CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

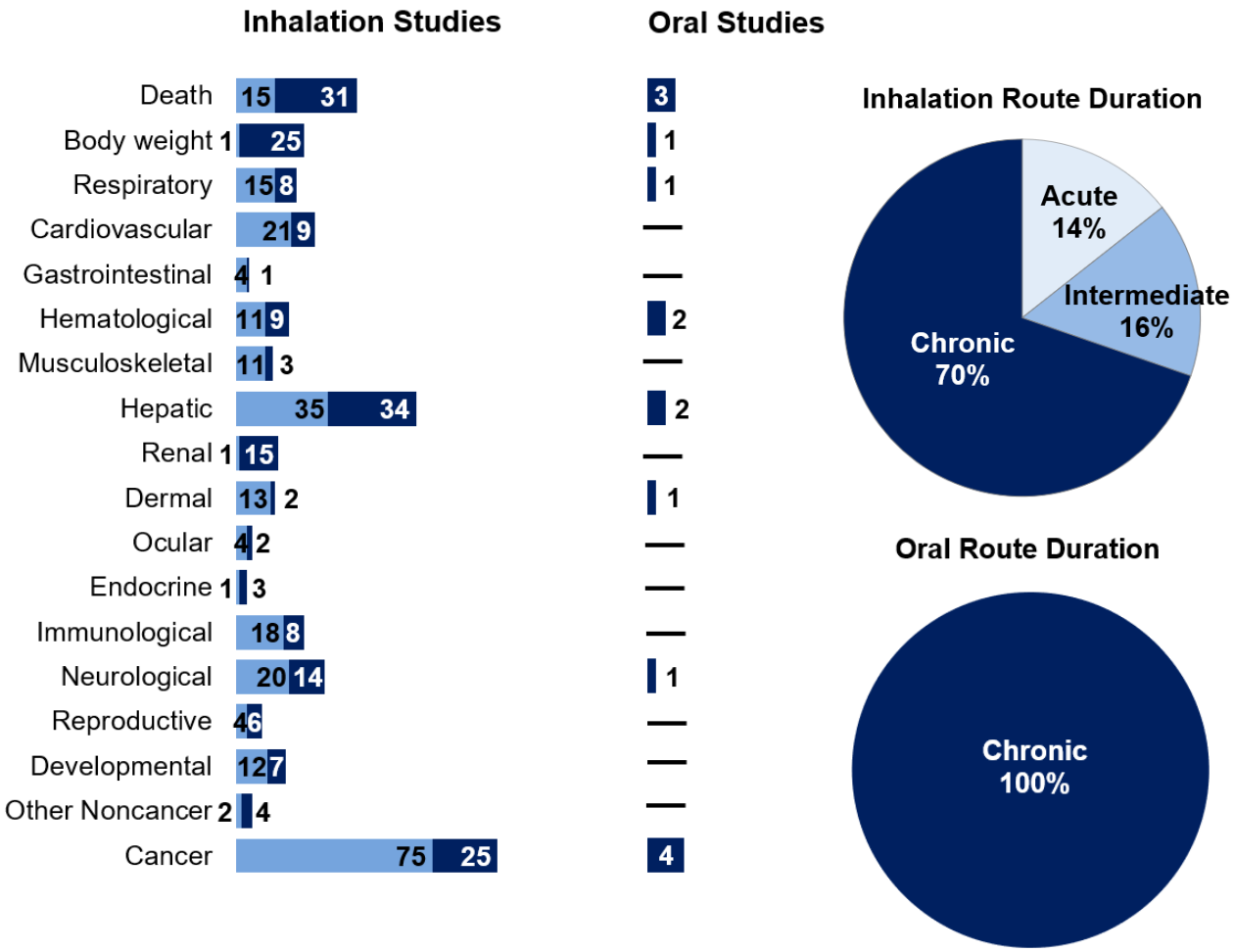
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl chloride that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of vinyl chloride. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Vinyl Chloride by Route and Endpoint*

Cancer, hepatic, and neurological effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **humans** (versus **animals**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No dermal studies in humans or animals were located. Most studies examined multiple endpoints.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL (no acute-duration oral studies are available). Acute-duration oral studies providing data at low doses are needed.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL (no intermediate-duration oral studies were available). Intermediate-duration oral studies providing data at low doses are needed.

Chronic-Duration MRLs. The inhalation database is inadequate to derive a chronic-duration inhalation MRL as data for the most likely sensitive effect (hepatic) was not reported for noncancer effects in chronic-duration studies. Chronic-duration inhalation studies providing data on noncancer liver effects at low doses are needed. The oral database is adequate to derive a chronic-duration MRL.

Health Effects. Identification of data needs for health effects in animal studies is limited to targets included in the systematic review.

Hepatic Toxicity. Hepatic effects are fairly well studied in humans. Liver effects in animals have been characterized in acute- and intermediate-duration inhalation studies and chronic-duration oral studies. Data on potential noncancer hepatic effects following chronic-duration inhalation exposure and acute- and intermediate-duration oral exposure may be helpful.

Immunotoxicity. Studies of workers occupationally exposed to vinyl chloride suggest that an autoimmune-like syndrome may develop. Immunotoxicity studies in animals that are known to have a propensity for developing autoimmune diseases may be useful in further evaluating this syndrome.

Neurotoxicity. Vinyl chloride is a central nervous system depressant following brief high-level inhalation exposures in humans. Limited animal studies found degenerative effects in central nervous system tissue following chronic-duration inhalation exposure to high levels of vinyl chloride. A study examining the effects of a range of lower doses would be informative. In addition, studies present suggestive evidence that vinyl chloride may also produce peripheral nerve damage in humans exposed chronically via inhalation. Animal studies examining histopathological and electrophysiological endpoints in peripheral nerves would be helpful for

assessing what doses may be associated with this effect. Epidemiological studies examining exposed populations for subclinical peripheral nerve damage would also be helpful.

Developmental Toxicity. Older epidemiological studies that addressed developmental toxicity in offspring of vinyl chloride workers have limitations. A few recent case-control studies evaluated the association between potential developmental effects and exposure to multiple compounds in air and drinking water during pregnancy; these found no effects. Additional, multiple- and low-dose concentration exposures in animal studies may help to further elucidate potential developmental effects and whether a dose-response exists. There are no developmental studies for oral exposures. Because of this deficiency, oral studies examining a range of developmental end points would be useful in assessing the possibility of these effects in humans.

Epidemiology and Human Dosimetry Studies. Virtually all of the data on effects in humans following inhalation exposure to vinyl chloride come from epidemiological studies of workers exposed during the production of PVC. Many of these studies are limited by the absence of information on individual exposure levels. In North America and Western Europe, only limited numbers of females have been studied. For the most part, studies examining the carcinogenic potential of vinyl chloride are adequate to distinguish an increased incidence of the rare cancer, angiosarcoma. However, many studies used cohorts that were too small to detect increases in other types of cancer (respiratory, central nervous system, lymphatic, or hematopoietic). Epidemiological studies designed to investigate reproductive and developmental effects of vinyl chloride have not been useful, in part because of a poor choice of statistical analysis, inadequate controls, lack of effects due to current low levels of exposure, or failure to account for nutritional status and exposures to other chemicals. Additional cohort studies of these end points would be useful for examining these effects in humans.

Biomarkers of Exposure and Effect. Vinyl chloride measured in expired air is an adequate indicator of recent, moderate-to-high-level exposures. However, for low-level exposures or exposures that occur over 1–2 hours prior to the time of measurement, this biomarker is not useful. Thiodiglycolic acid, a major urinary metabolite of vinyl chloride, has been used to monitor workers occupationally exposed to vinyl chloride; however, this biomarker is rapidly excreted and not specific for vinyl chloride; because it may also be produced as a result of the metabolism of 1,1-dichloroethene, ethylene oxide, or 2,2-dichloroethylether. The DNA adducts 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine, remain in the body longer than free vinyl chloride or thiodiglycolic acid; however, these adducts may also result from exposure to other compounds (e.g., vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene,

1,2-dichloroethane). Studies attempting to identify a metabolite more specific to vinyl chloride may be helpful in developing a biomarker suitable for improved medical surveillance, thereby useful for early detection and initiation of possible treatment.

Vinyl chloride-induced genetic alterations have been identified in the Ki-*ras* oncogene and the p53 tumor suppressor gene. Oncoproteins and p53 antibodies have been detected in the serum of cancer patients with angiosarcoma. Statistical analyses suggest a relationship between vinyl chloride exposure and the presence of these serum biomarkers. Further investigation into the ability of these assays to predict individuals at increased risk for developing angiosarcoma of the liver would be useful. Further work identifying the correlation between specific DNA adducts and genotoxicity would also be useful.

Absorption, Distribution, Metabolism, and Excretion. There are few data on humans for all toxicokinetic parameters across all exposure routes. There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of vinyl chloride administered via the oral route and the inhalation route but few describing the toxicokinetics of vinyl chloride administered via the dermal route. No information is available regarding dermal absorption of vinyl chloride from liquid or solid media (i.e., water, soil). Dermal exposure from these media is expected to be minimal; however, a study confirming this assumption would be useful. Furthermore, the intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. Therefore, information regarding differences in the metabolic pattern according to sex, age, nutritional status, and species and correlations to differences in health effects would also be useful.

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

Children's Susceptibility. Data needs relating to prenatal exposure and developmental effects are discussed in the Developmental Toxicity subsection above. Carcinogenicity studies with animals suggest that younger animals may be more sensitive to the toxicity and carcinogenicity of vinyl chloride than

mature animals. Further mechanistic research may be useful in establishing the mechanism of early life stage sensitivity in laboratory animals and determining whether it is anticipated to be relevant to humans. For example, the human embryonic liver does not express CYP2E1, but its expression rapidly increases during the first 24 hours after birth. Between the developmental ages of 1 and 10 years, children's CYP2E1 protein levels and enzyme activity are comparable to adults (EPA 2000). No studies were located that specifically address the toxicokinetics of vinyl chloride in children; however, the toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults. Further information on the toxicokinetics and toxicodynamics of vinyl chloride and metabolites during pregnancy, lactation, and early childhood would be valuable.

Physical and Chemical Properties. The physical and chemical properties of vinyl chloride are sufficiently well characterized to permit estimation of its environmental fate (Amoore and Hautala 1983; Cowfer and Gorensek 2006; EPA 1985a; Fire 1986; IARC 2012; Lewis 1996; Lyman et al. 1982; NLM 2023).

Production, Import/Export, Use, Release, and Disposal. Vinyl chloride is released primarily to the atmosphere via emissions from vinyl chloride and PVC manufacturing facilities (Hartmans et al. 1985; SRI 1990a, 1990b, 1993, 1994; TRI21 2023a). The risk of exposure to vinyl chloride is highest for workers in the plastics industry and populations living near industrial areas or hazardous waste sites. Production, use, and manufacturing methods are well described in the literature (Cowfer and Magistro 1985; NLM 2023; IARC 2012; SRI 1990a, 1990b, 1993, 1994; TRI21 2023a; USITC 1994). More current information on releases and disposal methods might assist in estimating potential exposures to vinyl chloride, particularly for populations living near hazardous waste sites.

Environmental Fate. Vinyl chloride primarily partitions to the air where it is degraded relatively quickly by photochemically produced hydroxyl radicals (Kwok and Atkinson 1995). It is removed from surface water and soils mainly by volatilization and photodegradation (EPA 1976). Biodegradation and hydrolysis also occur (Barrio-Lage et al. 1990; Castro et al. 1992a, 1992b; Davis and Carpenter 1990; EPA 1976; Gossett 2010), but these reactions are generally slow as compared to the volatilization rate. Bacterial communities capable of degrading vinyl chloride in aquatic environments under both aerobic and anaerobic conditions have been identified (Coleman and Spain 2003; Coleman et al. 2002; Danko et al. 2006; Puentes Jacome et al. 2019; Richards et al. 2022; Zalesak et al. 2021). More information regarding the transformation and degradation in soil and water would be helpful for defining the potential pathways for human exposure.

Bioavailability from Environmental Media. Vinyl chloride can be absorbed following inhalation (Bolt et al. 1977; Krajewski et al. 1980; Withey 1976), oral (Feron et al. 1981; Watanabe et al. 1976a; Withey 1976), and to a much lesser extent, dermal exposure (Hefner et al. 1975a). These routes of exposure may be of concern to humans because of the potential for vinyl chloride to contaminate air (Bloomdahl et al. 2014; Gordon and Meeks 1977; Jia and Foran 2013; Lim and John 2020; McCarthy et al. 2006; Stephens et al. 1986), water (McMahon et al. 2019; Squillace et al. 2004; USGS 2006, 2014; Walter et al. 2011), and food (Gilbert et al. 1980; McNeal et al. 2003). Information regarding the bioavailability from ingestion and dermal contact with contaminated soils would be helpful, particularly for populations living near hazardous waste sites, although vinyl chloride is not believed to be considerably absorbed through skin.

Food Chain Bioaccumulation. Vinyl chloride can bioconcentrate to a limited extent in aquatic organisms (EPA 1982a; Freitag et al. 1985). Biomagnification of vinyl chloride in terrestrial and aquatic food chains does not appear to be important because of its high volatility and the fact that it is readily metabolized by higher-trophic-level organisms (Freitag et al. 1985; Lu et al. 1977). No data were located regarding biomagnification in terrestrial food chains.

Exposure Levels in Environmental Media. Vinyl chloride has been detected in air, water, sediment, soil, cigarette smoke, and food (references in Section 5.5). Site-specific data on concentrations of vinyl chloride in air, soil, and water would be helpful in estimating the risk of exposure for populations living in the vicinity of hazardous waste sites. Data on the extent of release of vinyl chloride from PVC pipes has been reported (Borrelli et al. 2005). Data on the potential release of vinyl chloride from car interiors would assist the estimation of the risk of exposure of the general population.

Exposure Levels in Humans. Vinyl chloride has been detected in exhaled breath of humans (Baretta et al. 1969; Conkle et al. 1975), but no other body burden studies are available. More information on exposure levels for populations living in the vicinity of hazardous waste sites would be helpful. This information is necessary for assessing the need to conduct health studies on these populations. It is noted that it is difficult to directly analyze for vinyl chloride in humans, which may limit the practicality of conducting these tests.

Exposures of Children. No data exist regarding the levels of vinyl chloride in children. Children are exposed to vinyl chloride by the same pathways that affect adults; inhalation of ambient air and the

ingestion of foods or drinking water. Data regarding the use of PVC in children's products is limited; as of 2012, no determinative use of PVC in products intended for children has been reported in the United States. According to information from CDR for 2020, there are no reported consumer or commercial uses of vinyl chloride in products intended for children from reporting facilities in the United States. Data for 2012 and 2016 include one facility in the United States where the use intended for children's products is unknown or not reasonably ascertainable (ChemView 2023; EPA 2021). Data regarding global product of products intended for children would be useful. Quantitative determination of residual vinyl chloride monomer that can be extracted or emitted from children's products produced with PVC would assist in estimating potential exposure to children.

6.3 ONGOING STUDIES

There are several ongoing studies evaluating the potential adverse effects of vinyl chloride exposure in humans and laboratory animals, as well as underlying mechanisms of toxicity (Table 6-1).

Table 6-1. Ongoing Studies on Vinyl Chloride

Investigator	Affiliation	Research description	Sponsor
Human, animal, and mechanistic research			
Matthew C. Cave	University of Louisville	Collaborative research program, the Environmental Liver Disease Revolutionizing Innovative, Visionary Environmental Health Research Program (ELD-RIVER)	NIEHS
Animal toxicity studies (some with associated mechanistic studies)			
Christopher J. States	University of Louisville	Multidisciplinary research on multi-organ toxicology, cancer, and neurodevelopmental effects of industrial chemicals.	NIEHS
Arun Kumar Pandiri	NIEHS	Evaluation of the genomic and epigenomic alterations in chemical carcinogenesis studies using *in vitro* and *in vivo* models	NIEHS
Juliane Beier	University of Pittsburgh	Study mitochondrial dysfunction, endoplasmic reticulum stress and autophagy as mechanisms of nonalcoholic fatty liver disease modified by vinyl chloride	NIDDK

Table 6-1. Ongoing Studies on Vinyl Chloride

Investigator	Affiliation	Research description	Sponsor
Mechanistic studies			
Deyu Li	University of Rhode Island	Investigate key mechanisms and critical differences that influence repair of the etheno DNA adducts and how cells minimize the harmful consequences of these lesions	NIGMS

DNA = deoxyribonucleic acid; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NIGMS = National Institute of General Medical Sciences

Source: National Institute of Health (NIH) RePORTER 2023