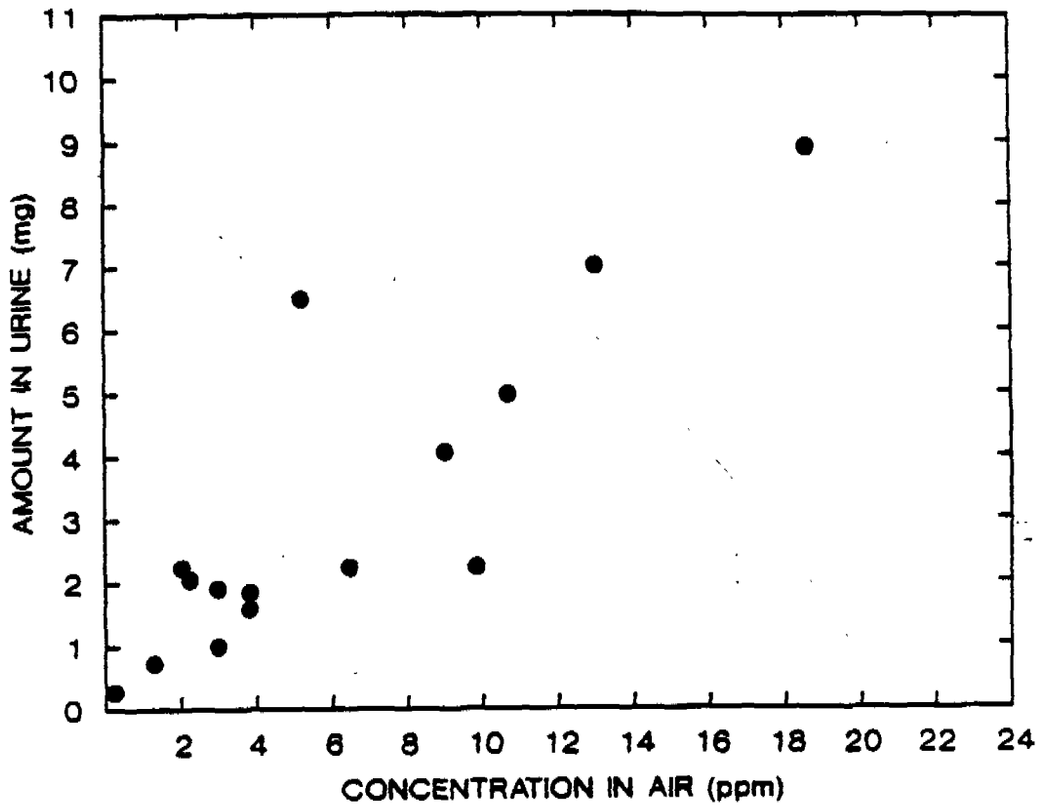


Fig. 2.5. Urinary output of thiodiglycolic acid from volunteers 12 h after exposure to vinyl chloride in air for 12 h. *Source:* **Tarkowski 1984.**

found near vinyl chloride production plants (Gordon and Meeks 1977, Pellizzari et al. 1979, IARC 1979, EPA 1985b), and levels have ranged from undetectable to 23.4 $\mu g/m^3$ (0.01 ppm) over landfills (Stephens et al. 1986, Baker and Mackay 1985). It is unlikely that levels in ambient air would result in significant exposure.

Several epidemiological studies associated occupational exposure with adverse health effects, including cancer; however, these studies (see Sect. 4, Toxicological Data) did not quantify exposure. A NIOSH survey of three vinyl chloride manufacturing plants reported a time-weighted average concentration of 0.18 to 69 mg/m^3 (0.07 to 27 ppm) in workplace air (Fishbein 1979). Concentrations in some plants were as high as 100 to 800 mg/m^3 (39 to 315 ppm) (Fishbein 1979). There seems little doubt that occupational exposure remains the most important source of exposure to vinyl chloride.

Levels in drinking water as high as 10 $\mu g/L$ have been detected (Dyksen and Hess 1982, HSDB 1987), but most monitoring studies have reported no detectable vinyl chloride in drinking water (HSDB 1987, Coniglio et al. 1980). Data were not located regarding the monitoring of vinyl chloride in soil, but exposure from contact with contaminated soil is likely to be negligible because dermal absorption is not considered significant (Hefner et al. 1975a).

In the past, vinyl chloride had been detected in various foods, as a result of migration from polyvinyl chloride food wrappings and containers (EPA 1985b). Currently, the FDA regulates the use of vinyl-chloride-containing polymers to maintain levels of vinyl chloride in food at ≤5 ppb. A recent report suggests that migration of vinyl chloride into food from polymers containing very low levels would be negligible, and that intake from food is expected to be negligible (Kontominas et al. 1985).

2.2.3.2 Human exposure potential

Monitoring data indicate that people living in the vicinity of vinyl chloride, PVC, or vinyl chloride copolymer manufacturers, or hazardous waste sites that contain vinyl chloride, would be exposed to this compound through inhalation of contaminated air, whereas people not living near these sources would be exposed to negligible levels. Locations of large industrial sources include, but are not limited to: Plaquemine, Louisiana; Houston, Texas; Lake Charles, Louisiana; Calvert City, Kentucky; Point Comfort, Texas; Oklahoma City, Oklahoma; Baton Rouge, Louisiana; Delaware City, Delaware; Pensacola, Florida; and Aberdeen, Massachusetts (CMR 1986a,b). The greatest likelihood for human inhalation exposure to vinyl chloride is occupational. NIOSH estimated that 27,000 workers are definitely exposed to vinyl chloride, and workers probably exposed may be as many as 2.2 million (Sittig 1985).

The level of vinyl chloride in drinking water is expected to be highest in areas where the raw water supplies are contaminated with vinyl chloride. The most probable source of surface water contamination is wastewater from vinyl chloride, PVC, and vinyl chloride copolymer manufacturers. The most probable sources of groundwater contamination are landfills. It has been shown that use of PVC pipes may result in leaching of vinyl chloride monomer into drinking water supplies;

however, the concentrations in drinking water that occur from these pipes are below those expected to cause adverse health effects.

2.3- ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic 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.

(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 section identifies data gaps in current knowledge relevant to developing levels of significant exposure for vinyl chloride. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for vinyl chloride, and for other areas, such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the adequacy of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for vinyl chloride will be developed by ATSDR, NTP, and EPA in the future.

2.3.2 Adequacy of the Database for Health Effect End Points

2.3.2.1 Introduction and graphic summary

The adequacy of the database for health effect end points in humans and animals is depicted in bar graphs in Figs. 2.6 and 2.7, respectively.

The bars of full height indicate that there are "adequate" data to meet at least one of the following conditions:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no-effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).

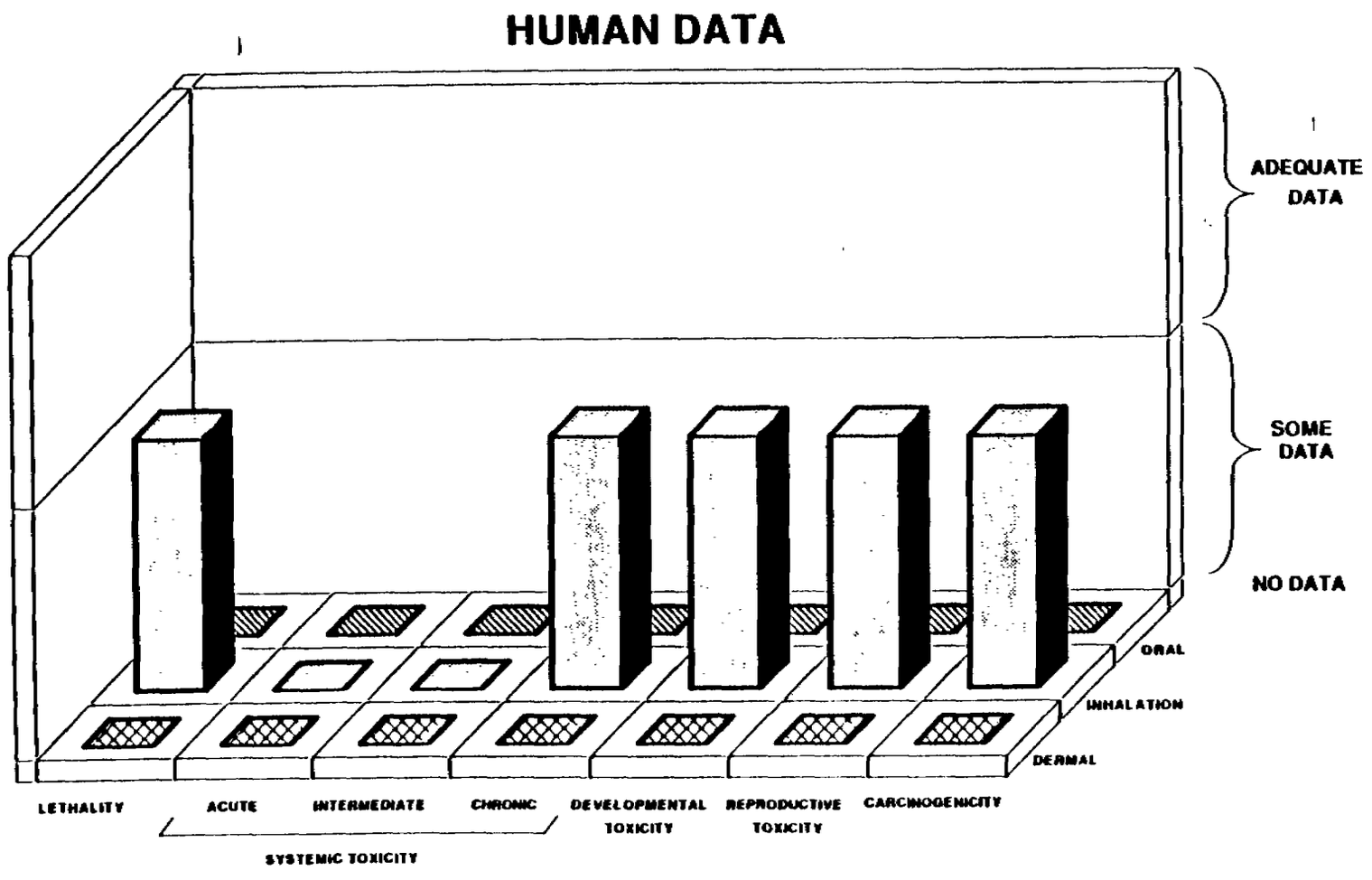


Fig. 2.6. Adequacy of the database on health effects of vinyl chloride (human data).

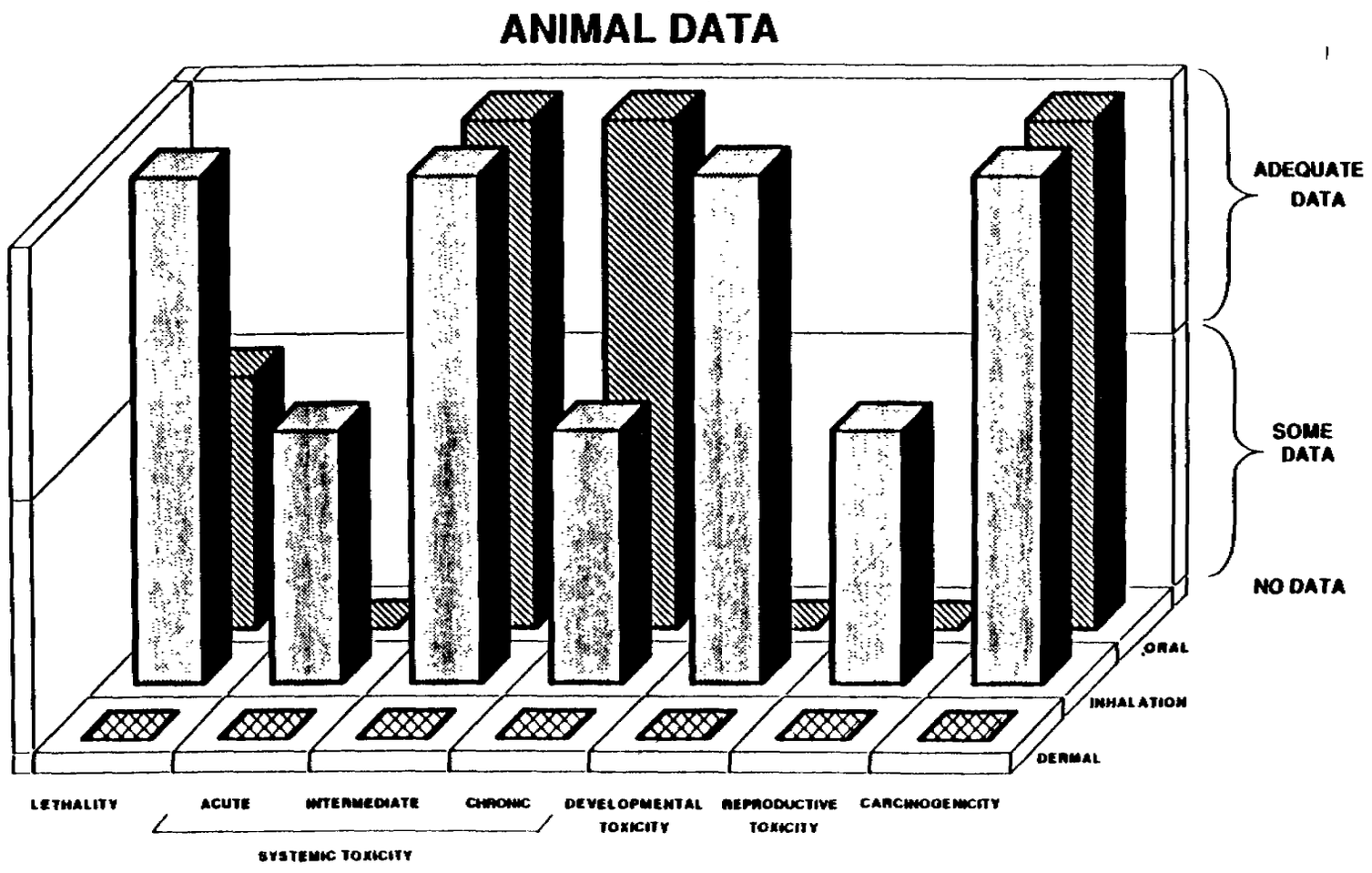


Fig. 2.7. Adequacy of the database on health effects of vinyl chloride (animal data).

2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the data are sufficient to derive a cancer potency factor.

4. There are studies that show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" data for the end point exist but do not meet any of the criteria for "adequate" data.

2.3.2.2 Descriptions of highlights of graphs

Figure 2.6 shows that human dose response data for oral and dermal exposure are lacking. Data are available that associate high inhalation levels of vinyl chloride with mortality in acute occupational exposure, but exposure levels were not quantified; therefore, the graphs indicate "some" but not "adequate" data. Data were not located for acute or intermediate inhalation exposure to vinyl chloride. Many epidemiological studies and case studies have characterized the syndrome known as vinyl chloride disease in occupationally exposed humans (see paragraph on vinyl chloride disease from inhalation exposure, human, in Sect. 4.3.2.3). There are also data implicating vinyl chloride as a cause of fetal loss (see Sect 4.3.3.1 on developmental toxicity from inhalation exposure, human). Because exposure levels were not quantified, the graphs for chronic toxicity and developmental toxicity indicate "some" data. Two studies suggest that occupational exposure interferes with normal sexual activity and compromises gynecological health (Makarov 1984, Makarov et al. 1984). These data are inadequately reported for critical evaluation, and consequently, the graph for reproductive toxicity indicates "some" data. Although vinyl chloride is clearly a human carcinogen based on occupational data (see Sect. 4.3.6.1 on carcinogenicity from inhalation exposure, human), exposures were not quantified, and the data are classified as "some."

The lack of dermal data is not problematical since dermal absorption of vinyl chloride vapor is expected to be insignificant compared with inhalation absorption (Hefner et al. 1975a). Although there is a lack of oral data in humans, data in relevant animal models are sufficient to estimate significant levels of exposure for intermediate and chronic oral exposure. Deficiencies in the human inhalation toxicity data are somewhat more noteworthy because animal data are sufficient for estimating a minimal risk level for intermediate duration but not for chronic inhalation exposure.

From Fig. 2.7, it is apparent that the database for inhalation exposure in animals is more extensive than for humans. Inhalation data for acute lethality, intermediate duration toxicity, developmental toxicity, and carcinogenicity are sufficient for critical evaluation and are defined as "adequate." Inhalation data for chronic systemic toxicity

are inadequate for defining a range of toxicity and, therefore, are graphically depicted as "some."

The oral database is more nearly complete. Data "adequate" for risk assessment are available for intermediate and chronic toxicity and carcinogenicity. However, acute lethality data, limited to an LD_{50} in rats (Sax 1984), were judged to be "some." Data were lacking for acute systemic, developmental, and reproductive toxicity. Since oral exposure is possible, the data gap regarding developmental and reproductive toxicity should be filled.

2.3.2.3 Summary of relevant ongoing research

Peter Foiles at the American Health Foundation in New York City will conduct a study sponsored by the National Cancer Institute to develop monoclonal antibodies that will aid in the detection of cyclic DNA adducts in humans exposed to environmental carcinogens. The study may contribute to our knowledge of adducts that are formed in humans from vinyl chloride exposure and the role these adducts play in human carcinogenesis (NTIS 1987).

Peter Guengerich at the Department of Biochemistry at Vanderbilt University in Nashville, Tennessee, will investigate the bioactivation and covalent binding of metabolites of vinyl halides, including vinyl chloride. This work, sponsored by the National Institute of Environmental Health Sciences, may contribute to our understanding of the impact of specific enzymes in the liver and other organs to the toxification and detoxification of vinyl chloride (NTIS 1987).

D.P. Brown at NIOSH in Cincinnati, Ohio, is updating cohort mortality studies on several chemicals and mixtures, including vinyl chloride. It is hoped that the updated studies may provide sufficient statistical analyses to provide more definitive information regarding the association of vinyl chloride with various types of cancer (NTIS 1987).

J.R. Giacin at Michigan State University has been investigating the migration of monomers in plastics into food stimulants. This project, sponsored by the U.S. Department of Agriculture, may allow more accurate estimation of the exposure of the population to vinyl chloride from foods packaged in plastic (NTIS 1987).

2.3.3 Adequacy of the Database for Other Information Needed for Risk Assessment

2.3.3.1 Pharmacokinetics and mechanisms of action

The pharmacokinetics of vinyl chloride in humans exposed by inhalation is relatively well understood, but little is known of oral and dermal pharmacokinetics. The gap in human pharmacokinetic knowledge is not a concern because the pharmacokinetics of oral vinyl chloride in relevant animal models is well understood, and dermal exposure is not likely to be significant. Metabolism to an epoxide and an aldehyde provides reactive intermediates thought to be responsible for the carcinogenicity and probably the hepatotoxicity of the compound in

animals and humans. Further understanding of the mechanism of action on other systems, such as the CNS, could be gained.

2.3.3.2 Monitoring of human biological samples

The most practical biological monitoring procedure appears to be quantification of urinary output of thiodiglycolic acid, the predominant urinary metabolite of vinyl chloride (Heger et al. 1982). Individual variation, however, renders this method unreliable at exposure concentrations <5 ppm (Tarkowski 1984).

2.3.3.3 Environmental considerations

Limited data are available regarding the vinyl chloride levels in foodstuffs. Monitoring data on levels of vinyl chloride in food contained in PVC packaging materials are needed. Intake of vinyl chloride by ingestion of contaminated food was assumed to be negligible, based on strict FDA regulations and one laboratory study (Kontominas et al. 1985) that simulated actual food packaging and food storage conditions. This assumption should be verified with monitoring data.

Data on the amount of leaching of vinyl chloride from rigid PVC water pipes into drinking water need to be obtained. Monitoring data alone cannot reveal the extent of the leaching problem, because monitoring data frequently reflect levels in drinking water supplies before transport through PVC distribution systems.

Limited data are available on the persistence of vinyl chloride in the environment, particularly in surface waters, soil, and groundwater. Although a half-life for vinyl chloride in surface water has been estimated, significant uncertainty exists. Due to lack of data, it was not possible to estimate a half-life for vinyl chloride in soil or groundwater.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of vinyl chloride are listed in Table 3.1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of vinyl chloride are presented in Table 3.2.

Table 3.1. Chemical identity of vinyl chloride

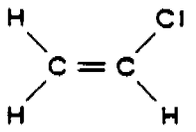
Parameter	Value	References
Chemical name	Chloroethene	SANSS 1987
Synonyms and trade names	Vinyl chloride, chloroethylene, ethylene monochloride, monochloroethylene, VC, VCM, vinyl C monomer	SANSS 1987
Chemical formula	C_2H_3Cl	HSDB 1987
Wiswesser line notation	G1U1	HSDB 1987
Chemical structure		
Identification numbers		
CAS Registry No.	75-01-4	HSDB 1987
NIOSH RTECS No.	KU9625000	HSDB 1987
EPA Hazardous Waste No.	U043	HSDB 1987
OHM-TADS No.	7216947	HSDB 1987
DOT/UN/NA/IMCO Shipping No.	1086	HSDB 1987
STCC No.	49 057 92	HSDB 1987
Hazardous Substances Data Bank No.	169	HSDB 1987
National Cancer Institute No.	None available	

Table 3.2. Physical and chemical properties of vinyl chloride

Property	Value	References
Molecular weight	62.5	Cowfer and Magistro 1983
Color	Colorless	Cowfer and Magistro 1983
Physical state	Gas	Cowfer and Magistro 1983
Odor	Mild, sweet	Verschueren 1983
Odor threshold		
Water	3.4 ppm (w/v)	Amoore and Hautula 1983
Air	3000 ppm (v/v)	Amoore and Hautula 1983
Melting point	−153.8°C	Cowfer and Magistro 1983
Boiling point	−13.4°C	Cowfer and Magistro 1983
Autoignition temperature	472°C	Cowfer and Magistro 1983
Solubility		
Water	2763 mg/L at 25°C	EPA 1985b
	1100 mg/L at 25°C	Cowfer and Magistro 1983
Organic solvents	Soluble in hydrocarbons, oil, alcohol, chlorinated solvents, and most common organic liquids	Cowfer and Magistro 1983
Density, g/cm^3	0.969 (−14.2°C)	Cowfer and Magistro 1983
Vapor density (air = 1)	2.15	Verschueren 1983
Log octanol-water partition coefficients	1.36	EPA 1987b
Vapor pressure	2660 mm Hg at 25°C	Verschueren 1983
Henry's Law constant	1.2 (atm-m^3)/mol at 10°C	EPA 1985b
Refractive index	1.3700 at 20°C	EPA 1985b
Flashpoint	−77.75 (open cup)	Cowfer and Magistro 1983
Flammability limits	4–22 vol %	Cowfer and Magistro 1983
Conversion factors		
ppm (v/v) to mg/m^3 in air	ppm (v/v) = 2.60 mg/m^3	
mg/m^3 to ppm (v/v) in air	mg/m^3 = 0.39 ppm (v/v)	
ppm (w/v) to mg/L in water	ppm (w/v) = mg/L = μg/mL	
ppm (w/w) to mg/kg in solid matrices	ppm (w/w) = mg/kg = μg/g	

4. TOXICOLOGICAL DATA

4.1 OVERVIEW

Much of the data summarized in this section is reviewed in two recent EPA documents (EPA 1985a,b). Respiratory and gastrointestinal absorption of vinyl chloride appears to be rapid. Humans retain ~42% of vinyl chloride inhaled at concentrations of 3 to 24 ppm. Animal studies suggest that gastrointestinal absorption is nearly complete. Dermal absorption of vinyl chloride vapors is not likely to result in toxicity. Distribution of absorbed vinyl chloride may be widespread, with highest levels of parent compound located in fat; but metabolism and excretion occur so rapidly that highest levels of excretory products are located in the liver and kidney, the primary organs of metabolism and excretion.

Regardless of the route of administration, inhalation or oral, metabolism proceeds via oxidation and subsequent conjugation with sulfhydryl groups. An important oxidative pathway involves mixed-function oxidase and results in reactive electrophilic intermediates, 2-chloroethylene oxide and 2-chloroacetaldehyde, which bind to liver macromolecules and may be responsible for the toxicity and oncogenicity associated with vinyl chloride. Excretion of polar metabolites is predominantly through the urine; when metabolic pathways are saturated, substantial amounts of unmetabolized vinyl chloride are exhaled.

At sublethal doses, the liver is the primary target organ for carcinogenic and noncarcinogenic effects of vinyl chloride in humans and animals. The significant feature of the toxicity of vinyl chloride is its carcinogenicity. In occupationally exposed humans and in animals exposed orally or by inhalation, an increased incidence of liver, lung, and brain tumors, and possibly other types of tumors, can be attributed to vinyl chloride. Other symptoms in occupationally exposed humans are collectively termed "vinyl chloride disease," and include acroosteolysis, circulatory disturbance in the extremities, Raynaud syndrome, scleroderma, hematological effects, and effects on the lungs, as well as effects on the liver. No counterpart of the human disease has been produced in experimental animals.

Wives of men occupationally exposed to vinyl chloride have suffered a greater number of miscarriages than wives of men otherwise employed. In occupationally exposed humans, vinyl chloride is genotoxic. This effect is associated with an increase in chromosomal aberrations in peripheral lymphocytes, and it appears to be reversible when exposures are reduced to ≤1 ppm. Vinyl chloride is mutagenic in a number of microbial and other test systems. Electrophilic metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been shown to bind to macromolecules. 2-Chloroethylene oxide forms adducts with DNA. These mechanisms may explain the toxicity and carcinogenicity of vinyl chloride.

4.2 TOXICOKINETICS

4.2.1 Absorption

4.2.1.1 Inhalation

Human. Krajewski et al. (1980) exposed young male volunteers to vinyl chloride monomer concentrations of 7.5 to 60 mg/m^3 (3 to 24 ppm) by gas mask for 6 h. By measuring the difference between inhaled and exhaled concentrations, an average retention of 42% was estimated. Although the results varied among the individuals tested, the percentage retained appeared to be independent of the concentration inhaled.

Animal. Animal data, while demonstrating that inhalation absorption of vinyl chloride occurs readily and rapidly, are not sufficient to quantitatively determine the proportion of an inhaled dose that is absorbed. Withey (1976) determined that peak blood levels occurred at 30 min in rats exposed head only to 7000 ppm. Bolt et al. (1977) placed rats that had been pretreated with 6-nitro-1,2,3-benzothiadiazole to completely block the metabolism of vinyl chloride in a closed chamber containing 0.4 to 0.5 ppm ^{14}C-vinyl chloride. Radioactivity in the chamber air declined only for the first 15 min of exposure, indicating that equilibrium between atmospheric and tissue levels of radioactivity had occurred, suggesting rapid uptake by the tissues of the rats.

4.2.1.2 Oral

Human. Data regarding the oral absorption of vinyl chloride by humans were not located.

Animal. Several studies in rats indicate that vinyl chloride is rapidly and probably completely absorbed from the gastrointestinal tract. Withey (1976) administered single 10 mL (44 to 92 mg/kg) oral doses of vinyl chloride in aqueous solution and observed that blood levels of vinyl chloride peaked in 10 to 20 min. Watanabe et al. (1976a) administered single gavage doses of 0.05, 1, and 100 mg/kg ^{14}C-vinyl chloride in corn oil and measured the amount of radioactivity excreted in expired air, urine, and feces, as well as the amount retained in the carcass, at 72 h. The fraction of the administered dose recovered in the feces, roughly indicative of the proportion unabsorbed, ranged from 0.47 to 2.39%, suggesting that absorption was nearly complete. Total recovery, however, ranged from 82.3 to 91.3%, suggesting substantial loss of radioactivity. Feron et al. (1981) provided rats with diets containing nominally 20, 60, or 200 ppm vinyl chloride monomer (from powdered polyvinyl chloride containing a high level of the monomer) for 4 h and measured the fecal excretion of vinyl chloride over 23 h from the start of the feeding period. Fecal excretion accounted for 8, 10, and 17% of the vinyl chloride present in the low, middle, and high diets, respectively. The investigators hypothesized that the vinyl chloride recovered from the feces was encapsulated by polyvinyl chloride and was not available to the rats for absorption, and that absorption of available vinyl chloride was virtually complete.

4.2.1.3 Dermal

Human. Data regarding the dermal absorption of vinyl chloride by humans were not located.

Animal. Animal data suggest that dermal absorption of vinyl chloride gas is not likely to be significant. Hefner et al. (1975a) placed all but the heads of two anesthetized rhesus monkeys in chambers containing 800 or 7000 ppm ^{14}C-vinyl chloride for 2.5 or 2 h, respectively, to measure the uptake of radioactivity. On the basis of vinyl chloride measured in expired air and radioactivity measured in selected tissues, the investigators estimated dermal absorption of 0.031 and 0.023% of the available vinyl chloride at 800 and 7000 ppm, respectively. The investigators concluded that dermal absorption was far less significant than inhalation absorption.

4.2.2 Distribution

4.2.2.1 Inhalation

Human. Data regarding the distribution of vinyl chloride in the tissues of humans exposed by inhalation were not located.

Animal. Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread but depends on metabolism. Buchter et al. (1977) exposed rats to ^{14}C-vinyl chloride to determine tissue distribution of radioactivity. In rats pretreated with 6-nitro-1,2,3-benzothiadiazole to block metabolism of vinyl chloride, the highest levels of radioactivity 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 radioactive metabolites were located in the liver and kidney. At 10 min after a 5-min exposure of rats to 20,000 ppm ^{14}C-vinyl chloride, Duprat et al. (1977) detected radioactivity in the liver, bile duct, digestive tract, and kidney. At 3 h after the exposure described above, radioactivity was also detected in the urinary tract, salivary and lacrimal glands, thymus, and skin. Immediately after a 5-h exposure to ^{14}C-vinyl chloride at 50 ppm, tissue levels of radioactivity, expressed as percent 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). Watanabe et al. (1976b) exposed rats to 10 or 100 ppm ^{14}C-vinyl chloride for 6 h and measured radioactivity in tissues 72 h later. In order of decreasing concentration, radioactivity (present as nonvolatile metabolites) was detected in the liver, kidney, skin, lung, muscle, carcass, plasma, and fat.

4.2.2.2 Oral

Human. Data regarding the tissue distribution of vinyl chloride in orally exposed humans were not located.

Animal. Watanabe et al. (1976a) measured the level of radioactivity present as nonvolatile metabolites in tissues of rats 72 h after single 0.05 to 100-mg/kg gavage doses of ^{14}C-vinyl chloride in corn oil. Highest levels occurred in the liver, ~2 to 5 times higher than in the other tissues examined (skin, plasma, muscle, lung, fat, and carcass).

4.2.2.3 Dermal

Data regarding the distribution of vinyl chloride following dermal exposure of humans or experimental animals were not located.

4.2.3 Metabolism

4.2.3.1 Inhalation

Human. In the only human data located, Sabadie et al. (1980) examined the ability of aryl hydrocarbon hydroxylase in the S-9 fraction from surgically obtained liver specimens to metabolize vinyl chloride to electrophiles mutagenic to *Salmonella typhimurium* TA1530. The number of revertants per plate were compared with that 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, but a 9-fold individual variation was observed.

Animal. Hefner et al. (1975b) exposed rats to vinyl chloride in a closed chamber at concentrations of ~50 to 1000 ppm for 52.5 to 356.3 min. 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, appeared to follow first-order kinetics with a half-life of 86 min at <100 ppm. At >220 ppm, metabolism was slowed to a half-life of 261 min, suggesting saturation of the pathway predominant at <100 ppm. Pretreatment with ethanol depressed the rate of metabolism >83% at <100 ppm but <47% at >1000 ppm. Pretreatment with SKF 525-A, however, had no effect at <100 ppm but depressed metabolism 19% at >1000 ppm. The authors postulated three alternative pathways for metabolism, as depicted in Fig. 4.1. 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 may have been oxidized by catalase in the presence of hydrogen peroxide (H_2O_2) to a peroxide, which may have undergone subsequent dehydration to form 2-chloroacetaldehyde. An alternative pathway may have involved oxidation by mixed-function oxidase to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranged to form 2-chloroacetaldehyde. Hefner et al. (1975b) reported urinary excretion of polar metabolites and 2-chloroacetic acid by rats exposed by inhalation.

Other animal data expand the hypotheses of Hefner et al. (1975b). Hultmark et al. (1979) used an in vitro technique to determine that metabolism was NADPH-dependent, located in the microsomal fraction of the liver, and probably involved mixed-function oxidase. Bolt et al. (1977) reported that pretreatment with 6-nitro-1,2,3-benzothiadiazole was sufficient to totally block metabolism of vinyl chloride in rats

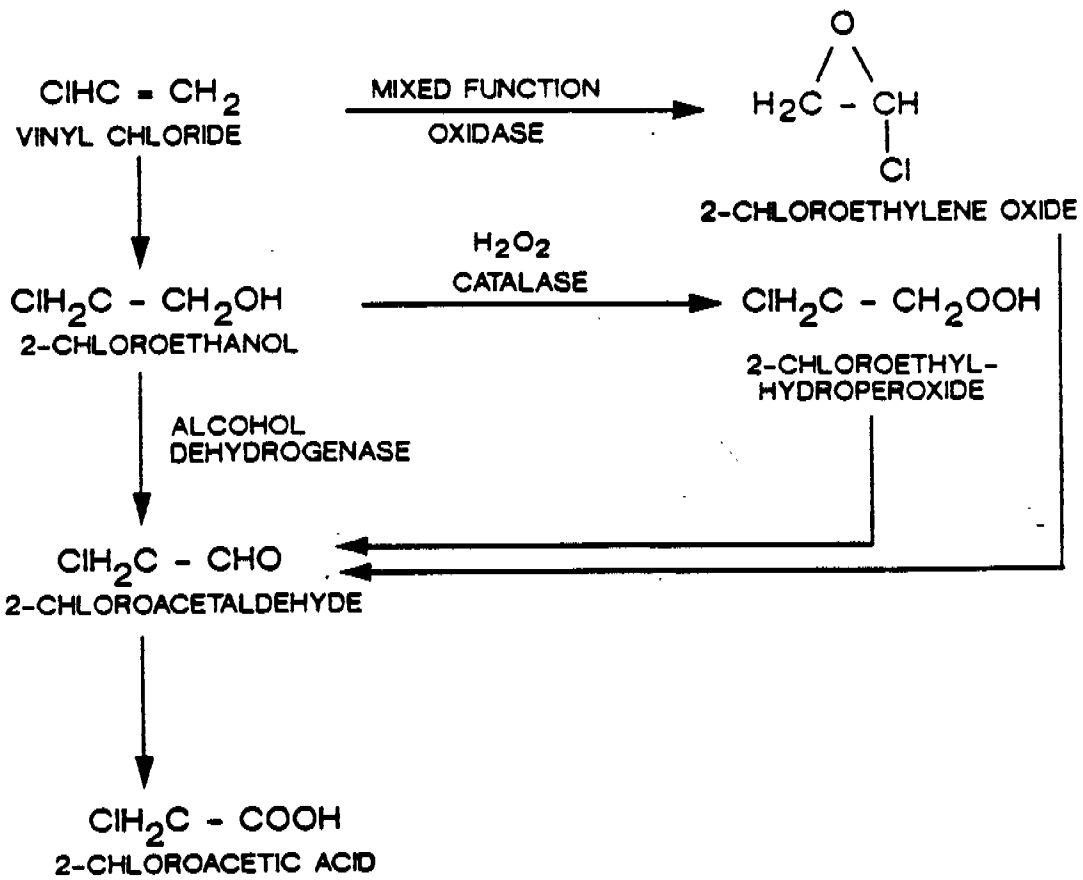


Fig. 4.1. Proposed metabolic pathways for vinyl chloride.

exposed to ~0.45 ppm in a closed system for 5 h. Bolt et al. (1977) and Bolt (1986) interpreted this observation to strongly suggest that metabolism of vinyl chloride proceeds primarily through a mixed-function oxidase pathway with likely production of an epoxide intermediate, because 6-nitro-1,2,3-benzothiadiazole is known to inhibit some microsomal cytochrome P-450 oxidation pathways. Bolt et al. (1977) and Filser and Bolt (1979) exposed rats in a closed system to 100 or 1000 ppm ^{14}C-vinyl chloride. By measuring the disappearance of radioactivity with time, they determined 250 ppm to be the threshold at which saturation of metabolic pathways occurs. A metabolic rate (V_{max}) of 110 μmol/h/kg was estimated for rats. In a similar experiment in rhesus monkeys, metabolic saturation was observed to occur at 200 ppm, with a V_{max} of 50 μmol/h/kg (Buchter et al. 1980). The V_{max} of 50 μmol/h/kg was suggested as a closer approximation of metabolism in humans than the value of 110 μmol/h/kg estimated for rats by Filser and Bolt (1979).

Inhalation exposure has been associated with reduction in liver nonprotein sulfhydryl concentration in the rat (Hefner et al. 1975b, Bolt et al. 1976b), particularly at exposure concentrations >100 ppm (Watanabe et al. 1978a, Jedrychowski et al. 1984). Urinary metabolites identified in rats exposed by inhalation include polar compounds resulting from conjugation with sulfhydryl groups at low exposure concentrations (Watanabe et al. 1976b, Hefner et al. 1975b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al. 1975b).

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 (Kappus et al. 1976; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Watanabe et al. 1978a,b). 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 may bind to DNA and RNA, and to its rearrangement product, 2-chloroacetaldehyde, which may bind to protein molecules (Guengerich et al. 1979, 1981; Guengerich and Watanabe 1979; Watanabe et al. 1978a,b; Kappus et al. 1976; Bolt 1986).

4.2.3.2 Oral

Human. Data regarding the metabolism of vinyl chloride by orally exposed humans were not located.

Animal. Urinary metabolites identified from rats orally exposed to ^{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, N-acetyl-S-(2-chloroethyl)cysteine, 2-chloroacetic acid, thiodiglycolic acid, and glutamic acid (Watanabe et al. 1976a; Watanabe and Gehring 1976; Green and Hathway 1975, 1977). Metabolic saturation appears to occur with a single gavage dose of >1 and <100 mg/kg/day (Watanabe et al. 1976a).

4.2.3.3 Dermal

Data regarding metabolism in humans or animals dermally exposed to vinyl chloride were not located.

4.2.4 Excretion

4.2.4.1 Inhalation

Human. Human data suggest that exhalation of unmetabolized vinyl chloride is not an important pathway of elimination at low exposure concentrations. Krajewski et al. (1980) exposed humans to air containing 7.5 to 60 mg/m^3 for 6 h and measured the mean concentration in expired air for 30 min at termination of exposure. Mean concentrations in expired air ranged from undetectable to 2.84 mg/m^3, representing up to 3.60 to 4.73% of the inhaled concentration.

In a study available as a brief abstract, Shu et al. (1986) reported that urinary concentration of thiodiglycolic acid increased with increasing air concentration of vinyl chloride in an occupational setting. Urinary concentrations of thiodiglycolic acid peaked within 20 h. The investigators suggested that daily urinary output of thiodiglycolic acid might be a satisfactory biological index of exposure to vinyl chloride.

Animal. 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 discussed in Sect. 4.2.3.1, in the subsection on metabolism in animals after inhalation exposure. The cumulative excretion of radioactivity over a 72-h postexposure period was measured in rats exposed to 10 or 1000 ppm (Watanabe and Gehring 1976, Watanabe et al. 1976b) or 5000 ppm (Watanabe et al. 1978b) ^{14}C-vinyl chloride for 6 h. Radioactivity expired as CO_2 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 presented in Table 4.1 suggest that metabolism was nearly complete at 10 ppm, because <2% of the recovered radioactivity occurred as unchanged parent compound. The predominant route for excretion of radioactive metabolites was through the urine, accounting for ~70% of the recovered radioactivity. Metabolism appeared to be saturated at 1000 ppm, since unchanged vinyl chloride increased to 12.3% and urinary radioactivity decreased to 56.3%. At 5000 ppm, more than half the recovered radioactivity appeared as unchanged vinyl chloride, and urinary excretion accounted for ~27% of the recovered activity. Generally, there was little change in the proportion of recovered radioactivity excreted in the feces or exhaled as CO_2. The percentage of the radioactivity retained in the carcass and tissues appeared to be somewhat decreased at 5000 ppm compared with 10 and 1000 ppm, suggesting preferential retention of metabolites rather than unchanged vinyl chloride.

Pulmonary excretion of unaltered vinyl chloride appeared to follow first-order kinetics regardless of exposure concentrations, with half-lives of 20.4, 22.4, and 30 min at 10, 1000, and 5000 ppm. The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for <3% of the total urinary excretion. Half-lives for the

Table 4.1. Excretion of radioactivity in rats exposed to ^{14}C-vinyl chloride in air for 6 h

	Radioactivity expressed as percent of total recovered		
	Exposure concentration (ppm)		
	10	1000	5000
Expired vinyl chloride	1.61	12.26	54.5
Expired CO_2	12.09	12.30	8.0
Urine	67.97	56.29	27.1
Feces	4.45	4.21	3.2
Carcass and tissues	13.84	14.48	7.3

Source: Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978b.

rapid (first-order) phase were estimated at 4.6, 4.1, and 4.5 h, respectively. Urinary metabolites included N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly S-(2-hydroxyethyl)cysteine.

4.2.4.2 Oral

Human. Data regarding the excretion of vinyl chloride by orally exposed humans were not located.

Animal. In experiments in the United States (Watanabe et al. 1976a, Watanabe and Gehring 1976) and Great Britain (Green and Hathway 1975), which studied the similarities of pharmacokinetics following inhalation and oral exposure, single oral doses of ^{14}C-vinyl chloride were administered to rats, and the excretion of radioactivity was monitored over a 72-h period. Details are presented in Table 4.2. A striking increase in exhalation of unchanged vinyl chloride and compensatory decreases in urinary and fecal excretion of radioactivity and exhalation of CO_2 were observed at ≥20 mg/kg, suggesting that metabolic saturation had occurred at that dosage. At ≤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 to 4 h, but excretion of metabolites continued for days (Green and Hathway 1975). Pulmonary excretion of vinyl chloride appeared to be monophasic at ≤1.0 mg/kg, with a half-life of ~55 to 58 min (Watanabe et al. 1976a). At 100 mg/kg, pulmonary excretion of vinyl chloride was biphasic, with half-lives of 14.4 and 40.8 min for the rapid and slower phases, respectively. Urinary excretion of radioactivity was biphasic, with the rapid phase accounting for >97% of total urinary radioactivity and having half-lives of 4.5 to 4.6 h for dosages of 0.05 to 100 mg/kg.

Metabolites identified in the urine of orally treated rats were consistent with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Watanabe et al. 1976a, Green and Hathway 1977), as postulated for metabolism following inhalation exposure. The major metabolite was identified as thiodiglycolic acid; nearly equivalent amounts of N-acetyl-S-(2-hydroxyethyl)cysteine were identified (Watanabe et al. 1976a, Green and Hathway 1975). Smaller amounts of radiolabeled S-(2-chloroethyl)cysteine, urea, glutamic acid, and 2-chloroacetic acid were also identified (Green and Hathway 1975).

4.2.4.3 Dermal

Data regarding the metabolism of vinyl chloride following dermal exposure of humans or animals were not located.

4.2.4.4 Parenteral

Human. Data regarding the metabolism of parenterally administered vinyl chloride in humans were not located.

Animal. The elimination of radioactivity following intraperitoneal administration of ^{14}C-vinyl chloride to rats resembles the pattern observed following inhalation and oral administration. Following an intraperitoneal dose of 0.25 mg/kg, exhalation of unchanged vinyl

Table 4.2. Percent of administered dose of radioactivity excreted 72 h following a single oral dose of ^{14}C-vinyl chloride in rats

	Dose (mg/kg)					
	0.05[a]	0.25[b]	1.0[a]	20[a]	100[a]	450[b]
Expired						
As vinyl chloride	1.43	3.7	2.13	41.6	66.64	91.9
As CO_2	8.96	13.5	13.26	4.8	2.52	0.7
Urine	68.34	75.1	59.30	22.6	10.84	5.4
Feces	2.39	4.6	2.20	1.0	0.47	0.7
Carcass	10.13	NR[c]	11.10	11.0	1.83	NR
Total	91.25	96.9	88.83	81.0	82.30	98.7

[a]Watanabe and Gehring 1976, Watanabe et al. 1976a.
[b]Green and Hathaway 1975.
[c]Not reported.

chloride, exhalation of CO_2, 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, CO_2 decreased to 0.7%, urinary radioactivity decreased to 2.6%, and fecal radioactivity remained unchanged.

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 intravenously to rats and recovered 80% of the dose within 2 min and 99% within 1 h as unchanged compound from expired air.

4.3 TOXICITY

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Inhalation

Human. ACGIH (1986a) and EPA (1985a) reviewed early reports of acute toxicity at high levels resulting in lethality among occupationally exposed workers. Deaths appeared to be due to narcosis. Exposure levels were not reported, and an LC_{LO} cannot be identified.

Animal. Patty et al. (1930) reported that narcosis and death occurred within 30 to 60 min in guinea pigs exposed to 10% vinyl chloride (100,000 ppm). EPA (1985a) reviewed a number of acute studies in animals and reported 2-h LC_{50} values ranging from 117 to 500 ppm for mice to 230 to 800 ppm for rabbits. Mastromatteo et al. (1960) exposed rats, mice, and guinea pigs (five per sex per group) to 10, 20, 30, or 40% (guinea pigs only) vinyl chloride in air (100,000, 200,000, 300,000, or 400,000 ppm) for 30 min. One guinea pig exposed to 40% died; all mice, rats, and one guinea pig exposed to 30% died; one mouse but no rats or guinea pigs exposed to 20% died.

Long-term studies in rats and mice associate intermittent exposure to 50 ppm with decreased longevity. Lee et al. (1977a, 1978) exposed rats and mice (36 per sex per species) to 0, 50, 250, or 1000 ppm, 6 h/day, 5 days/week for up to 12 months. Acute lethality associated with toxic hepatitis and tubular necrosis of the renal cortex occurred in mice after 5 to 9 days at 1000 ppm. Shortened life span attributed to noncarcinogenic effects of vinyl chloride occurred in all exposed groups of both species. In a subsequent study, Hong et al. (1981) exposed mice (8 to 28 per sex per group) and rats (4 to 16 per sex per group) to 0, 50, 250, or 1000 ppm, 6 h/day, 5 days/week for up to 6 months (mice) or 10 months (rats), followed by a 12-month observation period. A concentration- and duration of exposure-related decrease in longevity was observed in both species at all exposure concentrations, which was attributed to a combination of systemic toxicity and tumor development.

4.3.1.2 Oral

Human. Data regarding reduced longevity in humans orally exposed to vinyl chloride were not located.

Animal. Sax (1984) reported an oral LD_{50} in rats of 500 mg/kg. The key lifetime oral study is that submitted by Dow Chemical Company (1984) and Til et al. (1983), in which male and female Wistar rats were fed diets containing polyvinyl chloride with a high level of the monomer. Dietary intakes of vinyl chloride monomer were estimated at 0, 0.014, 0.13, and 1.3 mg/kg/day. Groups consisted of 100 rats per sex except for the high group, which contained 50 rats per sex. Mortality was slightly but significantly increased in high-group rats, starting at 68 weeks of treatment. No effects on longevity were observed at ≤0.13 mg/kg/day, which is considered the NOAEL for decreased survival.

An earlier lifetime study in rats from this laboratory (Feron et al. 1981) supports the NOAEL for reduced survival of 0.13 mg/kg/day. In this experiment, diets containing polyvinyl chloride with high levels of vinyl chloride monomer provided intakes of 0, 1.7, 5.0, or 14.1 mg/kg/day. A marked and statistically significant increase in mortality occurred at ≥5.0 mg/kg/day. Females at 1.7 mg/kg/day had a slight but not statistically significant increase in mortality.

4.3.1.3 Dermal

Data regarding lethality or reduced longevity in dermally exposed humans or animals were not located in the available literature.

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Hepatotoxicity

Inhalation, human. Several epidemiologic studies have associated occupational exposure with impaired liver function and/or biochemical or histological evidence of liver damage (Berk 1976, Buchancova et al. 1985, Gedigk et al. 1975, Marsteller et al. 1975, Popper and Thomas 1975, Doss et al. 1984, Lee et al. 1977b, Tamburro 1984, Tamburro et al. 1984). Several of these studies have been reviewed by EPA (1985a,b). Thresholds for hepatotoxicity cannot be identified, because data regarding exposure concentrations and duration were not available.

Inhalation, animal. In the Lee et al. (1977a) study described in Sect. 4.3.1.1, in the subsection on lethality and decreased longevity in animals after inhalation exposure, acute hepatotoxicity was observed in mice dying after intermittent exposure to 1000 ppm vinyl chloride for 5 to 9 days.

In an intermediate-length animal inhalation study (Torkelson et al. 1961), several species were exposed intermittently for up to 6 months, as detailed in Table 4.3. Air-exposed controls were maintained. Parameters of liver toxicity evaluated included gross and histopathologic examination, measurement of relative organ weights, and determination of serum levels of enzymes associated with liver damage. Biochemical parameters of liver status were within normal limits at all exposure concentrations, but histopathologic lesions occurred in rats exposed to 500 ppm and in rabbits exposed to 200 ppm. Elevated relative liver weights appeared to be the most sensitive indicator of hepatotoxicity and were observed in rats at 100 ppm, 7 h/day, but not at 50 ppm by the same schedule. In a study designed primarily to evaluate effects on the testis (see Sect. 4.3.4.1, in the subsection on

Table 4.3. Experimental protocol for animal exposure to vinyl chloride

Species	Number of animals/group		Dose of vinyl chloride (ppm)	Exposure schedule[a] (hours/day)	Exposure duration (months)
	Males	Females			
Rats	10	10	500	7	4.5
	20–24	24	50, 100, or 200	7	6
	5	0	100 or 200	0.5, 1, 2, or 4	6
	10	0	50	1, 2, or 4	6
Guinea pigs	10–12	8–12	50, 100, or 200	7	6
Rabbits	3	3	50, 100, or 200	7	6
Dogs	1	1	50, 100, or 200	7	6

[a] All animals were exposed 5 days/week.
Source: Torkelson et al. 1961.

reproductive toxicity in animals after inhalation exposure). Bi et al. (1985) reported a concentration-related and significant elevation in relative liver weight in rats exposed to 10, 100, or 3000 ppm, 6 h/day, 6 days/week for 6 months. The 10-ppm concentration is considered a LOAEL for liver effects in intermediate-length exposures. The longer-term study by Lee et al. (1977a) in which rats and mice were exposed to 0, 50, 250, or 1000 ppm, 6 h/day, 5 days/week for up to 12 months (Sect. 4.3.1.1, in the subsection on lethality and decreased longevity in animals after inhalation exposure) failed to identify a NOAEL for hepatotoxicity. Lee et al. (1977a) observed no adverse effects on biochemical parameters of rats or mice exposed to ≤250 ppm. Several mitotic figures, indicating increased rate of cell division, were observed in the livers of rats exposed to 50 or 1000 ppm at 8 to 9 months, and increased rate of DNA synthesis was observed at 50 ppm. Since the liver is a known target organ for the toxicity and oncogenicity of vinyl chloride, these effects are judged to be potentially adverse, and 50 ppm is considered an FEL in this study.

Feron et al. (1979a) exposed rats to 0 or 5000 ppm, 7 h/day, 5 days/week for 4, 13, 26, or 52 weeks and observed histopathologic alteration of the liver after 13 weeks and ultrastructural alteration after only 4 weeks of exposure.

Oral, human. Data were not located regarding hepatotoxicity in orally exposed humans.

Oral, animal. A gavage study in rats identifies 30 mg/kg as a NOAEL and 100 mg/kg as a LOAEL for liver effects in an intermediate-length study. Feron et al. (1975) administered vinyl chloride in soybean oil by gavage to groups of 15 rats per sex at 0, 30, 100, or 300 mg/kg, 6 days/week for 13 weeks. Parameters of liver toxicity evaluated included serum biochemistry, relative liver weight, and histopathologic and histochemical examination at all dosages and electron microscopy at 0 and 300 mg/kg. No effects were observed at 30 mg/kg, equivalent to 26 mg/kg/day. Reduced blood sugar and slightly altered hepatocytes were observed at 100 and 300 mg/kg. A dose-related increase in relative liver weight was observed and became statistically significant only at 300 mg/kg. Hypertrophic rough endoplasmic reticulum was observed at 300 mg/kg.

The key long-term oral study that defines thresholds for hepatotoxicity was reported by Dow Chemical Company (1984) and Til et al. (1983) and was described in Sect. 4.3.1.2, in the subsection on lethality and decreased longevity in animals after inhalation exposure. Diets provided daily dosages of 0, 0.014, 0.13, or 1.3 mg/kg/day to rats for their lifetime. There were no effects on general appearance, behavior, food consumption, body weight, or limited hematologic and biochemical parameters. Relative organ weights were not evaluated. Noncarcinogenic adverse histopathologic effects were confined to the liver and consisted of hepatocellular alteration and hepatic cysts in both sexes at 1.3 mg/kg/day. An increased incidence of basophilic foci were observed in both sexes at 1.3 mg/kg/day and only in females in the two lower dosage groups. Lacking a dose-related increase in the incidence of basophilic foci and histopathological evidence of adverse effects at 0.13 mg/kg/day, such as were observed at the higher dosage,

basophilic foci in the liver of rats of one sex may be considered a nonadverse, although compound-related, effect. The dosage of 0.13 mg/kg/day, therefore, may be considered a NOAEL, and 1.3 mg/kg/day may be considered a LOAEL for hepatotoxicity.

An earlier lifetime study from this laboratory supports the NOAEL for hepatotoxicity of 0.13 mg/kg/day. Feron et al. (1981) fed diets containing polyvinyl chloride with high levels of vinyl chloride monomer to rats that provided intakes of 0, 1.7, 5.0, or 14.1 mg/kg/day. An increased incidence of several histopathologic lesions, some of which were probably preneoplastic, were observed in the livers of rats from all treated groups.

Dermal. Data regarding hepatotoxicity associated with dermal exposure of humans or animals to vinyl chloride were not located.

General discussion. Symptoms and signs of liver disease associated with occupational exposure to vinyl chloride include pain or discomfort in the right-hand upper quadrant of the abdomen, hepatomegaly, splenomegaly, portal hypertension, thrombocytopenia, esophageal varices, and evidence of fibrosis and cirrhosis; however, these observations are not pathognomonic for vinyl chloride-induced liver disease (Lilis et al. 1975, Popper and Thomas 1975, Lee et al. 1977b). Severity of the clinical picture appeared to correlate positively with duration of exposure (Lilis et al. 1975). Biochemical screening and liver function tests generally have not been useful to monitor the presence or progress of the disease (Lee et al. 1977b, Lilis et al. 1975), although recently, Doss et al. (1984) noted that increased urinary porphyrin and coproporphyrin occurred consistently in cases of liver disease induced by vinyl chloride and other industrial hepatotoxins.

A number of investigators have noted that metabolites of vinyl chloride bind covalently to hepatocellular macromolecules and may be important in the mechanism of carcinogenesis (Bolt et al. 1976b, Bolt 1986, Kappus et al. 1976, Watanabe et al. 1978a, Watanabe and Gehring 1976). A mechanism for noncarcinogenic liver effects has not been postulated; however, since many of the lesions observed in the livers of vinyl chloride-exposed rats are considered preneoplastic (Feron et al. 1981), it seems reasonable to suspect that macromolecular binding of reactive intermediates may be involved in noncarcinogenic toxicity. Support is derived from the data of Jaeger et al. (1977), who observed that mixed-function oxidase inducers Aroclor 1254 and phenobarbital potentiate the acute hepatotoxicity in rats exposed to vinyl chloride by inhalation. Pretreatment with SKF 525-A, a mixed-function oxidase inhibitor, prevented vinyl chloride-induced toxicity.

It should be noted that the oral NOAEL for hepatotoxicity in a chronic study (Dow Chemical Company 1984) was far below the NOAEL in a subchronic study (Feron et al. 1975). At least for oral exposure, the duration of exposure appears to be of major importance.

4.3.2.2 Nervous system effects

Inhalation, human. Vinyl chloride was once considered for use as an inhalation anesthetic (ACGIH 1986a). Acute exposures to 0.8 to 2.0% vinyl chloride (8,000 to 20,000 ppm) have been associated with

dizziness, giddiness, euphoria, ataxia, headache, and narcosis (Nicholson et al. 1975, Lester et al. 1963). Recent data from the foreign literature suggest that subtle signs of neurotoxicity may be associated with occupational exposure. Mild distal axonal neuropathy was reported in the legs of 45/64 exposed vinyl chloride workers, which was suggestive to the investigators of a dying-back syndrome (Perticoni et al. 1986). Halama et al. (1985) associated neurologic and psychiatric disease with occupational exposure. Dinceva et al. (1985) reported electroencephalogram (EEG) changes that they thought were indicative of early evidence of neurotoxicity in workers exposed to vinyl chloride in combination with other organic solvents. Exposure levels were not reported by these authors.

Inhalation, animal. Oster et al. (1947) anesthetized dogs with ~7 to 50% (70,000 to 500,000 ppm) vinyl chloride and concluded that its use as an anesthetic was unsuitable because of cardiac and muscular effects. Lester et al. (1963) exposed rats to concentrations ranging from 5 to 15% (50,000 to 150,000 ppm) for up to 2 h to evaluate CNS effects. Moderate intoxication was observed at 5%, loss of reflexes was observed at 5 to 10%, and deep surgical anesthesia was reached at 15%. Patty et al. (1930) produced ataxia and narcosis in guinea pigs exposed to 2.5 to 5% (25,000 to 50,000 ppm) vinyl chloride for 2 to 5 min.

Oral. Neurologic effects in orally exposed humans or animals have not been reported.

Dermal. Neurologic effects in dermally exposed humans or animals have not been reported.

General discussion. CNS effects appear to be a manifestation of acute inhalation exposure to high levels of vinyl chloride in humans and animals (Nicholson et al. 1975, Lester et al. 1963) that may result in death, at least in animals (Lester et al. 1963, Mastromatteo et al. 1960). Recent data provide minimal evidence that chronic exposure to vinyl chloride may result in neurologic or psychiatric effects (Perticoni et al. 1986, Dinceva et al. 1985, Halama et al. 1985). Further investigation is needed.

4.3.2.3 Other systemic effects

Vinyl chloride disease from inhalation exposure, human. Vinyl chloride disease is the name given to the total clinical syndrome associated with occupational exposure. It includes a syndrome known as acroosteolysis or dissolution of the ends of the distal phalanges of the hands; circulatory disturbance in the extremities; Raynaud syndrome; scleroderma; hematologic effects, and effects on the lungs; as well as the liver effects previously discussed (Halama et al. 1985, Sakabe 1975, Lilis et al. 1975, Markowitz et al. 1972, Wilson et al. 1967, Dinman et al. 1971, Preston et al. 1976). In addition, Micu et al. (1985) reported obscure effects of unknown toxicological significance on enzyme levels of leukocytes and thrombocytes of exposed workers. Other investigators have reported elevated levels of circulating IgG (Bogdanikowa and Zawilska 1984) or immune complexes (Ward 1976) as part of the syndrome, but the biological significance of these effects is not clear.

Vinyl chloride disease from inhalation exposure, animal. Lee et al. (1977a, 1978) exposed rats and mice to vinyl chloride at 0, 50, 250, or 1000 ppm 6 h/day, 5 days/week for up to 12 months, as described in Sect. 4.3.2.1, in the subsection on hepatotoxicity in animals after inhalation exposure in this section. Parameters of toxicity evaluated included general appearance, feed consumption, body weight, hematology, clinical chemistry, macrophage counts of pulmonary washings, cytogenic examination of bone marrow cultures, senographic radiography of the long bones of the limbs, gross necropsy, selected organ weights, and histopathologic examination of a comprehensive set of organs and tissues. Abnormalities observed in the mice included body weight loss at 1000 ppm after 8 months of normal growth and elevated pulmonary macrophage count in mice from all exposure groups that had bronchioloalveolar adenoma. Because of its association with lung tumors, an elevated pulmonary macrophage count in mice in this study is not considered a noncarcinogenic toxic effect. Rats exposed to 1000 ppm had reduced body weights compared with controls. Other noncarcinogenic adverse effects were not observed in rats.

Bi et al. (1985) exposed rats to 10, 100, or 1000 ppm 6 h/day, 6 days/week for 12 months to evaluate effects on the testis (see Sect. 4.3.4.1, in the subsection on reproductive toxicity in animals after inhalation exposure. At termination of exposure, a concentration-related decrease in body weights was evident and became statistically significant at 100 ppm.

In a series of studies on rats exposed to 0 or 5000 ppm 7 h/day, 5 days/week for 1 year, adverse effects not previously discussed included slightly reduced growth, hematologic evidence of anemia, decreased blood clotting time, and minor biochemical alterations of uncertain biological significance (Feron et al. 1979a,b; Feron and Kroes 1979). Effects on the kidney were noted and included elevated relative kidney weights, slightly increased blood urea nitrogen (BUN), altered urinalysis parameters, and increased intensity of progressive nephrosis, all compared with controls. Other noncarcinogenic lesions seen in treated rats included mild alterations of the Zymbal glands and lungs, increased splenic hematopoiesis, degeneration of the myocardium and thickening of the walls of the arteries, and hyperplasia of the olfactory epithelium.

Vinyl chloride disease from oral exposure, human. Data regarding effects of vinyl chloride in orally exposed humans were not located.

Vinyl chloride disease from oral exposure, animal. In a 13-week study described in Sect. 4.3.2.1, in the subsection on hepatotoxicity in animals after oral exposure, Feron et al. (1975) treated rats with vinyl chloride at 0, 30, 100, or 300 mg/kg 6 days/week. Parameters of toxicity not previously discussed included general appearance and behavior, body weight, food consumption, hematology, selected blood chemistry and urinalysis tests, gross appearance on necropsy, relative weights of major organs, and histopathologic appearance of a wide range of organs and tissues. Minor hematologic and biochemical changes were observed but were not considered to be adverse. Decreased relative adrenal weight was observed in males at 300 mg/kg but was not considered toxicologically significant. No adverse response was reported in other organs or tissues.

In a lifetime study also described in Sect. 4.3.2.1, in the subsection on hepatoxicity in animals after oral exposure, Feron et al. (1981) fed rats diets that provided 0, 1.7, 5.0, or 14.1 mg/kg/day vinyl chloride. An additional group was treated by gavage with 300 mg/kg 5 days/week. Parameters of toxicity evaluated included general appearance and behavior, body weight, food consumption, hematology, blood chemistry, urinalysis, gross appearance at necropsy, and histopathologic examination of a wide range of tissues from controls and the two higher-dose groups, with a more limited histopathologic examination of low-dose rats. Lethargy and poor condition were reported at ≥5.0 mg/kg/day, apparently in rats that developed tumors. Noncarcinogenic effects included reduced blood clotting time and increased splenic hematopoiesis at ≥14.1 but not at 5.0 mg/kg/day.

Vinyl chloride disease from dermal exposure. Data regarding toxic effects of vinyl chloride in dermally exposed humans or animals were not located.

Vinyl chloride disease, general discussion. Vinyl chloride disease in humans appears to involve a large number of organ systems and tissues, including the liver, as discussed in Sect. 4.3.2.3, in the subsection on vinyl chloride disease in humans after inhalation exposure (Halama et al. 1985, Sakabe 1975, Lilis et al. 1975, Markowitz et al. 1972, Wilson et al. 1967, Dinman et al. 1971, Preston et al. 1976). It is not possible to determine the critical effect in humans (the effect that occurs at the lowest exposure), because quantitative human exposure data were not provided. Animals exposed orally or by inhalation manifest cancerous and noncancerous liver effects similar to those seen in humans; but other effects seen in humans, such as acroosteolysis, Raynaud syndrome, and scleroderma, have not been reproduced in animals, even at very high exposures. Liver effects appear to be the critical end point in animals, and therefore animals are probably a satisfactory model for noncancerous end points of toxicity in humans.

4.3.3 Developmental Toxicity

4.3.3.1 Inhalation

Human. Epidemiological data associate increased fetal loss with occupational exposure to vinyl chloride, although exposure data were not quantified. Using a questionnaire, Infante et al. (1976) and Waxweiler et al. (1977) studied the outcome of pregnancies of wives of 95 vinyl chloride workers and a control group of 158 unexposed rubber workers and polyvinyl chloride fabricators exposed to "very low" levels of vinyl chloride monomer. Data were obtained for the exposed cohort regarding pregnancies that occurred before and during employment in a vinyl-chloride-contaminated atmosphere. The most significant observation was that "age adjusted" fetal loss occurred in 8.8% of the pregnancies of wives of controls and in 15.8% of the pregnancies of wives of exposed workers. The most significant difference occurred in wives of men under age 30, where fetal loss was 5.3% for controls and 20.0% for exposed workers.

In a preliminary investigation of the potential for vinyl chloride exposure to increase the occurrence of congenital malformations, Infante

(1976) compared the number of malformations per 1000 live births in three Ohio cities where polyvinyl chloride production plants were located (index cities) with the incidence in the state as a whole and with the incidence in other parts of the counties in which the index cities were located. The incidence of malformations was greater in the three index cities by either comparison, and the difference was statistically significant. Greatest increases were noted in malformations of the CNS, upper alimentary tract, and genital organs, and in the incidence of clubfoot. An additional study of one of the Ohio cities revealed no association with parental occupation and no evidence that parents of malformed infants lived closer to the local polyvinyl chloride plant than did a randomly selected group of parents who delivered normal infants (Edmonds et al. 1975). Edmonds et al. (1975) concluded that there was no association of birth defects with exposure to vinyl chloride.

Theriault et al. (1983) investigated the incidence of birth defects in residents of a Canadian town where there is a vinyl chloride polymerization plant. The incidence of birth defects was significantly greater in the index town than in any or all of three matched towns with no potential exposure to vinyl chloride. The most commonly reported defects involved the musculoskeletal, cardiovascular, central nervous, and urogenital systems. The incidence rate peaked in March and was lowest in September for the index town, but no seasonal effect was observed in the comparison communities. The lowest incidence rate followed the time of lowest estimated ambient atmospheric levels of vinyl chloride by 8 months. In comparisons between parents of deformed infants and control parents in the index town, no correlations were noted with proximity of residence to the vinyl chloride plant or with parental occupation. Furthermore, there were several industries in the index town that emitted pollutants into the atmosphere. The investigators concluded that the available data did not substantiate an association between atmospheric vinyl chloride and an increased incidence of birth defects.

Edmonds et al. (1978) compared the incidence rates of CNS defects in a West Virginia county in which a polyvinyl chloride polymerization plant was located with those for other regions in the United States with no exposure to vinyl chloride. The incidence rates of the index county exceeded those of control areas by a factor of 1.5 to 2. By comparing data from parents of deformed infants with randomly chosen matched controls living in the index county, no correlation was noted for parental occupation, for proximity to the polyvinyl chloride plant, or for patterns of wind direction and air pollution. Furthermore, one major and several smaller chemical plants were located in the area.

Animal. Inhalation experiments in animals have not associated vinyl chloride with developmental toxicity at concentrations below those associated with maternal toxicity. John et al. (1977) exposed groups of 30 to 40 pregnant CF1 mice, 20 to 35 Sprague-Dawley rats, and 15 to 20 New Zealand white rabbits to vinyl chloride at 0 or 500 ppm 7 h/day on gestation days 6 to 15 for rats and mice and 6 to 18 for rabbits. Additional groups of mice were similarly exposed to 50 ppm, and additional groups of rats and rabbits were similarly exposed to 2500 ppm. Parameters of maternal and developmental toxicity were evaluated;

both the fetus and litter were evaluated. In mice, maternal effects were restricted to 500 ppm and included increased mortality, reduced body weight, and reduced absolute, but not relative, liver weight. Fetotoxicity, manifested as increased fetal resorption, decreased fetal body weight, reduced litter size, and retarded cranial and sternebral ossification, was observed only at 500 ppm. There was no evidence of a teratogenic effect in mice at either concentration. Maternal effects in rats at 500 ppm, but not at 2500 ppm, were were restricted to reduced body weight gain. Maternal effects in rats at 2500 ppm were death of one rat, elevated absolute and relative liver weights, and reduced food consumption. Reduced fetal body weight and an increase in the incidence of lumbar spurs were observed at 500 but not 2500 ppm and are not considered signs of chemical-related fetotoxicity. The incidence of dilated ureters, however, was increased at 2500 ppm and may represent a chemical-induced effect. Signs of maternal or developmental toxicity were not observed in rabbits at either 500 or 2500 ppm. For developmental toxicity the concentration of 2500 ppm represents a LOAEL in the rat and a NOAEL in the rabbit.

Ungvary et al. (1978) exposed groups of pregnant CFY rats continuously to ~1500 ppm on gestation days 8 to 14 or 14 to 21 in a study that identified a NOAEL for developmental toxicity in rats. Controls consisted of groups of rats that were chamber exposed to air only on gestation days 8 to 14 or 14 to 21. An additional control group consisted of unexposed rats that were not subjected to the chamber. Groups contained 14 to 28 litters, and the litter was a unit of comparison for fetal effects. Maternal toxicity was manifested by increased relative liver weight in dams exposed on gestation days 8 to 14 and slightly reduced body weight gain in dams exposed on days 14 to 21. There was no evidence of fetal toxicity or teratogenicity. In another part of this study, rats were exposed as described above on gestation days 1 to 9 and simultaneously injected subcutaneously with physiologic saline. Compared with air-exposed controls treated with physiologic saline, these rats had significantly increased relative liver weights and fetal wastage, and a slight but not statistically significant increase in the percentage of fetuses with body weights <3.3 g. The investigators also observed one fetus with anophthalmia and one with microphthalmia in rats exposed during days 1 to 9, as well as a tendency for increased fetal wastage in rats exposed on days 8 to 14. They suggested that the developmental toxicity of vinyl chloride should be tested by continuous exposure throughout the period of organogenesis.

In a Bulgarian study, Mirkova et al. (1978) exposed pregnant rats to 0 or 6.15 mg/m^3 (2.4 ppm) continuously throughout gestation. Fetotoxic effects included early postimplantation fetal loss, reduced fetal body weights, retarded ossification, and fetal hematomas. Teratogenic effects included anomalies of the brain. In offspring from rats allowed to deliver, liver function at 1 month of age was compromised, as indicated by increased hexobarbital sleeping time.

In a Russian study, Sal'nikova and Kotsovskaya (1980) exposed pregnant rats to 0, 4.8, or 35.5 mg/m^3 (0, 1.9, or 13.9 ppm) 4 h/day throughout gestation. Maternal effects included decreased RBC count and decreased urinary excretion of hippuric acid at 13.9 ppm. Fetal hemorrhages were reported at both exposure levels, and fetal edema was

reported at 35.5 mg/m^3. In offspring of rats allowed to deliver, behavioral changes were reported at 35.5 mg/m^3, and liver effects, hematologic and biochemical effects, and altered relative organ weights were reported in both groups.

4.3.3.2 Oral

Data regarding developmental toxicity in orally exposed humans or animals were not located.

4.3.3.3 Dermal

Data regarding developmental toxicity in dermally exposed humans or animals were not located.

4.3.3.4 General discussion

Epidemiologic data suggest an association between paternal occupational exposure to vinyl chloride and fetal loss (Infante et al. 1976, Waxweiler et al. 1977), but exposures were not quantified. In contrast, developmental toxicity was not reported in animals exposed to high levels for 7- to 12-day periods during organogenesis at levels below which maternal toxicity occurred (John et al. 1977, Ungvary et al. 1978). Ungvary et al. (1978), however, noted evidence of developmental toxicity in rats exposed in the first trimester compared with rats exposed later in gestation and suggested that valid testing should involve exposure during the entire gestation period. A Bulgarian study reported both fetotoxicity and teratogenicity in rats exposed continuously to a low concentration throughout gestation (Mirkova et al. 1978). The protocol and results were incompletely reported; hence, the study cannot be properly evaluated. Reporting problems also preclude proper evaluation of a Russian study (Sal'nikova and Kotsovskaya 1980) which reported developmental toxicity in rats intermittently exposed to low levels throughout gestation. These studies, however, underscore the need for further testing, using continuous exposure at low levels throughout gestation.

4.3.4 Reproductive Toxicity

4.3.4.1 Inhalation

Human. Russian studies examined sexual function and hormone levels in men (Makarov 1984) and sexual function and gynecological health in women (Makarov et al. 1984) occupationally exposed to vinyl chloride and in unexposed control groups. Sexual function was evaluated by questionnaire, hormone levels were measured, and women were given gynecological examinations. Exposures were reported as low, not exceeding 1 maximum allowable concentration (MAC) (30 mg/m^3 or ~12 ppm); average, in the range of 1 to 5 MAC (12 to 60 ppm); or significant, exceeding 5 MAC (60 ppm). An exposure- and duration-related decline in sexual function was reported in exposed men and women. Ovarian dysfunction, benign uterine growths, and prolapsed genital organs were reported in 77% of exposed women.

Animal. Bi et al. (1985) exposed adult male Wistar rats to 0, 10, 100, or 3000 ppm, 6 h/day, 6 days/week for up to 12 months to evaluate effects on the testes. Relative testicular weight, evaluated only after 6 months of exposure, was significantly reduced at 100 and 3000 ppm. Histopathological examination revealed a concentration-related increase in the incidence of testicular degeneration significant at 100 ppm.

4.3.4.2 Oral

Data regarding the reproductive effects of vinyl chloride in orally exposed humans or animals were not found in the literature .

4.3.4.3 Dermal

Data regarding the reproductive effects of vinyl chloride in dermally exposed humans or animals were not found.

4.3.4.4 General discussion

Data regarding the reproductive effects of exposure to vinyl chloride are limited. Human data associating occupational exposure with reduced sexual function in both sexes and impaired gynecological health in women (Makarov 1984, Makarov et al. 1984) are not adequately reported for proper evaluation; therefore, such data cannot be used to identify thresholds. Whereas animal data do associate exposure to vinyl chloride with testicular effects, sexual performance and fertility were not tested.

4.3.5 Genotoxicity

4.3.5.1 Human

Genotoxicity studies of vinyl chloride in humans include a large number of chromosomal aberration tests in the peripheral lymphocytes of occupationally exposed workers (Table 4.4). These tests have been consistently positive (Ducatman et al. 1975, Funes-Cravioto et al. 1975, Purchase et al. 1978, Hansteen et al. 1978, Kucerova et al. 1979, Katsova and Pavlenko 1985), with the exception of a less rigorously performed and reported Dow Chemical Company study (Kilian et al. 1975). The key study in this group is Hansteen et al. (1978), in which blood from 37 exposed workers and from 16 to 32 unexposed controls was examined twice at intervals of 2 to 2.5 years. Exposure levels during the time of first sampling were measured at 25 ppm, and there was a statistically significant increase in the percent of peripheral lymphocytes with chromosomal aberrations. When these workers were subsequently reexamined, exposure levels had dropped to 1 ppm, and there were no statistical differences between exposed and controls in the percentage of chromosomal aberrations.

Anderson et al. (1980) observed an increase in lymphocytes with chromosomal aberrations in another cohort at exposure levels estimated at 50 ppm. The incidence of aberrations was returning to normal, however, when the cohort was resampled after exposure levels had been reduced to <5 ppm. In a Russian paper (Katsova and Pavlenko 1985), 0.1 mg/m^3 (~0.04 ppm) was suggested as a no-effect level for chromosomal aberrations. The study was insufficiently reported to allow critical

Table 4.4. Genotoxicity of vinyl chloride in vivo

End point	Species/test system	Result	References
Recessive lethal	*Drosophila melanogaster*	+	Verburgt and Vogel 1977
Dominant lethal	*D. melanogaster*	−	Verburgt and Vogel 1977
	Mouse	−	Purchase et al. 1975, Anderson et al. 1976
Sex chromosome loss	*D. melanogaster*	−	Verburgt and Vogel 1977
Chromosomal translocation	*D. melanogaster*	−	Verburgt and Vogel 1977
Chromosomal aberration	Rat	+	Anderson and Richardson 1981
	Mouse	+	Walles and Holmberg 1984
	Human lymphocyte	+	Hansteen et al. 1978
Sister chromatid exchange	Human lymphocyte	−	Hansteen et al. 1978
	Human lymphocyte	+	Kucerova et al. 1979
Chromosomal aberration	Human lymphocyte	+	Kucerova et al. 1979
	Human lymphocyte	+	Purchase et al. 1975, 1978
	Human lymphocyte	+	Ducatman et al. 1975
Chromosomal aberration	Human lymphocyte	+	Funes-Cravioto et al. 1975
	Human lymphocyte	+	Katsova and Pavlenko 1985
	Human lymphocyte	−	Kilian et al. 1975
Micronucleus test	Mouse	+	Jenssen and Ramel 1980
RNA alkylation[a]	Rat	+	Laib and Bolt 1977
DNA alkylation	Rat	+	Laib et al. 1985
DNA alkylation	Mouse	+	Osterman-Golkar et al. 1977
	Rat	+	Green and Hathway 1978

[a]Although RNA alkylation is not a genotoxic effect, the results of this test are supportive evidence that vinyl chloride metabolites interact with nucleic acids.

evaluation, however, and the NOAEL from the Hansteen et al. (1978) study is accepted.

4.3.5.2 Nonhuman

It is beyond the scope of this document to evaluate all data regarding the mutagenicity of vinyl chloride in nonhuman systems. Representative data, largely taken from a recent EPA (1985b) review, are presented in Tables 4.4 and 4.5.

Vinyl chloride is mutagenic in *Salmonella typhimurium* (Rannug et al. 1974; Bartsch et al. 1975, 1976; Andrews et al. 1976; Simmon et al. 1977; Elmore et al. 1976; Poncelet et al. 1980; de Meester et al. 1980), but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations (Bartsch et al. 1976). Metabolic activation may be necessary for any mutagenic activity in this system (Rannug et al. 1974) or for a maximal response (Simmon et al. 1977). Results in other microbial systems were mixed. Vinyl chloride was positive for recessive lethal effects but negative for dominant lethal effects, chromosomal translocation, and sex chromosome loss in *Drosophila melanogaster* (Verburgt and Vogel 1977). The investigators suggested that the negative results in the dominant lethal test may indicate that metabolites capable of causing chromosomal damage did not reach the germ cells. Negative results were obtained for the dominant lethal test in mice (Purchase et al. 1975, Anderson et al. 1976).

Positive results were obtained in mutation and cell transformation tests and in chromosomal aberration tests in in vivo and in vitro mammalian systems (Styles 1977, Drevon and Kuroki 1979, Jenssen and Ramel 1980, Walles and Holmberg 1984, Laib and Bolt 1977, Laib et al. 1985, Anderson and Richardson 1981). Positive results were also reported for DNA alkylation tests in rats (Green and Hathway 1978) and mice (Osterman-Golkar et al. 1977) and for RNA alkylation in rat liver microsomes (Laib and Bolt 1977).

4.3.5.3 General discussion

Evidence strongly implicates the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde as being responsible for mutagenicity in the systems discussed above. Reports indicate that 2-chloroethylene oxide and 2-chloroacetaldehyde are manyfold more active in *S. typhimurium* than the parent compound or other oxidation products of vinyl chloride such as 2-chloroethanol or chloroacetic acid (Rannug et al. 1976, Bartsch 1976, McCann et al. 1975). 2-Chloroethylene oxide has also been shown to be responsible for base-pair substitutions in *Escherichia coli* (Barbin et al., 1985a), to be highly mutagenic in gene mutation and gene conversion tests in yeasts (Loprieno et al. 1977), and to induce mutations in Chinese hamster V79 cells (Huberman et al. 1975). In vitro testing has shown that 2-chloroethylene oxide is capable of alkylating DNA to form 7-(2-oxoethyl)guanine as the principal adduct (Barbin et al. 1985b). This adduct has not been shown to cause errors in DNA replication in an in vitro test with *E. coli* DNA polymerase I, and the role of DNA alkylation in mutagenesis is unclear.

Table 4.5. Genotoxicity of vinyl chloride in vitro

End point	Species/test system	Result		References
		Without activation	With activation	
Reverse mutation	*Salmonella typhimurium*	–	+	Rannug et al. 1974
	S. typhimurium	+	+	Bartsch et al. 1975, 1976
	S. typhimurium	+	+	Andrews et al. 1976
	S. typhimurium	+	+	Simmon et al. 1977
	S. typhimurium	–	NT[a]	Elmore et al. 1976
	S. typhimurium	+	+	Poncelet et al. 1980, de Meester et al. 1980
Forward or reverse mutation	*Escherichia coli*	–	+	Greim et al. 1975
Reverse mutation	*Saccharomyces cerevisiae*	–	NT	Shahin 1976
Forward mutation	*Schizosaccharomyces pombe*	–	+	Loprieno et al. 1977
Rec-repair	*Bacillus subtilis*	–	NT	Elmore et al. 1976
Forward mutation	Chinese hamster cell V79	+	NA[b]	Drevon and Kuroki 1979
Cell transformation	Neonatal hamster kidney cells	+	NA	Styles 1977
RNA alkylation[c]	Rat liver microsomes	+	NA	Laib and Bolt 1977

[a]Not tested.
[b]Not applicable.
[c]Although RNA alkylation is not a genotoxic effect, the results of this test are supportive evidence that vinyl chloride metabolites interact with nucleic acids.

4.3.6 Carcinogenicity

4.3.6.1 Inhalation

Human. Several reports (Tabershaw and Gaffey 1974, Monson et al. 1975, Waxweiler et al. 1976, Nicholson et al. 1975, Heath et al. 1975, Lilis et al. 1975, Popper and Thomas 1975, Bryen et al. 1976, Fox and Collier 1977, Heldaas et al. 1984, Geryk and Zudova 1986) associate human cancer with occupational exposure to vinyl chloride. The most recent review of the human data is that of EPA (1985b). Since none of the human studies quantify exposures sufficiently for quantitative risk assessment, no single report is chosen as a key study. In a review of these data, IARC (1979) concluded that the human data constitute "sufficient" evidence for the carcinogenicity of the compound. EPA (1985b) classified vinyl chloride in IARC Group 1; subsequently, EPA (1987b) placed this compound in Carcinogen Assessment Group A. Both classifications reflect the designation of vinyl chloride as a known human carcinogen.

The incidence of liver cancer, in particular angiosarcoma, provides the most convincing evidence for the carcinogenicity of vinyl chloride, because the expected background level (25 to 30 cases per year in the United States) is extremely low (Heath et al. 1975). Most of the epidemiologic studies cited above reported a higher observed/expected ratio for liver cancer than for cancers of any other site. Other cancers associated with vinyl chloride exposure include tumors of the brain and CNS, the lung and respiratory tract, the digestive tract, and the lymphocytic/hematopoietic system, although statistical significance was not necessarily reached (Monson et al. 1975, Waxweiler et al. 1976, Bryen et al. 1976). Fox and Collier (1977), however, concluded that there is no evidence that cancers other than those of the liver are associated with exposure to vinyl chloride. Heldaas et al. (1984) also reported an unusual number of cases of malignant melanoma of the skin in exposed workers. The Heldaas et al. (1984) study, however, is based on incidence of cancer rather than on death due to cancer, which may explain why other studies have not reported an increase in malignant melanoma.

Generally, prolonged exposure (employment) increased the risk of cancer, particularly if intermittent high exposures have occurred (Bryen et al. 1976, Heath et al. 1975). Tabershaw and Gaffey (1974) noted that an increased risk of malignancy correlated with an increased "exposure index," an interplay of level and duration of exposure. Fox and Collier (1977), however, reported little correlation with duration of exposure.

Animal. The key animal inhalation studies of carcinogenicity are the series of experiments by Maltoni et al. (1980, 1981) in Sprague-Dawley rats, Swiss mice, and golden hamsters. A report of interim results was published earlier (Maltoni and Lefemine 1975). 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. Mice and hamsters were exposed to vinyl chloride concentrations of 50 to 10,000 ppm for 30 weeks, followed by an observation period of 51 weeks (mice) or 79 weeks (hamsters). Exposure levels and results from the most

comprehensive and longest-term experiments in rats are presented in Table 4.6. The investigators noted that increased incidence of tumors occurred at ≥50 ppm in all species tested. All species showed an increase in the incidence of liver angiosarcoma. In addition to the tumor types presented in Table 4.6, the authors associated extra hepatic angiosarcomas, hepatomas, Zymbal gland carcinomas, and neuroblastomas in rats with exposure to vinyl chloride.

Other inhalation experiments support the carcinogenicity of vinyl chloride. Rats, mice, and hamsters were exposed to 50 to 2500 ppm vinyl chloride for 9 or 12 months (Keplinger et al. 1975, MCA 1980). All species developed liver angiosarcomas in a concentration-related manner at ≥50 ppm, the lowest level tested. Metastases to lymph nodes or lung were common. Rats also developed Zymbal gland tumors at ≥50 ppm and brain tumors at ≥200 ppm, and mice developed lung tumors at ≥50 ppm. Viola et al. (1971) exposed rats to 3% vinyl chloride (30,000 ppm) for 12 months and observed primary tumors of the skin, lungs, and bones. Feron and Kroes (1979) exposed rats to 0 or 5000 ppm for 52 weeks and observed primary tumors in treated rats in the brain, lung, Zymbal gland, and nasal cavity. Lee et al. (1977a, 1978) exposed rats and mice to 0, 50, 250, or 1000 ppm, 6 h/day, 5 days/week for up to 12 months; subsequently, they observed an increased incidence of hemangiosarcoma of the liver in rats at ≥250 ppm, as well as bronchioalveolar adenoma of the lung, mammary tumors, and hemangiosarcoma of the liver and other organs in mice at ≥50 ppm. In a later study from the same laboratory, Hong et al. (1981) exposed rats and mice to 0, 50, 250, or 1000 ppm, 6 h/day, 5 days/week for up to 6 months, followed by a 12-month observation period. Tumor types attributed to vinyl chloride exposure in rats were those observed by Lee et al. (1977a, 1978), in addition to bronchioalveolar lung tumors at ≥250 ppm and mammary tumors at all exposure concentrations.

Suzuki (1978, 1981, 1983) also observed lung tumors as a primary carcinogenic response of mice to vinyl chloride. Lung tumors developed in 26 of 27 mice exposed to 2500 or 6000 ppm for 5 to 6 months (Suzuki 1978). Concentration-related increased incidences of lung tumors were observed in studies in which mice were exposed to 0 to 100 or 0 to 600 ppm for 4 weeks and then observed for up to 41 weeks postexposure (Suzuki 1981, 1983). Although in neither study was statistical analysis performed, it appeared that 10 ppm was a low level associated with an increased incidence of lung tumors in both studies. Hehir et al. (1981) reported an increased incidence of lung tumors in mice given single 1-h exposures to 5000 or 50,000 ppm.

Inhalation data in three species suggest that age at exposure has an effect on carcinogenic response. Drew et al. (1983) exposed rats, mice, and hamsters to 50 to 200 ppm for periods from 6 to 24 months or from 6 to 12 months during different portions of their lifespans. All three species had a maximal oncogenic response when exposed during the first 12 months of life. Exposures begun after a 12-month holding period did not produce a carcinogenic response. Maltoni et al. (1983) and Cotti et al. (1983) exposed rats in utero from gestation day 12 and after birth to 1 year of age to 2500 ppm and observed very high incidences of liver and brain tumors. Liver angiosarcoma, with an average latency period of 50 weeks, developed in 32 of 56 males and in 38 of 55 females.

Table 4.6. Tumor incidence in male and female Sprague-Dawley rats exposed by inhalation to vinyl chloride 4 h/day, 5 days/week for 52 weeks

Exposure level (ppm)	Duration of study (weeks)	Incidence of liver angiosarcoma	Incidence of kidney nephroblastoma
0	135–147	0/363	0/363
1	147	0/118	0/118
5	147	0/119	0/119
10	147	1/119	0/119
25	147	5/120	1/120
50	135	1/60	1/60
100	143	1/120	10/120
150	143	6/119	11/119
200	143	12/120	7/120
250	135	3/59	5/59
500	135	6/60	6/60
2,500	135	13/60	6/60
6,000	135	13/59	5/59
10,000	135	7/60	5/60
30,000	68	18/60	NR[a]

[a]Not reported.
Source: Maltoni et al. 1980, 1981.

Brain tumors, with an average latency of 48 weeks, developed in 27 of 57 males and in 28 of 57 females. Lower incidences of tumors developed in rats exposed for only 7 days in utero. Maltoni et al. (1980, 1981) exposed rats to 6000 or 10,000 ppm in utero on days 12 to 18 of gestation and continued to observe them for 115 weeks. In 54 high-dose progeny, there were 3 with Zymbal gland carcinoma, 2 with angiosarcoma, and 1 with nephroblastoma of the brain. In 32 low-dose progeny, 1 developed Zymbal gland carcinoma and 2 had angiosarcoma.

4.3.6.2 Oral

Human. Data regarding the carcinogenicity of vinyl chloride in orally exposed humans were not found.

Animal. Cancer types observed in orally treated rats resemble those observed from inhalation exposure. In the key oral study, Feron et al. (1981) exposed groups of Wistar rats to vinyl chloride in the diet by incorporating polyvinyl chloride (PVC) powder containing a high level of the monomer. Diets were fed 4 h/day, and food consumption and body weights were monitored. Volatilization of vinyl chloride from the diet was estimated, and dosages of vinyl chloride available to the rats were also estimated. In addition, one group received vinyl chloride by gavage 5 days/week. Pertinent data are summarized in Table 4.7. Exposure was for the lifetime of the rats. Treatment of the 300-mg/kg gavage group was terminated at 84 weeks because of high mortality. The liver tumor incidence data presented in Table 4.7 suggest that angiosarcomas predominated at high dosages but that hepatocellular carcinomas predominated at low dosages. In addition to tumors of the liver and lung, the investigators attributed exposure to the development of extra hepatic abdominal angiosarcomas and Zymbal gland tumors. They also noted some evidence that exposure enhanced the development of abdominal mesotheliomas and adenocarcinomas of the mammary gland.

Other oral studies indicate that the type of tumor observed may depend on the dosage given. Maltoni (1977) treated rats by gavage at 16.7 or 50 mg/kg/day for 52 weeks followed by an 84-week observation period. An increased incidence of liver angiosarcomas and kidney nephroblastomas was attributed to vinyl chloride. Zymbal gland carcinomas may also have been the result of exposure to vinyl chloride. Dow Chemical Company (1984), in a lifetime study, administered vinyl chloride in the diet (from PVC containing a high level of of the monomer) to rats at dosages of 0.014 to 1.3 mg/kg/day. Males at 1.3 mg/kg/day and females at all dosages had an increased incidence of liver nodules and preneoplastic foci. Females at 1.3 mg/kg/day had increased incidence of hepatic neoplastic nodules, but no other carcinogenic response was reported.

4.3.6.3 Dermal

Data regarding the carcinogenicity of vinyl chloride in dermally exposed humans or animals were not found.

Table 4.7. Tumor incidence in Wistar rats orally exposed to vinyl chloride[a]

Sex	Dose[b] (mg/kg/day)	Duration of treatment (weeks)	Vehicle/method	Target organ	Tumor type	Tumor incidence (P value)
F	300	84	Soybean oil/ gavage	Liver	Neoplastic nodule	2/54
					Hepatocellular carcinoma	0/54
					Angiosarcoma	29/54
				Lung	Angiosarcoma	23/54
F	17.0	143	PVC/diet	Liver	Neoplastic nodule	44/57 ($P < 0.001$)[d]
					Hepatocellular carcinoma	29/57 ($P < 0.001$)[d]
					Angiosarcoma	9/57 ($P < 0.001$)[d]
				Lung	Angiosarcoma	5/57 ($P < 0.05$)[d]
F	5.6	143	PVC/diet	Liver	Neoplastic nodule	39/59 ($P < 0.001$)[d]
					Hepatocellular carcinoma	19/59 ($P < 0.001$)[d]
					Angiosarcoma	2/59
				Lung	Angiosarcoma	3/59
F	1.8	143	PVC/diet	Liver	Neoplastic nodule	26/58 ($P < 0.01$)[d]
					Hepatocellular carcinoma	4/58
					Angiosarcoma	0/58
				Lung	Angiosarcoma	0/58
F	0.0	NA[c]	Untreated diet only	Liver	Neoplastic nodule	2/57
					Hepatocellular carcinoma	2/57
					Angiosarcoma	0/57
				Lung	Angiosarcoma	0/57
M	300	84	Soybean oil/ gavage	Liver	Neoplastic nodule	3/55
					Hepatocellular carcinoma	1/55
					Angiosarcoma	27/57
				Lung	Angiosarcoma	19/55
M	17.0	143	PVC/diet	Liver	Neoplastic nodule	23/59 ($P < 0.001$)[d]
					Hepatocellular carcinoma	8/59 ($P < 0.001$)[d]
					Angiosarcoma	27/59 ($P < 0.001$)[d]
				Lung	Angiosarcoma	19/59 ($P < 0.01$)[d]
M	5.6	143	PVC/diet	Liver	Neoplastic nodule	7/56 ($P < 0.01$)[d]
					Hepatocellular carcinoma	2/56 ($P < 0.01$)[d]
					Angiosarcoma	6/56 ($P < 0.05$)[d]
				Lung	Angiosarcoma	7/56

Table 4.7 (continued)

Sex	Dose[b] (mg/kg/day)	Duration of treatment (weeks)	Vehicle/method	Target organ	Tumor type	Tumor incidence (*P* value)
M	1.8	143	PVC/diet	Liver	Neoplastic nodule	1/58
					Hepatocellular carcinoma	1/58
					Angiosarcoma	0/58
				Lung	Angiosarcoma	0/58
M	0.0	NA	Untreated diet only	Liver	Neoplastic nodule	0/55
					Hepatocellular carcinoma	0/55
					Angiosarcoma	0/55
				Lung	Angiosarcoma	0/55

[a] Duration of study was 143 weeks; purity of compound was not reported.
[b] Dosage given 5 days/week.
[c] Not applicable.
[d] Compared with controls using chi-square.
Source: Feron et al. 1981.

4.3.6.4 General discussion

The data reviewed indicate that there is a similarity in cancer types in experimentally exposed animals and occupationally exposed humans. The human data present the strongest statistical case for associating occupational exposure with liver angiosarcoma (Monson et al. 1975, Waxweiler et al. 1976, Bryen et al. 1976, Fox and Collier 1977). The incidence of cancer of the brain, lung, and digestive tract, although not always statistically significant, is suggestive of a vinyl chloride etiology. The substantial amount of animal data also presents the strongest association for liver angiosarcoma (Maltoni et al. 1980, 1981; MCA 1980; Feron and Kroes 1979). Statistically significant increases have also been observed for lung cancer in mice (Lee et al. 1978; Hong et al. 1981; Suzuki 1978, 1981, 1983), and biologically significant increases have been reported for brain cancer in rats (Feron and Kroes 1979; MCA 1980; Maltoni et al. 1980, 1981). Animal data suggest that both the young and the prenatal organism are susceptible to vinyl chloride-induced cancer (Maltoni et al. 1980, 1981, 1983; Drew et al. 1983).

It is generally agreed that oxidation to 2-chloroethylene oxide, a highly electrophilic intermediate, is responsible for the mutagenicity of vinyl chloride (Gwinner et al. 1983, Vaino 1978). In vitro testing has shown 2-chloroethylene oxide capable of alkylating DNA to form 7-(2-oxoethyl)guanine as the principal adduct (Barbin et al. 1985b). This adduct has not been shown to be involved in genetic miscoding, and the role of DNA alkylation in carcinogenesis is unclear.

4.4 INTERACTIONS WITH OTHER CHEMICALS

A series of investigations describes the interactions of vinyl chloride with various other compounds, which clarifies the role of metabolism in the toxicity of this compound. In all studies, the acute toxicity to the liver of rats exposed by inhalation to high concentrations, as manifested by serum levels of enzymes indicative of liver damage and the histopathological appearance of the liver, was the end point evaluated. In the first study (Jaeger et al. 1974), pretreatment of rats with phenobarbital resulted in liver damage as measured by biochemical and histopathological parameters. Liver damage was not detected in nonpretreated rats. The investigators suggested that phenobarbital had induced the mixed-function oxidase (MFO) system to enhance metabolism of vinyl chloride to a toxic intermediate. In subsequent experiments (Reynolds et al. 1975, Conolly et al. 1978), pretreatment with the polychlorinated biphenyl (PCB) mixture Aroclor 1254 was also observed to cause acute exposure to vinyl chloride to result in hepatotoxicity. The same mechanism, induction of hepatic MFO, was suggested to result in oxidation of vinyl chloride to the epoxide, 2-chloroethylene oxide.

Conolly and Jaeger (1978, 1979) investigated the effect of chemicals that regulate xenobiotic metabolism on vinyl chloride-induced hepatotoxicity. Trichloropropene oxide (TCPO), which depletes glutathione and inhibits epoxide hydrase conversion of an epoxide to its corresponding less-toxic alcohol, was found to enhance the toxicity of vinyl chloride in fasted PCB-pretreated rats, but not in fed pretreated

rats. Since nonprotein sulfhydryl concentrations in the liver in TCPO-treated rats did not differ from those in control rats, the investigators suggested that the enhanced toxicity in TCPO-treated rats resulted from inhibition of epoxide hydrase rather than from glutathione depletion. The lack of effect in fed rats was judged to underscore the importance of epoxide hydrase in the detoxification of epoxide in glutathione-depleted rats.

In other parts of these same studies, cysteine, the rate-limiting precursor of glutathione, was able to block depletion of nonprotein sulfhydryl in the liver and thus reduce the intensity of liver toxicity in PCB-pretreated, vinyl chloride-exposed rats. Treatment of fed rats with diethylmaleate, another glutathione depleting agent, reduced liver nonprotein sulfhydryl to levels attained in fasted rats, but did not increase hepatotoxicity.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

Vinyl chloride is produced at 10 locations in the United States. During 1986, an estimated 8.5 to 8.6 billion lb of this chemical was produced in the United States. It is produced by thermal cracking of ethylene dichloride. Vinyl chloride is used almost exclusively in the United States for the production of polyvinyl chloride (PVC) and several copolymers. These compounds yield a wide range of end-use products which are used by industries and consumers.

5.2 PRODUCTION

Domestic production of vinyl chloride during 1986 was estimated to range between 8.5 and 8.6 billion lb. This was ~94 to 98% of available production capacity in 1986. In 1985, 7.8 billion lb of vinyl chloride was produced in the United States (C&EN 1987).

Manufacturers and sites of production are as follows (CMR 1986a): Borden Chemical in Geismar, Louisiana; Dow Chemical in Oyster Creek, Texas, and Plaquemine, Louisiana; Formosa Plastics in Baton Rouge, Louisiana, and Point Comfort, Texas; BF Goodrich in Calvert City, Kentucky, and La Porte, Texas; PPG Industries in Lake Charles, Louisiana; Shell Oil in Deer Park, Texas; and Vista Chemical in Lake Charles, Louisiana.

Vinyl chloride is produced commercially by thermal cracking of ethylene dichloride (EDC). EDC used in this process is made by either direct chlorination of ethylene using liquid chlorine, or oxychlorination of ethylene using dry hydrochloric acid and oxygen (Cowfer and Magistro 1985). Vinyl chloride is usually supplied as a liquid under pressure (IARC 1979). The technical grade product is available in 99.9% purity (Sax and Lewis 1987).

5.3 IMPORT

Imports of vinyl chloride were ~200 million lb in 1987 (C&EN 1987).

5.4 USES

The use pattern for vinyl chloride is as follows (CMR 1986a): polyvinyl chloride (PVC), 85%; exports, 13%; and other, mostly copolymer use, 2%. This use pattern indicates that vinyl chloride monomer is used almost exclusively in the United States by the plastics industry. Very small amounts are used as a refrigerant gas and as an intermediate in the production of chlorinated compounds (Curry and Rich 1980, Gosselin et al. 1984, IARC 1979). Limited quantities of vinyl chloride were used in the United States as an aerosol propellant, and as an ingredient of

drug and cosmetic products; however, these practices have been discontinued (EPA 1985b).

Vinyl chloride is industrially important because of its inherent flame retardant properties, its wide variety of end-use products, and the low cost of producing polymers from vinyl chloride (Cowfer and Magistro 1985). Principal end-use products include: PVC pipes, wire and cable coatings, packaging materials, furniture and automobile upholstery, wall coverings, housewares, and automotive parts and accessories; vinyl chloride-vinyl acetate copolymer floor coverings, phonographic records, and flexible film; vinyl chloride-acrylonitrile battery cell separators; and vinyl chloride-vinylidine chloride copolymer food packaging film (Curry and Rich 1980, Salkind and Pearlman 1978, Farkas 1980).

5.5 DISPOSAL

EPA requires that persons who generate, transport, treat, store, or dispose of this compound comply with regulations of the Federal Resource Conservation and Recovery Act (RCRA). The recommended method of disposal, reported by Sittig (1985), involves the incineration of this chemical after mixing it with another combustible fuel. Care should be taken to ensure that complete combustion has taken place in order to avoid formation of phosgene. An acid scrubber is required to remove HCl. In addition to this method, other disposal techniques have been developed for the recovery of vinyl chloride from PVC latexes (Sittig 1985).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

Effluents and emissions from vinyl chloride and PVC manufacturers are responsible for the majority 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 to 1.8 days). Reaction products include HCl, formaldehyde, formyl chloride, acetylene, chloroacetaldehyde, chloroacetylchloranil, and chloroethylene. In photochemical smog situations, vinyl chloride has a half-life of 3 to 7 h. When released to water, volatilization is expected to be the primary fate process (half-life = 8.7 to 43.3 h). 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.

6.2 RELEASES TO THE ENVIRONMENT

The major source of release of vinyl chloride to the environment is believed to be emissions and effluents from plastic industries (primarily vinyl chloride and PVC manufacturers). Vinyl chloride released in wastewater is expected to volatilize fairly rapidly (on the order of hours to days) into the atmosphere. Other sources of release include disposal of vinyl chloride wastes in landfills, incomplete combustion of PVC, tobacco smoke, spills, and biodegradation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in groundwater (IARC 1979, HSDB 1987, Wakeman and Johnson 1978, Wilson and Wilson 1985, Smith and Dragun 1984). EPA estimated that prior to 1975, 110 million kg/year of vinyl chloride escaped into the atmosphere from PVC production facilities in the United States (IARC 1979). Worldwide emissions of vinyl chloride into the atmosphere during 1982 was ~400 million lb (Hartmans et al. 1985).

6.3 ENVIRONMENTAL FATE

6.3.1 Air

Based on a vapor pressure of 2660 mm Hg at 25°C, essentially all vinyl chloride in the atmosphere is expected to exist in vapor form (Verschueren 1983, Eisenreich et al. 1981). Consequently, removal from the atmosphere by dry deposition is not expected to be an important fate process. Vinyl chloride has a relatively high partition coefficient between air and water (H = 50), which suggests that significant amounts of vinyl chloride would not be removed from the atmosphere by wet deposition (EPA 1985b).

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 typical atmosphere has been ~1.5 to 1.8 days (EPA 1985b). Products of this reaction are HCl, formaldehyde, formyl chloride, carbon monoxide, carbon dioxide, chloroacetaldehyde, acetylene, chloroethylene, chloroacetylchloranil, and H_2O (EPA 1985b). In photochemical smog situations, the reaction half-life of vinyl chloride is predicted to range between 3 and 7 h (HSDB 1987). Reaction with ozone (half-life = 4.2 to 33 days), reaction with oxygen atoms [$O(^3P)$] (half-life = 373 to 532 days), and direct photolysis are relatively insignificant degradation mechanisms in the atmosphere (EPA 1985b).

6.3.2 Water

The primary loss process for vinyl chloride in natural water systems is volatilization into 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 h, respectively. These values are based on an experimentally determined reaeration rate ratio of ~2 and assumed oxygen reaeration rates of 0.008, 0.04, and 0.01 $hour^{-1}$ for a typical pond, river, and lake, respectively (EPA 1985b). 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 (EPA 1985b). In waters containing photosensitizers, such as humic materials, photodegradation may be fairly rapid. This suggests that in some waters sensitized photodegradation would also be a significant removal mechanism (HSDB 1987, EPA 1985b).

Chemical hydrolysis of vinyl chloride does not appear to be environmentally important. The hydrolytic half-life for vinyl chloride has been estimated to be <10 years (EPA 1985b). Vinyl chloride is not expected to oxidize chemically by reaction with photochemically generated hydroxyl radicals, molecular oxygen, or alkyl peroxy radicals in natural water systems. Limited available data on the biodegradation of vinyl chloride indicate that this compound is resistant to microbial degradation under aerobic conditions (EPA 1985b). Vinyl chloride is not expected to adsorb significantly to suspended solids and sediments in water or bioaccumulate significantly in aquatic organisms (HSDB 1987).

6.3.3 Soil

The relatively high vapor pressure of vinyl chloride (2660 mm Hg at 25°C) indicates that this compound should volatilize quite rapidly from dry soil surface. The effective half-life (due to volatilization) of vinyl chloride placed 10 cm deep in dry soil is predicted to be 12 h (EPA 1985b). Evaporation from moist soil surfaces is also expected to be significant since this compound does not adsorb strongly to soil and appears to volatilize fairly rapidly from water.

Experimental data regarding adsorption of vinyl chloride to soil were not located. Based on the regression equations given by Lyman et al. (1982) and Sabljic (1984), the soil adsorption coefficient (K_{OC}) for vinyl chloride has been estimated to range between 17 and 131. These K_{OC}

values suggest that this compound would be highly mobile in soil. Thus, vinyl chloride has the potential to leach into groundwater.

Based on data in aquatic media, chemical reaction of vinyl chloride in soil does not appear to be a significant fate process, and it appears that vinyl chloride would be resistant to biodegradation under aerobic conditions.

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

Anthropogenic sources are responsible for all of the vinyl chloride found in the environment. Most of the vinyl chloride released to the environment will eventually locate in the atmosphere while much smaller amounts will eventually locate in groundwater. Vinyl chloride has been detected in the ambient air in the vicinity of vinyl chloride and PVC manufacturing plants and hazardous waste sites. Vinyl chloride is expected to leach into groundwater from spills, landfills, and industrial sources.

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 2100 μg/day. The average daily intake of vinyl chloride by inhalation is expected to be essentially zero for the remainder of the population. However, short-term inhalation exposure to relatively high levels may occur during use of new cars. This is due to volatilization of vinyl chloride from vinyl polymers within the car interior.

The majority of the general population is not expected to be exposed to vinyl chloride through ingestion of drinking water. However, people who have PVC water pipes that have not been treated adequately to remove vinyl chloride monomer may ingest ~0.06 to 2.8 μg/day of vinyl chloride from drinking water. The average daily intake of vinyl chloride through diet is predicted to be essentially zero.

NIOSH estimated that 27,000 workers are definitely exposed to vinyl chloride and that workers probably exposed may be as many as 2.2 million. Intake is expected to occur primarily through inhalation and less importantly by absorption through skin. Workplace air in some PVC manufacturing plants was found to contain 100 to 800 mg/m^3 (39 to 312 ppm) vinyl chloride with peak concentrations of up to 87,300 mg/m^3 (34,000 ppm). A NIOSH survey of three vinyl chloride manufacturers reported a time-weighed-average exposure of 0.18 to 69 mg/m^3 (0.07 to 27 ppm) vinyl chloride in workplace air.

7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

7.2.1 Air

Air in rural/remote and urban/suburban areas of the United States typically contain no detectable amount of vinyl chloride (Stephens et al. 1986; Grimsrud and Rasmussen 1975a,b; Harkov et al. 1984; Wallace et al. 1984; EPA 1985b). Limited monitoring data indicate that in areas near vinyl chloride and polyvinyl chloride manufacturers, the

concentration of vinyl chloride in air typically ranges from trace levels to ~105 $\mu g/m^3$ (Gordon and Meeks 1977, Pellizzari et al. 1979, IARC 1979, EPA 1985b), but may exceed 2600 $\mu g/m^3$ (1 ppm) (Fishbein 1979). Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste landfills. Concentrations ranging from below detection limits to 5 to 8 $\mu g/m^3$ (0.002 to 0.003 ppm) have been monitored in the air above some landfills (Stephens et al. 1986, Baker and Mackay 1985). Homes near a hazardous waste site in Southern California were found to contain levels as high as 1040 $\mu g/m^3$ (0.4 ppm) (Stephens et al. 1986).

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 intake of air is 20 m^3/day, the average daily intake of vinyl chloride by people living in source-dominated areas has been estimated to range from trace amounts to 2100 μg/day.

7.2.2 Water

Vinyl chloride has been detected at varying concentrations in surface, ground, and drinking waters throughout the United States (EPA 1985b). Concentrations as high as 9.8 $\mu g/L$ in surface water, 380 $\mu g/L$ in groundwater, and 10 $\mu g/L$ in drinking water have been reported (Dyksen and Hess 1982, HSDB 1987). There was no report in the literature of vinyl chloride being detected in sediment.

The level of vinyl chloride in groundwater in the United States was determined during the 1982 EPA Groundwater Supply Survey. Water supplies from 945 sites geographically located throughout the United States were studied. Results indicate that vinyl chloride was positively identified in only 0.74% of groundwater supplies (detection limit 1 $\mu g/L$). The maximum concentration detected was 8.4 $\mu g/L$ (Westrick et al. 1984). Other studies have also reported the occurrence of vinyl chloride in groundwater throughout the United States at levels at or below 380 $\mu g/L$ (Cotruvo 1985, Goodenkauf and Atkinson 1986, Page 1981, Coniglio et al. 1980, Stuart 1983).

The concentration of vinyl chloride in finished drinking waters in the United States was studied during the 1976-1977 EPA National Organics Monitoring Survey (NOMS). Only 2 samples out of 113 contained detectable levels (>0.1 $\mu g/L$), and these averaged 0.14 $\mu g/L$ (HSDB 1987). Results of other studies also indicate that the majority of drinking water supplies in the United States contain no detectable levels of vinyl chloride (HSDB 1987, Coniglio et al. 1980). Based on these studies, it is assumed that the average daily intake of vinyl chloride by ingestion of drinking water for most persons in the United States would be essentially zero. Estimates provided in EPA (1985a) indicate that 0.9% of the United States population is exposed to levels of vinyl chloride in drinking water $\geq$1.0 $\mu g/L$, and 0.3% of the population is exposed to levels >5 $\mu g/L$.

7.2.3 Soil

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

7.2.4 Other

In the past, vinyl chloride had been detected in various foods as a result of migration from polyvinyl chloride food wrappings and containers (EPA 1985b). Vinyl chloride has been found in vinegar at levels up to 9.4 ppm, in edible oils at 0.15 to 14.8 ppm, and in butter at 0.05 ppm when these foods were packaged and stored in PVC containers (IARC 1979). At present, the Food and Drug Administration (FDA) regulates use of vinyl chloride polymers available for use in production of articles intended to contact food. These articles include food-packaging materials, coatings, plastisols, gaskets, and parts for food-processing (see Sect 9, Regulatory and Advisory Status). A recent study on the migration of vinyl chloride from PVC under conditions closely simulating actual food packaging and storage revealed that at very low concentrations of vinyl chloride in PVC packaging material, there was essentially zero migration of vinyl chloride (Kontominas et al. 1985).

It is reported that migration of vinyl chloride from rigid PVC water pipes into drinking water occurs, and that it is directly proportional to the residual level of vinyl chloride in the pipe itself. Under certain conditions, reaction with chlorine in the water may result in the complete removal of vinyl chloride from drinking water (Fishbein 1979, Ando and Sayato 1984). During one study, it was found that drinking water which ran through recently installed PVC pipes contained vinyl chloride at 1.4 $\mu g/L$, while water which ran through a 9-year-old system contained 0.03 to 0.06 $\mu g/L$ (HSDB 1987). This suggests that use of PVC pipe in water distribution systems contributes to intake of vinyl chloride through ingestion of contaminated drinking water. Assuming that the average daily intake of water is 2 L, the average intake of vinyl chloride from water contaminated with vinyl chloride from PVC pipes is expected to range from 0.06 to 2.8 $\mu g/day$.

The interior air of two new cars was analyzed and the level of vinyl chloride was found to range from 824 to 3120 $\mu g/m^3$ (0.3 to 1.2 ppm) (EPA 1985b). The source of vinyl chloride was believed to be volatilization from vinyl plastics found in the car interiors. Levels of vinyl chloride in the air in new cars may exceed estimates of minimal risk levels for acute and intermediate exposure.

Vinyl chloride has been detected in tobacco smoke (EPA 1985b). Cigarettes and little cigars have been found to contain 5.6 to 28 ng vinyl chloride per cigarette (IARC 1979).

7.3 OCCUPATIONAL EXPOSURES

NIOSH estimates definite worker exposure to vinyl chloride to be 27,000 persons and probable worker exposure to be 2.2 million (Sittig 1985). This includes ~5000 workers employed in vinyl chloride synthesis, 5000 workers involved with polymerization processes, and as many as 350,000 workers associated with fabrication plants. Exposure is believed to occur primarily through inhalation and less frequently by absorption

through skin (Sittig 1985). In the past, concentrations of vinyl chloride in workplace air in some plants producing PVC have been reported to range from 100 to 800 mg/m^3 (39 to 315 ppm) with peak concentrations up to 87,300 mg/m^3 (34,000 ppm) (IARC 1979). Currently, the Occupational Safety and Health Administration (OSHA) sets standards for occupational exposure to vinyl chloride (see Sect. 9, Regulatory and Advisory Status). A recent NIOSH survey of three vinyl chloride plants indicated that the time-weighted-average exposure to vinyl chloride varied between 0.2 to 70 mg/m^3 (0.08 to 27 ppm) (IARC 1979).

7.4 POPULATIONS AT HIGH RISK

Data were not located specifically regarding subpopulations unusually sensitive to the effects of vinyl chloride. Individuals located near or downwind of production facilities, hazardous waste disposal sites, and landfills may potentially be exposed to higher ambient atmospheric levels.

Workers involved in the production or polymerization of vinyl chloride may constitute a group at risk because of the potential for occupational exposure. Since the mid 1970s, however, atmospheric levels in the workplace have often been reduced to ≤1 ppm (Fishbein 1979, Kilian et al. 1975, Hansteen et al. 1978). Occupationally exposed men may represent a sensitive subgroup because occupational exposure in men has been associated with an increased incidence of fetal loss in their wives (Infante et al. 1976, Waxweiler et al. 1977). No threshold concentration has been determined for this effect. Women (or couples) of child-bearing age may constitute a group at risk, because data suggest that ambient exposure to low (but not quantified) environmental levels is associated with an increase in the incidence of malformations at birth (Infante 1976; Edmonds et al. 1975, 1978; Theriault et al. 1983). No threshold has been determined for this effect.

Inhalation studies in animals demonstrated that exposure early in life resulted in greater risk of developing cancer than did exposure later in life (Drew et al. 1983). Although human studies that address the effect of age on cancer risk were not located, the animal data suggest that exposure during the younger years may result in increased cancer risk. Other animal studies suggest that prenatal exposure may increase cancer risk (Maltoni et al. 1980, 1981). Although human data were not located, the animal data may suggest that the prenatal exposure of humans to vinyl chloride may increase risk of cancer.

Animal studies have demonstrated that pretreatment with xenobiotics or drugs that induce mixed-function oxidase (MFO) potentiates the hepatotoxicity of vinyl chloride (Jaeger et al. 1974, Reynolds et al. 1975, Conolly et al. 1978). Although human data were not located, the animal data suggest that human exposure to environmental pollutants or drugs that induce MFO may result in increased sensitivity to vinyl chloride.

8. ANALYTICAL METHODS

A variety of methods are available for the analysis of vinyl chloride in environmental and biological matrices. The methods of choice will depend on the nature of the sample matrix, the required precision, accuracy and detection limit, the cost of analysis, and the turnaround time of the methodology. Pre-concentration of samples may not only increase the sensitivity but also, in certain instances, decrease the time required for sample separation prior to quantification. The best sensitivity and specificity for vinyl chloride quantification are obtained with Hall detectors and photoionization detectors (Reding 1987). Mass spectrometry, although less sensitive than the most sensitive detectors, is often used as a confirmatory tool for vinyl chloride analysis. Details of analytical methodologies for vinyl chloride are given in IARC (1978).

8.1 ENVIRONMENTAL MEDIA

Some of the more commonly used analytical methods for the quantification of vinyl chloride are given in Table 8.1. Other methods that are less sensitive (e.g., infrared analyzer and continuous monitoring instruments) and less commonly used (e.g., semiconductor devices) are given in IARC (1978). Details of sample collection, sample preservation, sample pretreatment, and quantification methods are provided in the cited references in Table 8.1.

8.2 BIOMEDICAL SAMPLES

The concentrations of vinyl chloride measured in environmental samples may not reflect the concentration to which persons are exposed. Proper biological monitoring not only can be used to support environmental monitoring but also potentially may provide more accurate data on exposure levels. The two biological media that have been used most extensively as promising indicators of vinyl chloride exposure are breath and urine. A close agreement has been found between postexposure breath concentrations and the ambient vinyl chloride levels in both environmental and industrial conditions (Baretta et al. 1969, Tarkowski 1984). However, problems with quantification of low concentrations of vinyl chloride in exhaled air at ambient air levels of <50 ppm has led to limited application of this method (Tarkowski 1984).

A reasonable correlation was noted between urinary output of thiodiglycolic acid, the principal metabolite of vinyl chloride, and ambient levels to which persons were exposed (Heger et al. 1982). Measurement of urinary thiodiglycolic acid can be used as an indicator of vinyl chloride intake only as long as individual variability in metabolism due to such factors as liver disease, use of drugs, alcohol intake, etc., can be accounted for. Therefore, it appears that there is

Table 8.1. Analytical methods for the quantification of vinyl chloride

Sample matrix	Sample preparation	Quantification method[a]	Detection limit	Accuracy/ % recovery	References
Occupational air	Vinyl chloride in air absorbed in activated carbon trap and desolved by CS_2	GC/FID	0.8 ppb	94% at 0.4–26 ppm	NIOSH 1984
Ambient indoor and outdoor air	Air containing vinyl chloride passed through activated carbon trap and desolved by dichloromethane or carbon disulfide	GC/FID	4 ppb	NR[b]	IARC 1978, Miller and Beizer 1985
Air	Adsorption on Tenax GC; thermal desorption	HRGC/MS	0.33 ppb	NR	Krost et al. 1982
Air	Grab sample collected in electro-polished stainless steel cans	GC/MS at subambient temperature	0.005 ppb	NR	Grimsrud and Rasmussen 1975a,b
Air	Air prefiltered by $Na_2S_2O_3$-treated glass fiber filter was passed through spherocarb adsorbent cartridge and thermally desorbed	HRGC/FID and HRGC/MS	0.005 ppb	NR	Harkov et al. 1983, 1984
Automobile exhaust	Exhaust samples taken into aluminized plastic bags	HRGC/FID	20 ppb	NR	Hästinea et al. 1979
Air	Trapped in cold Tenax-GC trap; thermal desorption	GC/FID	NR	79–104 at 6–60 ppb	Ives 1975
Air	Sample collected in pressurized canister is passed through a freezeout loop and subsequently heated	GC/ECD	0.01 ppb	NR	Rasmussen et al. 1977, Harsch et al 1979
Air	Sample collected in polyester-coated plastic bags concentrated by freezeout and subsequently heated	GC/FID	0.006 ppb	NR	McMurry and Tarr 1978
Drinking water and wastewater	Purge and trap in Tenax GC; thermal desorption	GC/HSD, GC/MS (EPA Method No 601 and 624)	0.18 ppb (HSD)	102% at 0.82–32.3 ppb	EPA 1982a, APHA 1985

Table 8.1 (continued)

Sample matrix	Sample preparation	Quantification method[a]	Detection limit	Accuracy/ % recovery	References
Groundwater, liquid, and solid matrices	Purge at 45°C and trap in Tenax GC; thermal desorption	GC/HSD (EPA Method No-8010)	0.18 ppb	102% at 0.82–32.3 ppb	EPA 1982b
Drinking water	Purge and trap in Tenax GC; thermal desorption	HRGC/Hall detector, HRGC/PID (EPA Method 502.2, 524.2)	0.04 ppb (Hall) 0.02 (PID)	100–119 at 5–10 ppb	Reding 1987
Migration of monomer into *drinking water* for polyvinyl pipes	Small sections put in water in sealed serum vial for a number of days at 20°C; solution directly injected into a GC	GC/FID	NR	NR	Ando and Sayáto 1984
Water	Sample in sealed vial is equilibrated at constant temperature; headspace gas injected into a GC	GC/FID	<1 ppb	NR	IARC 1978
Landfill gas	Gas from landfill sites sampled by PTFE tubing inside drive-in piezometers was absorbed in Tenax GC 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
Sediment and oyster	Homogeneous sample mixed with water and vinyl chloride purged into a closed loop; gas in closed loop injected into a GC	GC/ECD	2 ppb (sediment)	NR	Wang et al. 1985
Food (orange *drink*, wine, olive oil)	Sample sealed in vials and equilibrated at 40°C for 2 h; headspace gas injected into GC	GC/FID	NR	NR	Chudy and Crosby 1977
Foodstuffs	Sample sealed in vials and equilibrated at 40°C for a minimum of 2 h; headspace gas injected into GC	GC/FID	1–5 ppb	NR	IARC 1978
Breath	Cryogenic trapping of expired air; thermal desorption into GC	GC/FID, GC/ECD and GC/MS	NR	NR	Conkle et al 1975

Table 8.1 (continued)

Sample matrix	Sample preparation	Quantification method	Detection limit	Accuracy/ % recovery	References
Breath	Breath collected in Tedlar bag is concentrated by Tenax GC adsorbent and thermally desorbed	GC/MS	1 ppt	77-110	Umana et al. 1985
Whole blood, plasma, and serum	Sample equilibrated in a sealed vial at 65°C; headspace gas injected into GC	GC/ECD	NR	NR	Ramsey and Flanagan 1982
Blood, urine	Sample purged and trapped in Tenax GC; thermally desorbed	GC/MS	Screening method	NR	Bulkon and Leary 1979
Urine	Sample solvent extracted, extract methylated, and cleaned by ion-exchange resin	GC/MS or HRGC/MS	50 ppb (urinary thiodiglycolic acid)	NR	van Sittert and deJong 1985, Müller et al. 1979
Tissue (liver, lung, kidney, brain)	Homogenized samples mixed with ethanol-water mixture equilibrated in a sealed vial at 70°C; headspace gas injected into GC	GC/FID	30 ppb	75-92%	Zuccato et al. 1979
Tissue	Sample mixed with a proteolytic enzyme incubated at 65°C; headspace gas analyzed	GC/ECD	NR	NR	Ramsey and Flanagan 1982

[a]GC = Gas chromatography; HRGC = high-resolution gas chromatography; FID = flame ionization detection; MS = mass spectrometry; ECD = electron capture detector; HSD = halide-sensitive detector; PID = photoionization detector.

[b]Not reported.

no suitable biological medium that can be used as a reliable indicator for vinyl chloride exposure (Tarkowski 1984). The commonly used methods for the quantification of vinyl chloride in biological media are given in Table 8.1.

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

Advisory guidance issued by the World Health Organization (WHO) for vinyl chloride was not located in the available literature.

9.2 NATIONAL

9.2.1 Regulations

9.2.1.1 Air

The Occupational Safety and Health Administration (OSHA 1983) regulations for vinyl chloride state that a worker must not be exposed to a concentration of >1 ppm over any 8-h period and that a worker must not be exposed to >5 ppm for any period of time exceeding 15 minutes. Direct contact with liquid vinyl chloride is prohibited.

EPA (1982c) has established emission standards for vinyl chloride released to the atmosphere by vinyl chloride and polyvinyl chloride plants. Emissions are not to exceed 10 ppm.

9.2.1.2 Water

Pursuant to the Safe Drinking Water Act, EPA (1987c) promulgated a maximum contaminant level (MCL) for vinyl chloride of 0.002 mg/L, equivalent to an estimated cancer risk of 10^{-5}. This regulation is to become effective January 9, 1989 and is to apply to all community drinking water systems that regularly serve the same 25 persons for at least 8 months/year.

9.2.1.3 Food

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

9.2.1.4 Other

EPA (1982d) has designated vinyl chloride as a hazardous constituent of solid waste and requires that it be handled in accordance with the regulations governing the same. EPA (1987d) lists a reportable quantity (RQ) for vinyl chloride of 1 lb, but proposes that the RQ be changed to 10 lb. The RQ is the quantity that, if released to the environment, must be reported immediately to the National Response Center.

9.2.2 Advisory Guidance

9.2.2.1 Air

The American Conference of Governmental Industrial Hygienists (ACGIH 1986b) recommends a Threshold Limit Value (TLV)-TWA for vinyl chloride of 5 ppm and a Short-Term Exposure Limit (STEL) of 10 ppm with the notation that the compound is a recognized human carcinogen. The National Institute of Occupational Safety and Health (NIOSH 1975) concluded that a TLV for vinyl chloride was inappropriate because of its carcinogenicity. NIOSH (1975) recommended that any workers exposed to vinyl chloride should wear an air-supplied respirator.

9.2.2.2 Water

EPA (1980), based on a human q_1^* of 1.74×10^{-2} $(mg/kg/day)^{-1}$ calculated from the incidence of tumors in a preliminary report of an inhalation study in rats (Maltoni and Lafemine 1975), estimated levels in ambient water of 20, 2, and 0.2 $\mu g/L$ associated with cancer risks of 10^{-5}, 10^{-6}, and 10^{-7}, respectively, assuming daily consumption of 2 L water and 6.5 g fish and shellfish. For consumption of fish and shellfish alone, water concentrations of 5246, 525, and 52.5 $\mu g/L$ correspond to cancer risk estimates of 10^{-5}, 10^{-6} and 10^{-7}, respectively. More recently, EPA (1985a, 1987b) estimated that cancer risk levels of 10^{-4}, 10^{-5}, and 10^{-6} would result from daily consumption of drinking water containing vinyl chloride at 1.5, 0.15, and 0.015 $\mu g/L$, respectively.

EPA (1985a, 1987a) promulgated health advisories for vinyl chloride in drinking water. A 10-day health advisory of 2.6 mg/L was based on a NOAEL of 30 mg/kg/day in a 13-week gavage study by Feron et al. (1975). Because data were not sufficient for derivation of a 1-day health advisory, the 10-day health advisory was adopted as a conservative 1-day health advisory. Longer-term health advisories of 0.013 mg/L for a 10 kg child and 0.046 mg/L for an adult were estimated from the NOAEL of 0.13 mg/kg/day in a lifetime dietary study in rats (Dow Chemical Company 1984, Til et al. 1983).

9.2.3 Data analysis

9.2.3.1 Reference doses (RfDs)

Reference doses for vinyl chloride have not been estimated by EPA.

9.2.3.2 Carcinogenic potency

EPA (1985a) classified vinyl chloride in IARC Group 1, and more recently, EPA (1987a) assigned the compound to Carcinogen Assessment Group (CAG) Class A. By either classification scheme, the designations have the same meaning, that evidence for carcinogenicity to humans is so convincing as to be considered "sufficient." EPA has derived several estimates of carcinogenic potency for vinyl chloride for both oral and inhalation exposure. In an early estimate, EPA (1980) derived a q_1^* for human oral exposure of 1.74×10^{-2} $(mg/kg/day)^{-1}$ based on preliminary reports of the incidence of total tumors in rats of both sexes exposed to vinyl chloride by inhalation at concentrations up to 10,000 ppm

(Maltoni and Lefemine 1975). A subsequent estimate of potency for oral exposure is 2.3 $(mg/kg/day)^{-1}$, which appears in EPA (1985a, 1987a) and represents the most recent analysis by CAG (EPA 1987a). This estimate was based on the incidence of lung and liver tumors in both sexes of rats exposed for lifetime to diets that contained vinyl chloride (Feron et al. 1981).

The first estimate for carcinogenic potency by inhalation exposure, 2.5×10^{-2} $(mg/kg/day)^{-1}$ derived in EPA (1984), was based on the same preliminary inhalation data (Maltoni and Lefemine 1975) that was used as the basis of the EPA (1980) oral estimate. A more recent estimate of 2.95×10^{-1} $(mg/kg/day)^{-1}$ (EPA 1985b) was based on the final report of the incidence of liver angiosarcomas in male and female rats exposed for up to 1 year to concentrations up to 30,000 ppm (Maltoni et al. 1980, 1981).

9.3 STATE

(Regulations and advisory guidance from the states were still being compiled at the time of printing.)

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11. GLOSSARY

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

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 time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--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.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

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.

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

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration(LO) (LCLO)--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) (LDLO)--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.

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

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of 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 chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) 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 a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are 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.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

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

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

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

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb 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-h 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 T xicity--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-h workday or 40-h workweek.

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 humans, (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.

APPENDIXES

APPENDIX A: PEER REVIEW

A peer review panel was assembled for vinyl chloride. The panel consisted of the following members: Dr. Richard Monson, Harvard University; and Dr. Anthony Guarino, South Alabama University. 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 the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated into 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 this record.

APPENDIX B: FEDERAL REGISTER ANNOUNCEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
ENVIRONMENTAL PROTECTION AGENCY
(ATSDR-2; FRL-3269-7)

NOTICE OF AVAILABILITY OF TOXICOLOGICAL PROFILES

AGENCIES: Department of Health and Human Services (DHHS): Agency for Toxic Substances and Disease Registry (ATSDR); and Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Superfund Amendments and Reauthorization Act (SARA) (Public Law 99-499) amends the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund) (42 U.S.C. 9601 et seq.) by establishing certain requirements for the Agency for Toxic Substances and Disease Registry (ATSDR) of DHHS and EPA with regard to hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List (NPL). Among these statutory requirements is a mandate for the Administrator of ATSDR to prepare toxicological profiles for each substance previously included on the first priority list of 100 chemicals. The list identified the first 100 chemicals which both Agencies determined posed the most significant potential threat to human health. This list was published in the Federal Register on April 17th, 1987 (52 FR 12866) as required by SARA section 110.

This notice announces the expected availability dates of the first 25 draft toxicological profiles for review and comment.

AVAILABILITY: The following draft toxicological profiles are expected to be publicly available by the date indicated:

Date/Profile	CAS #
October 17, 1987:	
Benzo(a)anthracene	56-55-3
Benzo(a)pyrene	50-32-8
Beryllium	7440-41-7
Chloroform	67-66-3
Chromium	7440-47-3
Chrysene	218-01-9
Dibenzo(a,h)anthracene	53-70-3
Heptachlor/Heptachlor epoxide	76-44-8 / 1024-57-3
Nickel	7440-02-0
N-Nitrosodiphenylamine	86-30-6
October 29, 1987:	
Aldrin/dieldrin	309-00-2 / 60-57-1
Arsenic	7440-38-2
Benzo(b)fluoranthene	205-99-2
PCBs - Aroclor 1260, 1254, 1248,	11096-82-5, 11097-69-1, 12672-29-6
1242, 1232, 1221,	53469-21-9, 11141-16-5, 11104-28-2
1016	12674-11-2
2,3,7,8- Tetrachlorodibenzo-p-dioxin	1746-01-6
November 5, 1987	
Benzene	71-43-2
Bis(2-ethylhexyl)phthalate	117-81-7
Cadmium	7440-43-9
1,4-Dichlorobenzene	106-46-7
Methylene chloride	75-09-2
November 30, 1987	
Cyanide	57-12-5
Lead	7439-92-1
Tetrachloroethylene	127-18-4
Trichloroethylene	79-01-6
Vinyl chloride	75-01-4

A full 90-day public comment period will be provided for each profile, starting from the actual release date. The close of the comment period for each draft profile will be indicated on the front of each profile.

Requests for draft toxicological profiles should be sent to:

Ms. Georgi Jones
Director, Office of External Affairs
Agency for Toxic Substances and Disease Registry
Chamblee 28 South
1600 Clifton Rd.
Atlanta, GA 30333

Specify the profiles you wish to review. One copy of each profile requested will be forwarded, free of charge, as they become available. In the case of undue delays, requestors will be notified.

Five copies of all comments should be sent to Ms. Jones at the above address by the end of the comment period. All written comments and the draft profiles will be available for public inspection at the Agency for Toxic Substances and Disease Registry (ATSDR), Building 28 South, Room 1103, 4770 Buford Highway, NE, Chamblee, GA, from 8am to 4:30pm, Monday through Friday, except legal holidays. Written comments and other data submitted in response to this notice and the draft toxicological profiles should bear the docket control number ATSDR-2.

SUPPLEMENTARY INFORMATION:

I. BACKGROUND

On October 17, 1986, the President signed the Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499), which extends and amends the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund, 42 U.S.C. 9601 et seq.).

Section 110 of SARA amends section 104(i) of CERCLA by establishing requirements for the preparation of: (1) lists of hazardous substances in order of priority, (2) toxicological profiles of those substances, and (3) a research program to fill data gaps associated with the substances.

In compliance with section 104(i)(2)(A) of CERCLA, ATSDR and EPA published on April 17, 1987 (52 FR 12866) the first priority list of 100 hazardous substances. This priority list of 100 was further broken down into four groups of 25 chemicals. The first group of 25 was to be the subject of the second phase of the requirements, i.e., the development of the first set of toxicological profiles. Section 104(i)(3) of CERCLA spells out the content of these profiles and the timetable by which they must be developed. Profiles on at least 25 substances on the first priority list were to be completed within one year of the enactment of SARA (by October 17, 1987). The remaining seventy-five are to be completed at a rate of at least twenty-five per year with the total 100 completed within four years after the enactment of the SARA amendments. Revision and republication is mandated as necessary but no less often than once every three years.

Each profile is required to include an examination, summary and interpretation of available toxicological information and epidemiologic evaluations. This information and data are to be used to ascertain the levels of significant human exposure for the substance and the associated health effects. The profiles must also include a determination of whether adequate information on the health effects of each substance is available or in the process of development. The Agencies' intention is that this information be used to identify the key toxicological testing needs that when filled will improve our ability to define significant human exposure levels.

The toxicological profiles are to be provided to the States and made available to the public. The profiles are to be prepared in accordance with the guidelines developed by ATSDR and EPA. These guidelines were published along with the priority list of 100 in the April 17, 1987 Federal Register Notice (52 FR 12870).

This current notice announces the projected availability dates of the first 25 draft toxicological profiles. The documents have undergone extensive internal review and have been subject to scientific and technical peer review by outside experts. We are now announcing their availability and encouraging public participation and comment on the further development of these profiles. Although the profiles will not be completed by the October 17, 1987 deadline, we believe that the extra time given to peer review and public review and comment is important to the development of quality profiles of scientific merit.

Although we are reasonably confident that the key studies for each of the 25 substances were considered during the profile development process, this *Federal Register* notice solicits any significant studies, including unpublished data, which may aid the revision of these draft profiles.

II. LEVELS OF SIGNIFICANT HUMAN EXPOSURE

The setting of specific levels of significant human exposure has presented a unique set of problems. The significance of a specific level of a hazardous substance depends on the context in which that level is evaluated. For example, a low level that may be insignificant with respect to causing acute, immediately debilitating symptoms may be highly significant with respect to causing gradual, chronic effects over a longer term. Since these profiles are intended for use by a diverse group of people who have different situations in which to interpret the significance of specific levels, it was considered appropriate at this time to describe the range of exposures over which effects may occur (where data are available), and to allow the user to make determinations as to which type of effect is significant in any particular instance. A format for graphically displaying the levels of significant human exposure has been developed and is used in the profiles to present the ranges over which effects may be observed.

We encourage public comment and recommendations on this specific issue.

III. SOLICITATION OF PUBLIC COMMENT

We are soliciting public comment on all phases of the development of the toxicological profiles. A previous Federal Register notice, published on April 17, 1987 (52 FR 12866) solicited comment on the first priority list of hazardous substances. We are currently reviewing those comments and are evaluating the impact that those comments may have on the priority list and the methods used in its development.

As the first 25 toxicological profiles become available in draft form, we are eager to provide them to the States, industry, public health professionals, scientists and the general public. We welcome comment and feedback on the content of the profiles; the format and scope of the documents; the process used in the development of the levels of significant human exposure and the overall process used in the development of the profiles.

There are specific items that we would like to draw to the attention of the reader and would strongly encourage as candidates for close attention during the comment period.

A. PUBLIC HEALTH STATEMENT

The draft profiles include a public health statement which is intended to provide the lay public with a concise statement of the general health risks associated with the chemical of concern. The summary as originally planned should be able to stand alone. If removed from the rest of the document, it should still be capable of conveying

to the public the substantive health concerns associated with the substance. We are also considering the development of more abbreviated versions of the public health statements and are evaluating a number of different formats. This notice specifically invites comments on the existing public health effects statements in the draft profiles and solicits recommendations for alternative approaches.

B. DATA/STUDIES USED IN THE DEVELOPMENT OF THE PROFILES

In general, and for each chemical-specific profile, have the appropriate studies been used in the development of these documents? Our concern here is that we capture the critical, or "key", studies but not miss other data that may be important in the valid evaluation of the toxicological profile chemicals.

C. FORMAT AND CONTENT OF THE PROFILES

The draft profiles represent our best effort to provide the information required by Section 104 (i)(3) of CERCLA in the most useful format for the various identified users of the profiles, given the constraints of the tight timeframe. Every effort has been made to define sections clearly and to format the documents in such a way that they can be used as resource documents by many different audiences. We specifically request comment on the format and content of the initial set of profiles, including how the format might be modified for subsequent sets of profiles.

D. LEVELS OF SIGNIFICANT HUMAN EXPOSURE

What is the most useful way of presenting this type of information? For this first generation of profiles we have selected a graphic presentation that reflects a "range" of values that covers both upper and lower bounds of effect levels. Is this more useful than a single number? Are there other ways of presenting this type of information that would be more useful to the eventual user?

E. IDENTIFICATION OF SIGNIFICANT DATA GAPS

The process used to develop the draft profiles has resulted in the identification of the full range of health effects data gaps associated with each chemical. However, depending on individual circumstances some subset of the identified data gaps may be essential in determining levels of significant exposure, while other data gaps may be less immediate. ATSDR, EPA, and the National Toxicology Program (NTP) have been exploring ways to identify the critical data elements that are needed to establish significant human exposure levels. This notice specifically requests comment and suggestions for approaching this phase of the toxicological profile process.