DRAFT

TOXICOLOGICAL PROFILE FOR VINYL CHLORIDE

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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.

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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 t 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

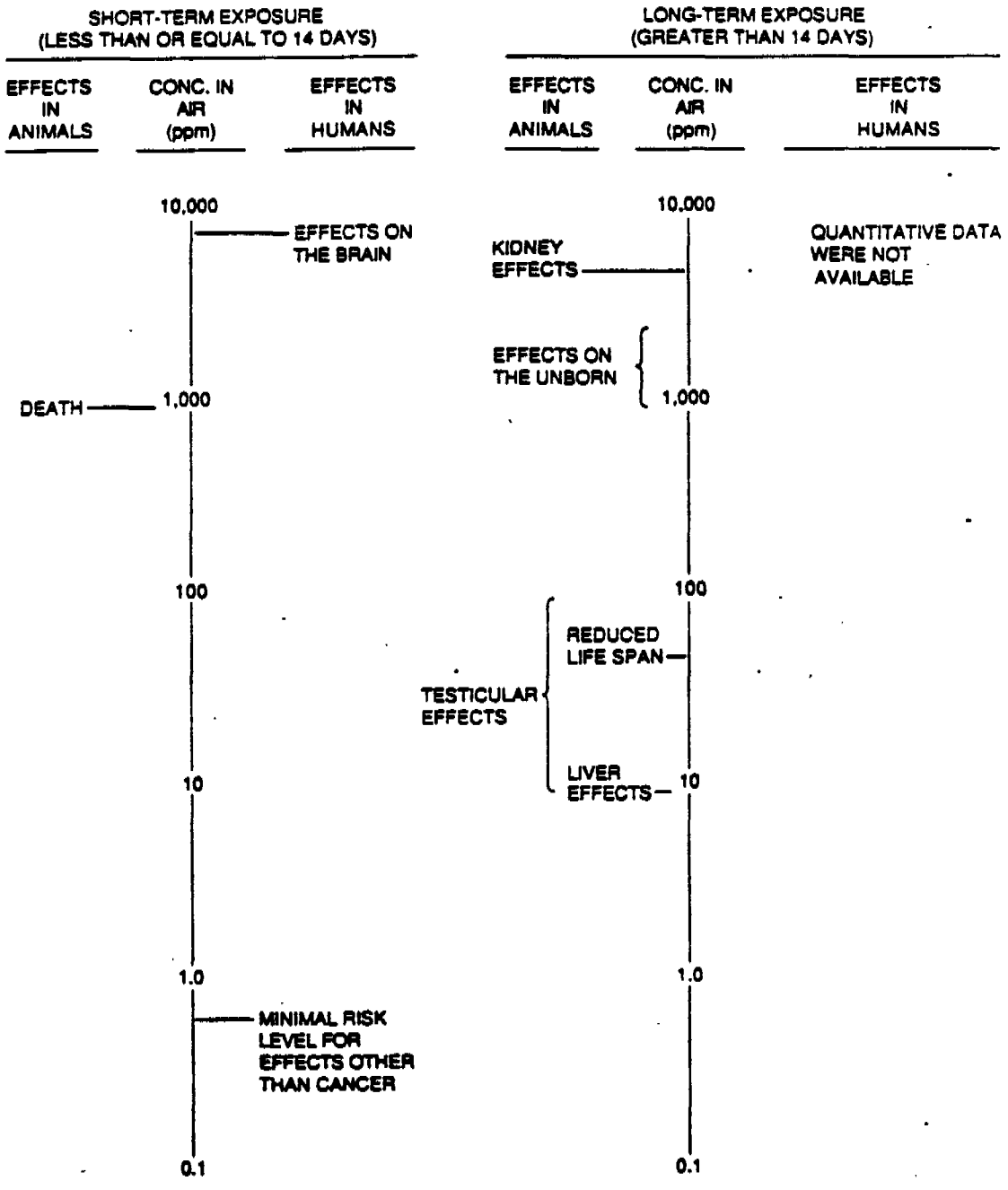

Fig. 1.1. Health effects from breathing vinyl chloride.

of air (ppm). In the second set of graphs, the same relati nship 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

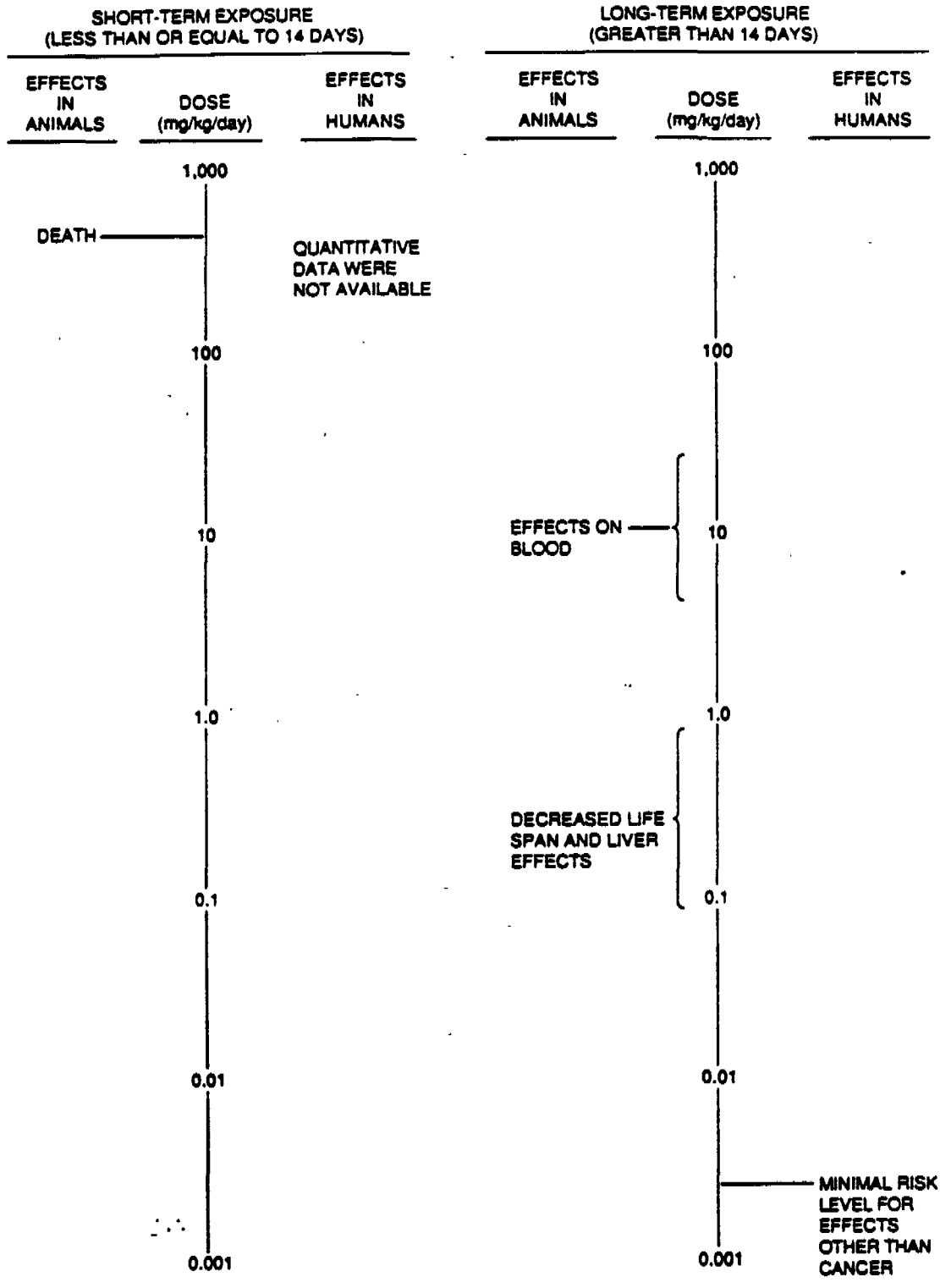

Fig. 1.2. Health effects from ingesting vinyl chloride.

the drinking water to 0.002 mg/L, starting January 9, 1989. In rder to limit ingesti n of vinyl chloride in food, the Fo d 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 where 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 pr fessionals 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

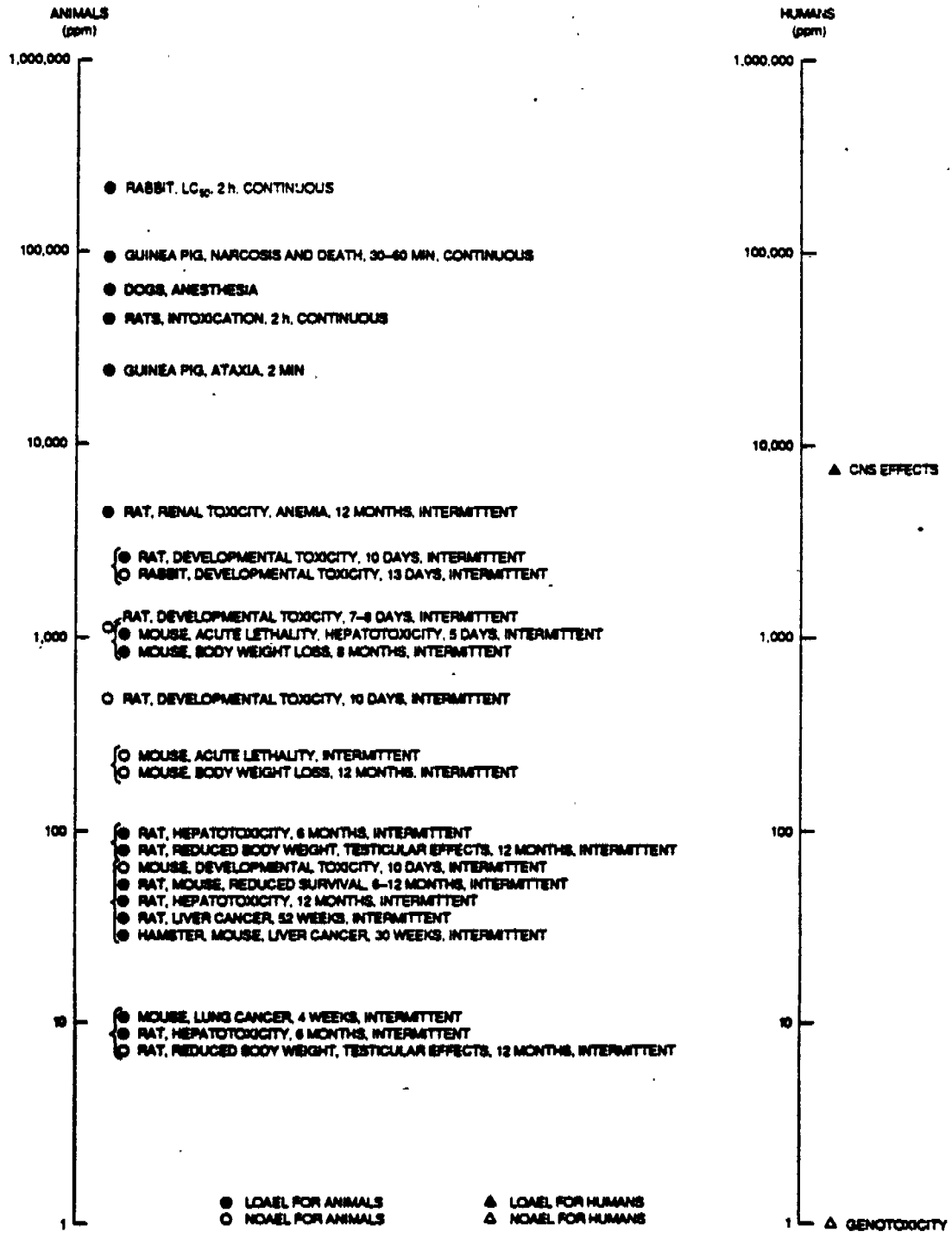

Fig. 2.1. Effects of vinyl chloride—inhalation exposure.

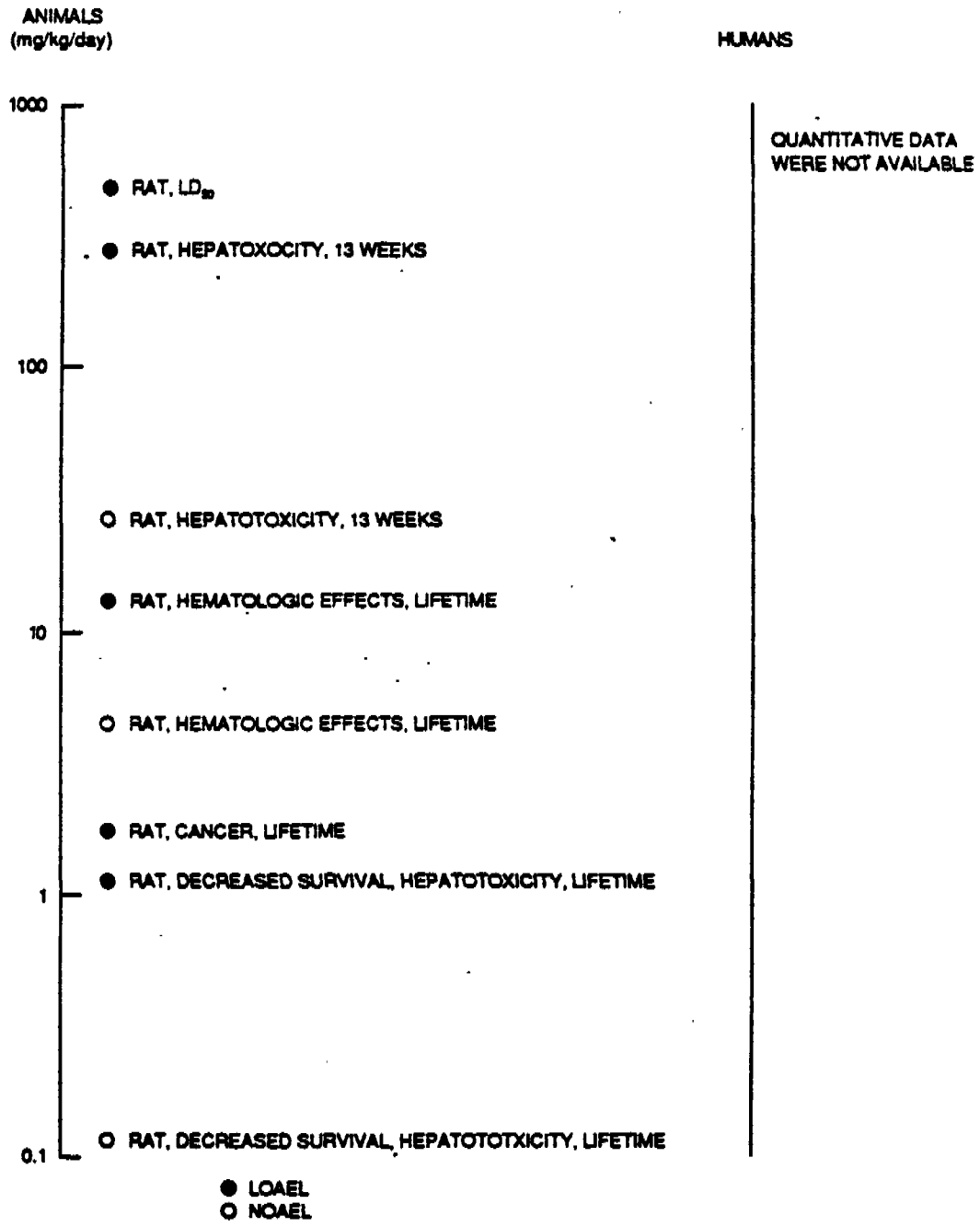

Fig. 2.2. Effects of vinyl chloride—oral exposure.

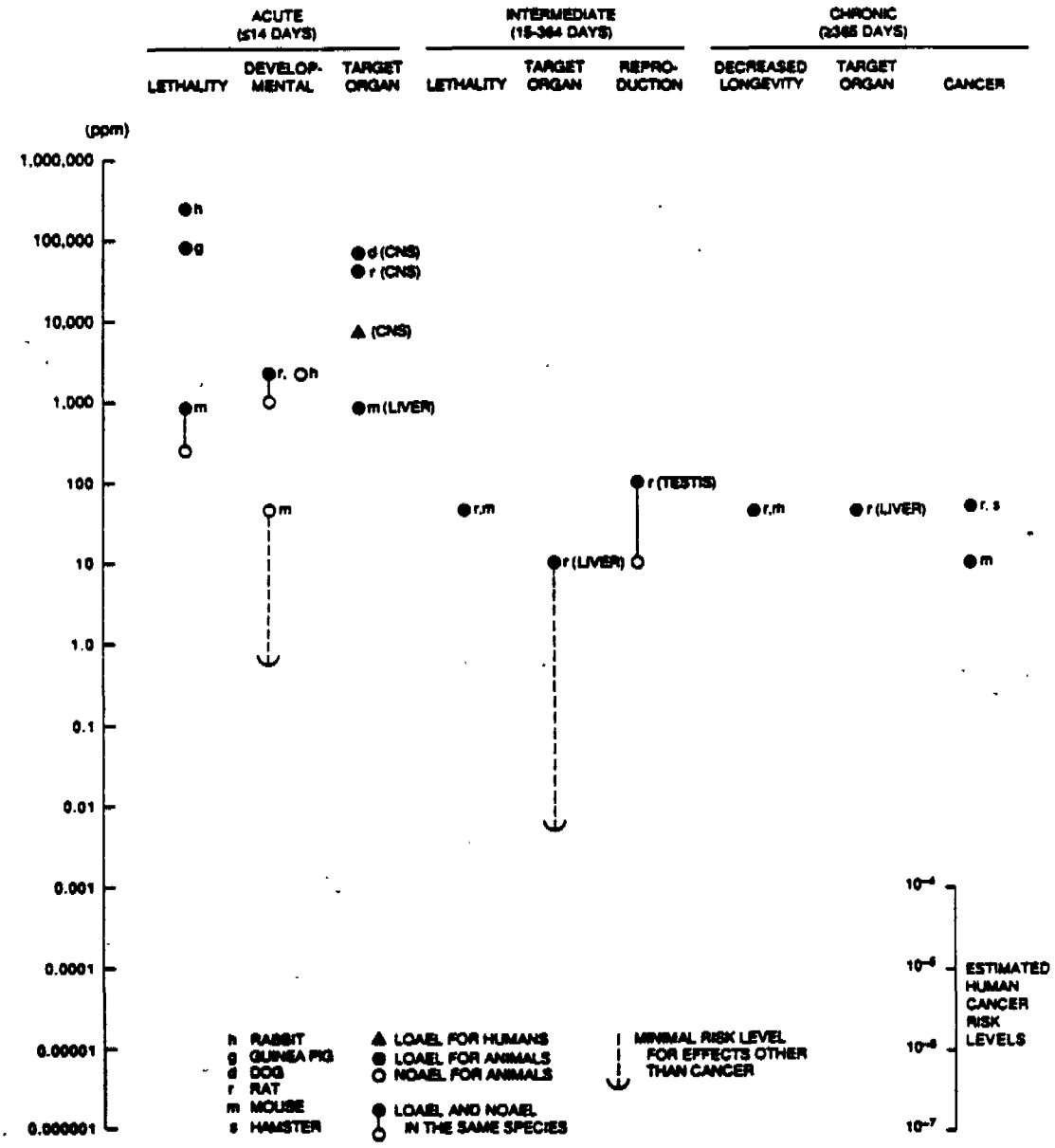

Fig. 2.3. Levels of significant exposure for vinyl chloride—inhalation.

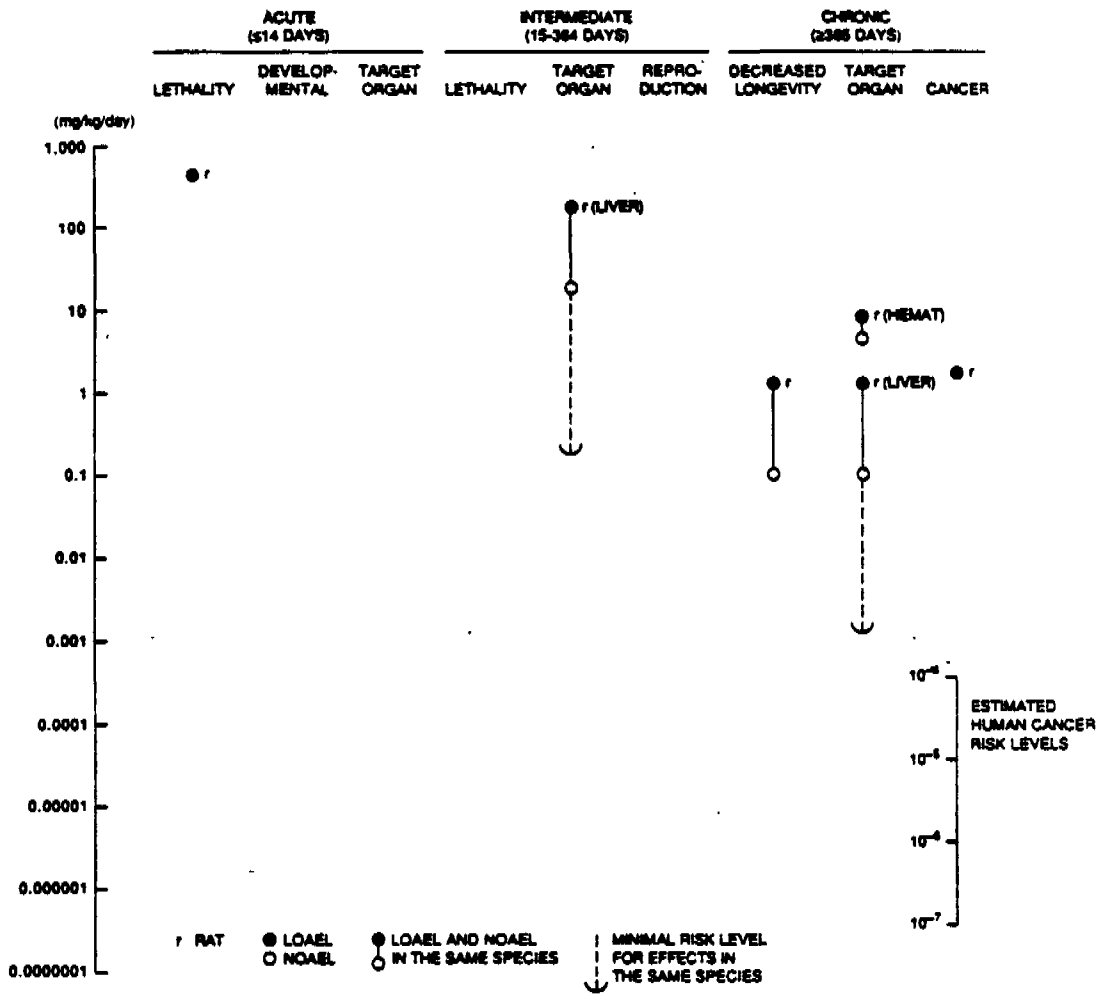

Fig. 2.4. Levels of significant exposure for vinyl chloride—oral.

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 c mfortably below the NOAEL of 250 ppm for lethality in mice and below the frank effect lev l 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

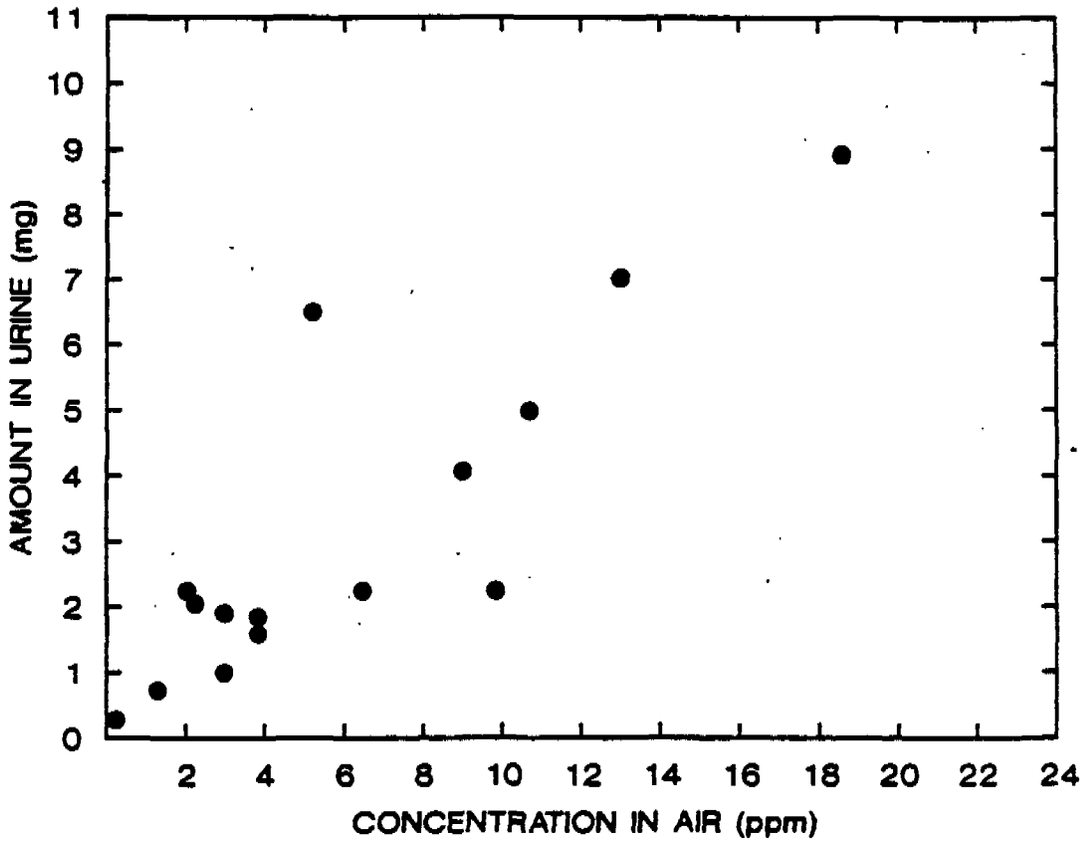

Fig. 2.5. Urinary output of thiodiglycolic acid from volunteers 12 h after exposure to vinyl chloride in air for 12 h. *Source*: Tarkowski 1984.

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).

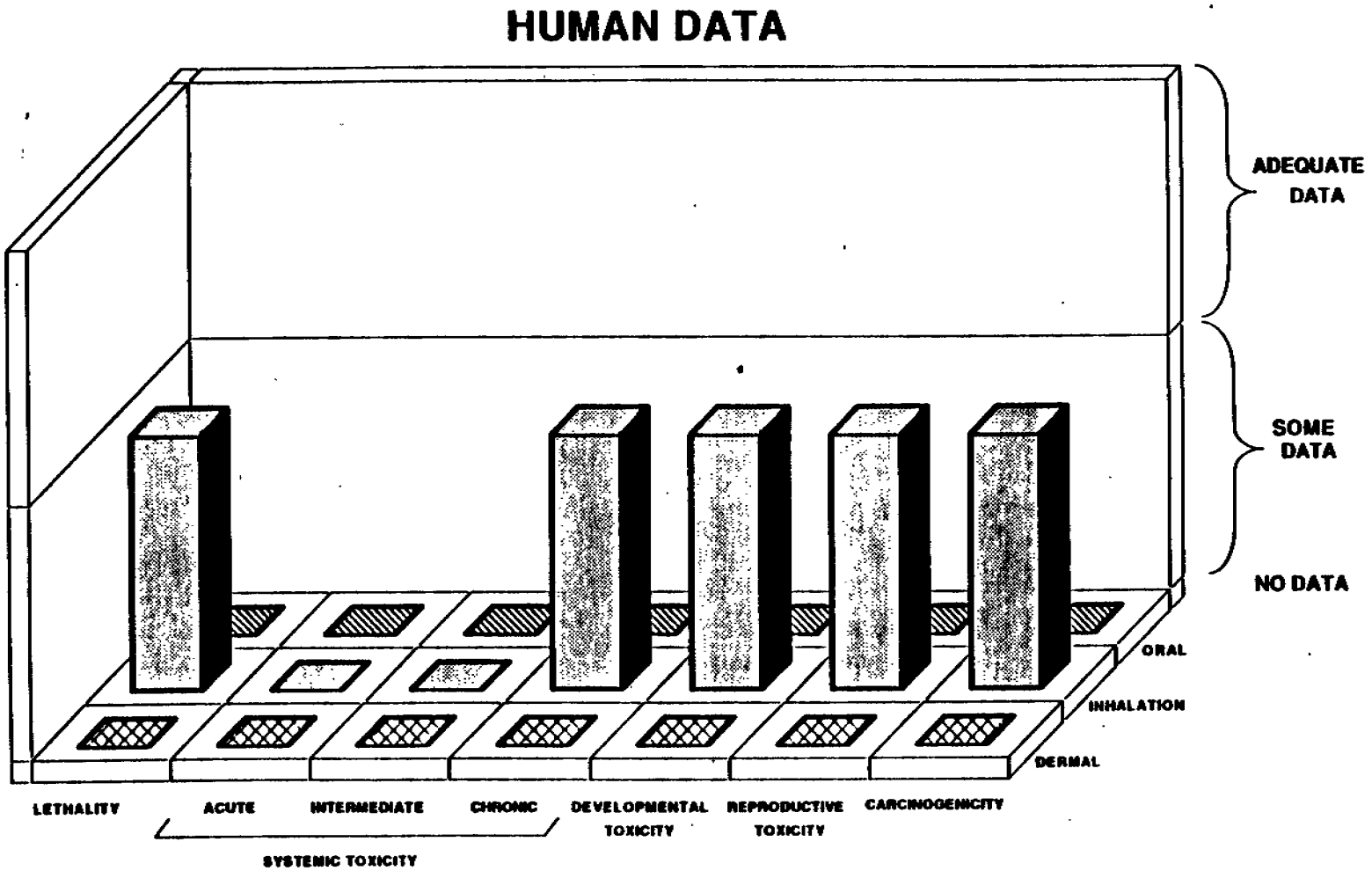

Fig. 2.6. Adequacy of the database on health effects of vinyl chloride (human data).

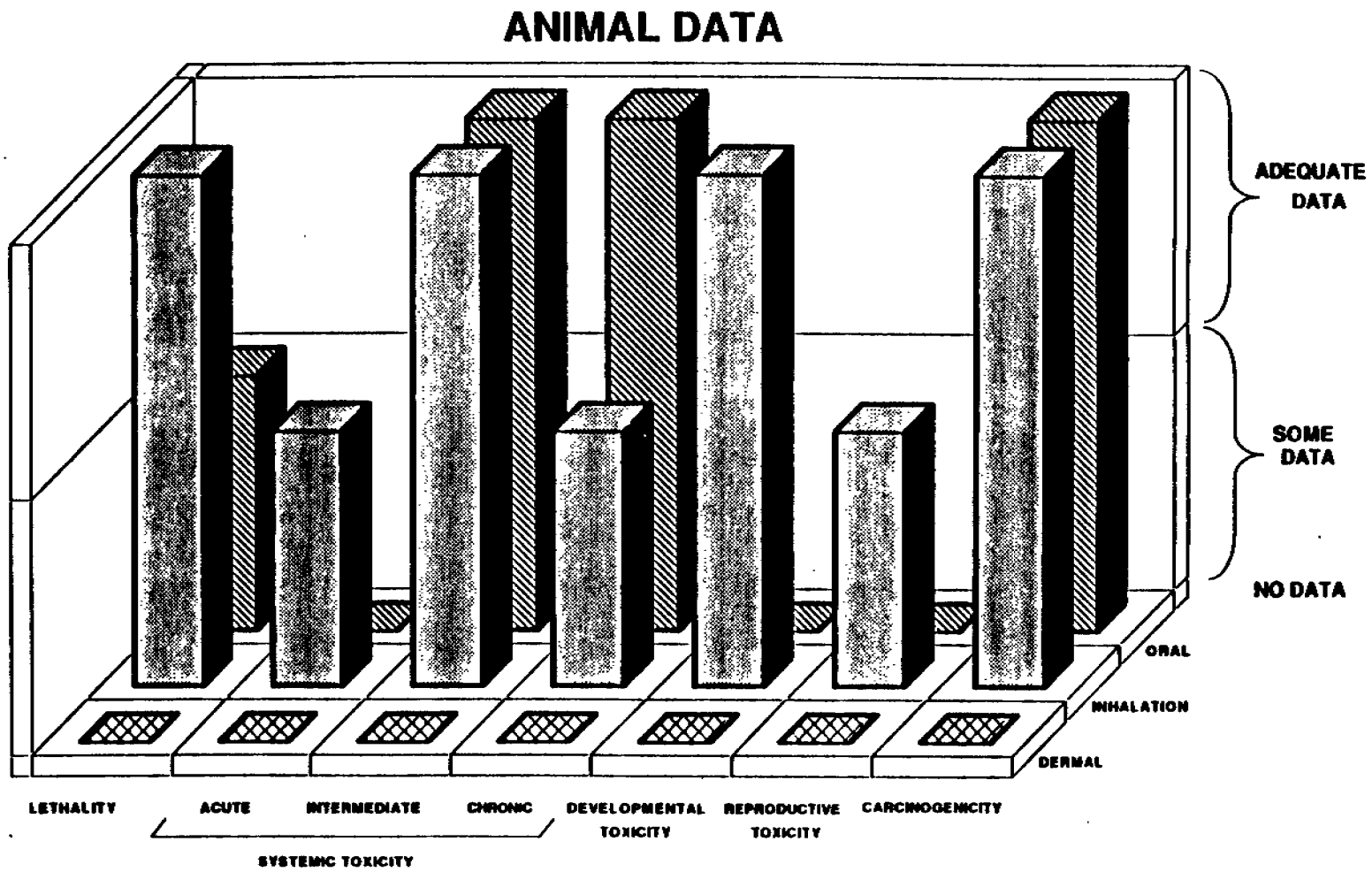

Fig. 2.7. Adequacy of the database on health effects of vinyl chloride (animal data).

2. F r human carcinogenicity, a substance is classified as either a "kn wn 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 d fining a range f 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 ther 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.