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 acetate 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 acetate.

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.

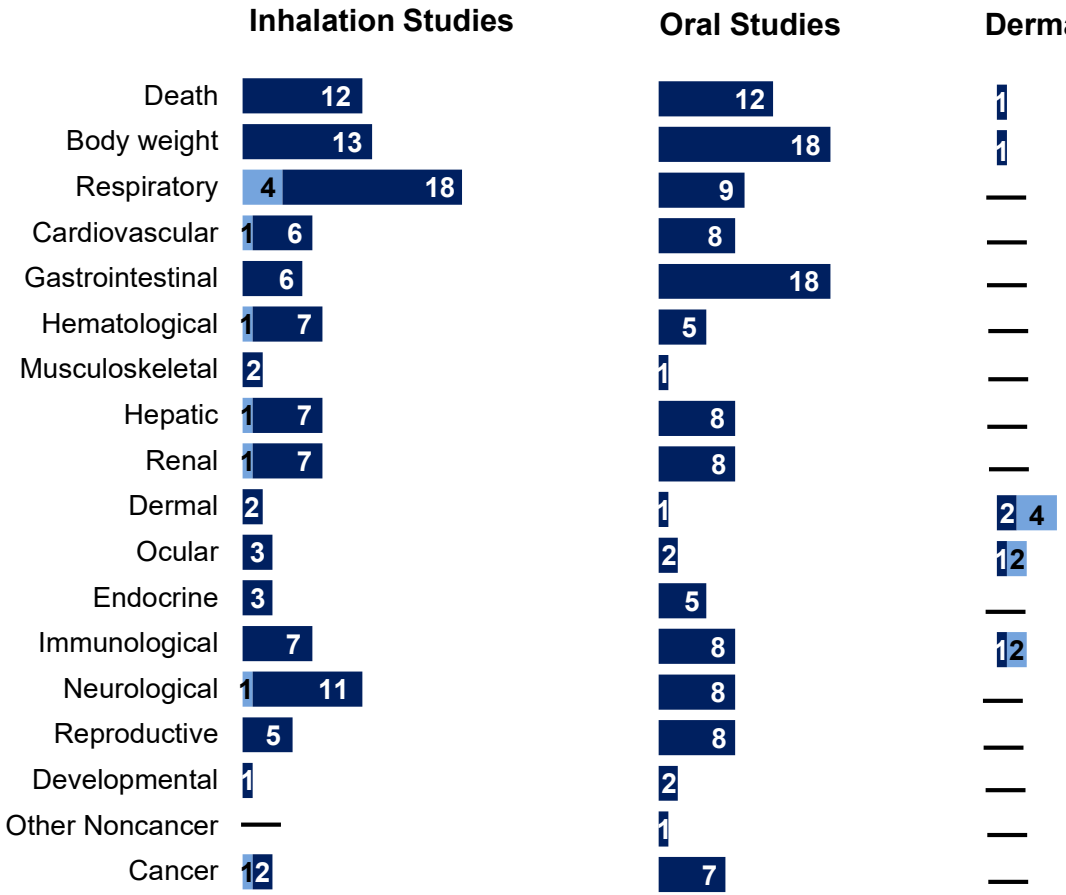
6.1 INFORMATION ON HEALTH EFFECTS

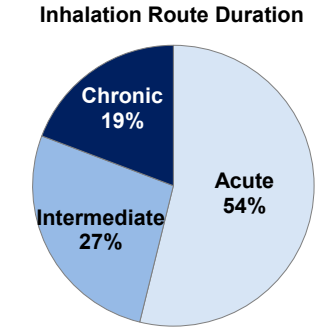
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl acetate that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of vinyl acetate. The number of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

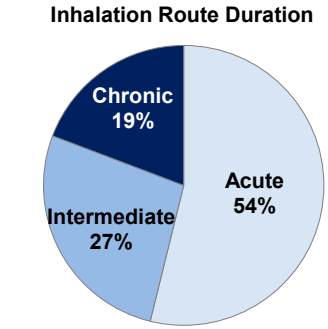
As illustrated in Figure 6-1, most of the data on the toxicity of vinyl acetate come from inhalation and oral studies in laboratory animals. The most examined endpoints in these studies were death, body weight, respiratory, and gastrointestinal effects. The dermal animal database is limited to six acute-duration studies and one intermediate-duration study, evaluating limited endpoints. The available human studies were limited to a few controlled exposure and occupational studies. These were predominantly focused on evaluation of respiratory, dermal, and ocular effects.

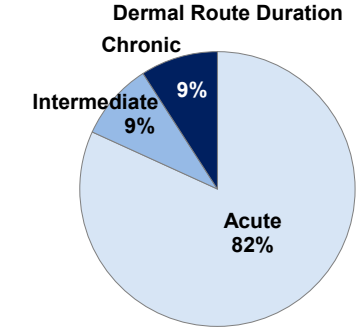
Figure 6-1. Summary of Existing Health Effects Studies on Vinyl Acetate by Route and Endpoint*

Potential for death, body weight, respiratory, and gastrointestinal effects were the most studied endpoints
The majority of the studies examined inhalation or oral exposure in **animals** (versus **humans**)









*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; most studies examined multiple endpoints.

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.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 598.5 ppm for nasal lesions, and its associated NOAEL of 199.6 ppm (Bogdanffy et al. 1997), would be useful. Nasal lesion data between 199.6 ppm (0% incidence) and 598.5 ppm (100% incidence) could better inform the dose-response curve for this effect following acute-duration exposure, decreasing uncertainty in the acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL; no adverse effects were identified below the lowest reported acute oral LD_{50} value of 1,613 mg/kg (Goeva 1966). Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the acute effects of vinyl acetate following oral exposure may not be necessary.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 598.5 ppm for nasal lesions, and its associated NOAEL of 199.6 ppm (Bogdanffy et al. 1997), would be useful. Nasal lesion data between 199.6 ppm (0% incidence) and 598.5 ppm (100% incidence) could better inform the dose-response curve for this effect following intermediate-duration exposure, decreasing uncertainty in the intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL. The only adverse effects identified (decreased body weights in adults and offspring) may be due, at least in part, to observed decreases in water intake associated with palatability issues. Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the effects of vinyl acetate following intermediate-duration oral exposure may not be necessary.

Chronic-Duration MRLs. The inhalation database is adequate to derive a chronic-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 200.5 ppm for nasal lesions, and its associated NOAEL of 49.4 ppm (Bogdanffy et al. 1994a; Hazleton 1988), would be useful. Nasal lesions data between 49.4 ppm (<10% incidence) and 200.5 ppm (>88%% incidence) could better inform the dose-response curve for this effect following chronic-duration exposure, decreasing uncertainty in the chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration oral MRL. The only adverse effects identified (decreased body weights) may be due, at least in part, to observed decreases in water intake associated with palatability issues and/or decreased food consumption. No other non-neoplastic effects were identified below chronic-duration doses associated with cancer and/or death. Therefore, the chronic-duration oral exposure database was deemed inadequate to derive an MRL. Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the chronic effects of vinyl acetate following oral exposure may not be necessary.

Health Effects. Identification of data needs for health effects is limited to targets included in the systematic review and endpoints with major data gaps.

Respiratory. The upper respiratory tract has been identified as a sensitive target following acute-, intermediate-, and chronic-duration inhalation exposure in animals. However, the available studies have wide dose-spacing between the NOAEL and LOAEL concentrations, resulting in low-to-no lesions at the NOAEL, and ~90–100% lesions at the LOAEL. Additional studies designed to define the shape of the dose-response curve between the NOAEL and LOAEL values for upper respiratory lesions could be useful.

Reproductive. No information is available in humans to indicate that vinyl acetate affects reproductive function. Reproductive function has not been assessed in animals following inhalation exposure; however, there is no evidence of damage to reproductive organs following intermediate- or chronic-duration exposure. No significant reproductive effects were noted in a 2-generation drinking water study in rats. Therefore, although the available reproductive studies indicate that vinyl acetate probably has no adverse effects on reproductive performance in animals following oral exposure, further investigation by the inhalation route is warranted to clarify whether this chemical has the potential to affect reproduction in humans.

Developmental. No information is available in humans to indicate that vinyl acetate affects fetal development. Growth retardation and delayed ossification have been observed in pups born to rats exposed to vinyl acetate via inhalation during gestation (Hurtt et al. 1995), and decreased body weight was observed in F1 pups at weaning following exposure of rats to vinyl acetate in drinking water in a 2-generation study (Mebus et al. 1995). These effects were observed at levels causing decreased body weight gain in dams. Additionally, water intake was significantly decreased in dams in the 2-generation study, which may have caused decreased milk production. No adverse developmental effects have been observed in animals following oral exposure to vinyl acetate during gestation only (Hurtt et al. 1995). Any additional developmental toxicity testing should be by the inhalation route of exposure since limited information exists on developmental toxicity following exposure to vinyl acetate by this route (no 2-generation study) and it is the most relevant route for humans.

Epidemiology and Human Dosimetry Studies. Human studies are limited to three acute-duration inhalation exposure studies focused on respiratory and/or ocular irritation (Deese and Joyner 1969; Hinderliter et al. 2005; Union Carbide 1973), three occupational studies/reports evaluating dermal effects (Gruvberger et al. 1998; Tanaka and Lucas 1984; Union Carbide 1958), one occupational hygiene study (Deese and Joyner 1969), and one occupational cross-sectional study (Khoshakhlagh et al. 2023). These studies provide evidence of respiratory, ocular, and dermal irritation following exposure to vinyl acetate. All studies are limited by small sample size and limited endpoint evaluation. The most likely identifiable subpopulation exposed to vinyl acetate is chemical workers involved in its production and use. Well-designed epidemiological studies of exposed workers that specifically examine the effects of vinyl acetate on respiratory, reproductive, and developmental systems would be useful to further characterize the extent of possible injury to these systems in humans.

Biomarkers of Exposure and Effect. Metabolic studies have shown that vinyl acetate is quickly hydrolyzed to acetaldehyde and acetate, which then enters normal metabolic cycles to produce primarily CO_2 and water (Hazleton 1979a; Simon et al. 1985a). A small amount also has been shown to be excreted in the urine as urea and other unidentified metabolites (Hazleton 1980a). Because of the relatively rapid hydrolysis and the fact that metabolites are incorporated into normal metabolic pathways, it would be difficult to use vinyl acetate or its metabolites as biomarkers of exposure to this chemical (Hazleton 1979a; Simon et al. 1985a). Additional investigation of the utility of biomarkers of exposure in characterizing human exposure to vinyl acetate would be useful.

Exposure to vinyl acetate *in vitro* has been shown to result in various positive genotoxic endpoints in human lymphocytes (e.g., micronuclei, chromosomal aberrations, sister chromatid exchange, and DNA cross-links) (He and Lambert 1985; Jantunen et al. 1986; Lambert et al. 1985; Maki-Paakkanen and Norppa 1987; Norppa et al. 1985, 1988). However, these results are from *in vitro* tests and many other chemicals can also induce such abnormalities; therefore, these should not be considered specific biomarkers of vinyl acetate effects. While vinyl acetate does not form adducts with DNA, its metabolite acetaldehyde forms protein or hemoglobin adducts, suggesting these types of adducts could potentially be used as markers of effect for vinyl acetate. Stable protein acetaldehyde adducts (Izumi et al. 1988; Lin and Lumeng 1988) and hemoglobin acetaldehyde adducts (Peterson et al. 1988) have also been shown to be formed following chronic alcohol ingestion, though, so acetaldehyde adducts are also not useful as specific biomarkers of effect for vinyl acetate. No other biomarkers (specific or otherwise) have been identified following exposure to vinyl acetate. Additional animal or epidemiological studies that measure changes in body fluids or enzyme levels following vinyl acetate exposure would be useful to determine if such biomarkers exist and to devise sensitive and specific early biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. The metabolism of vinyl acetate has been characterized in humans. Additionally, the toxicokinetics of vinyl acetate in rats and mice are relatively well characterized following oral and inhalation exposure. Since the dermal route is a relevant exposure route for human, quantitative absorption data may be useful.

Comparative Toxicokinetics. The toxicokinetics of inhaled vinyl acetate in humans are similar to those that have been observed in rats and mice, although some differences may occur due to differences in carboxylesterase distribution and/or activity. PBPK models for vinyl acetate have been developed to simulate characteristics of the anatomy and physiology of the rat and human that are thought to contribute to interspecies differences in dose-response relationships for nasal lesions. A PBPK model evaluating interspecies differences between the mouse and human may be useful. While no oral toxicokinetic data are available in humans, data in laboratory animals indicate that toxicokinetics are similar between routes and species. Oral tissue carboxylesterase activities were similar between rats and mice.

Children's Susceptibility. No human data are available regarding children's susceptibility; epidemiological data for children would be useful to address this data gap. Available data from inhalation and oral developmental studies do not indicate that developing animals are uniquely susceptible to toxicity following exposure to vinyl acetate. However, the inhalation database is limited to a single gestation-only exposure study, and the oral database is limited due to palatability issues with drinking

water exposure. Additional inhalation studies (e.g., a 2-generation study) and oral studies below doses associated with palatability issues would be useful to address these data gaps.

Physical and Chemical Properties. The physical/chemical properties of vinyl acetate are sufficiently well defined to enable assessment of the environmental fate of this compound (Tables 4-1 and 4-2).

Production, Import/Export, Use, Release, and Disposal. Vinyl acetate is used primarily as a chemical intermediate in the production of polymeric materials and is contained in polymeric consumer products only as residual monomer. Data pertaining to production, import, and export of vinyl acetate are available through 2019 (EPA 2022a). Vinyl acetate is released to the environment as a result of its commercial production, use, storage, transport, and disposal. Releases of the compound from industrial processes are mainly to the atmosphere. Underground injection is also an important source of release for certain facilities. It is uncertain whether the United States is incinerating or using landfill disposal for vinyl acetate, as identified regulations for vinyl acetate are outdated (EPA 1981, 1991). Additional information on disposal methods and pertinent regulations would be useful in evaluating the potential for release of and exposure to vinyl acetate.

Environmental Fate. Based on its physical/chemical properties, vinyl acetate is expected to partition to the atmosphere, surface water, and groundwater (Fujisawa and Masuhara 1981; Hansch and Leo 1979). Vinyl acetate is not expected to persist, bioconcentrate, or biomagnify (Fujisawa and Masuhara 1981; Hansch and Leo 1979). The most important transformation processes for vinyl acetate are photooxidation and hydrolysis (Joshi et al. 1982; Mabey and Mill 1978); the relative importance of biodegradation is unknown (Chou et al. 1979; Pahren and Bloodgood 1961; Price et al. 1974; Stuckey et al. 1980). A data requirement is identified for additional information regarding the transport/partitioning and transformation/degradation of vinyl acetate in all media in order to confirm the predicted behavior described above and establish the relative importance of the various transformation processes. This information would be helpful in defining the relative importance of various routes of exposure to the compound in environmental media.

Bioavailability from Environmental Media. No information was found regarding human absorption of vinyl acetate following inhalation, oral, or dermal exposures from environmental media. Limited data from laboratory animals suggest that absorption may occur following exposure by all of these routes (Hazleton 1979a, 1980a; Smyth and Carpenter 1948). Additional information is needed on the uptake of

vinyl acetate following inhalation of workplace and ambient air, dermal contact with or ingestion of contaminated soils, and ingestion of contaminated drinking water. This information would be useful in determining the bioavailability of the compound from environmental media.

Food Chain Bioaccumulation. No studies were identified that were designed to evaluate bioconcentration of vinyl acetate by plants, aquatic organisms, or animals, or the biomagnification of the compound in terrestrial or aquatic food chains. On the basis of the reactivity, volatility, and water solubility of the compound, bioconcentration and biomagnification are not expected to be important environmental fate processes (Fujisawa and Masuhara 1981; Hansch and Leo 1979). Additional information is needed to confirm this predicted behavior. This information would be useful in establishing the importance of food chain bioaccumulation as a source of human exposure to vinyl acetate.

Exposure Levels in Environmental Media. Vinyl acetate has been detected infrequently and at low levels in ambient air, surface water, groundwater, sediment, and soil. Limited monitoring data at Superfund sites are available. No biomonitoring data for drinking water or food were located. This information would be useful in estimating human exposure to vinyl acetate.

Exposure Levels in Humans. Biomonitoring data in humans are not available due to a lack of a reliable biomarker. Vinyl acetate metabolism is rapid; *in vivo* tests with laboratory animals indicate that most of the compound is eliminated within 24 hours after exposure (Hazleton 1979a, 1980a). Therefore, it would be difficult to measure the presence of vinyl acetate or acetaldehyde after reasonable periods following exposure to vinyl acetate. Acetaldehyde and acetate may also not be useful as indicators of vinyl acetate exposure. Because these compounds are incorporated into normal metabolic pathways, it would be difficult to determine which metabolites were due to vinyl acetate exposure and which were endogenous in biological tissues and fluids. Investigations into the utility of biomarkers of exposure in characterizing human exposure to vinyl acetate would be useful.

Exposures of Children. Exposure pathways for children will be similar to those for adults. As with adults, biomonitoring data for children are not available due to a lack of a reliable biomarker. If a reliable biomarker is identified, biological monitoring studies for children of workers employed in industries that produce, transport, or store this product, or for children who reside in close proximity to facilities that produce vinyl acetate would be useful.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.