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 chloroethane 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 chloroethane.

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

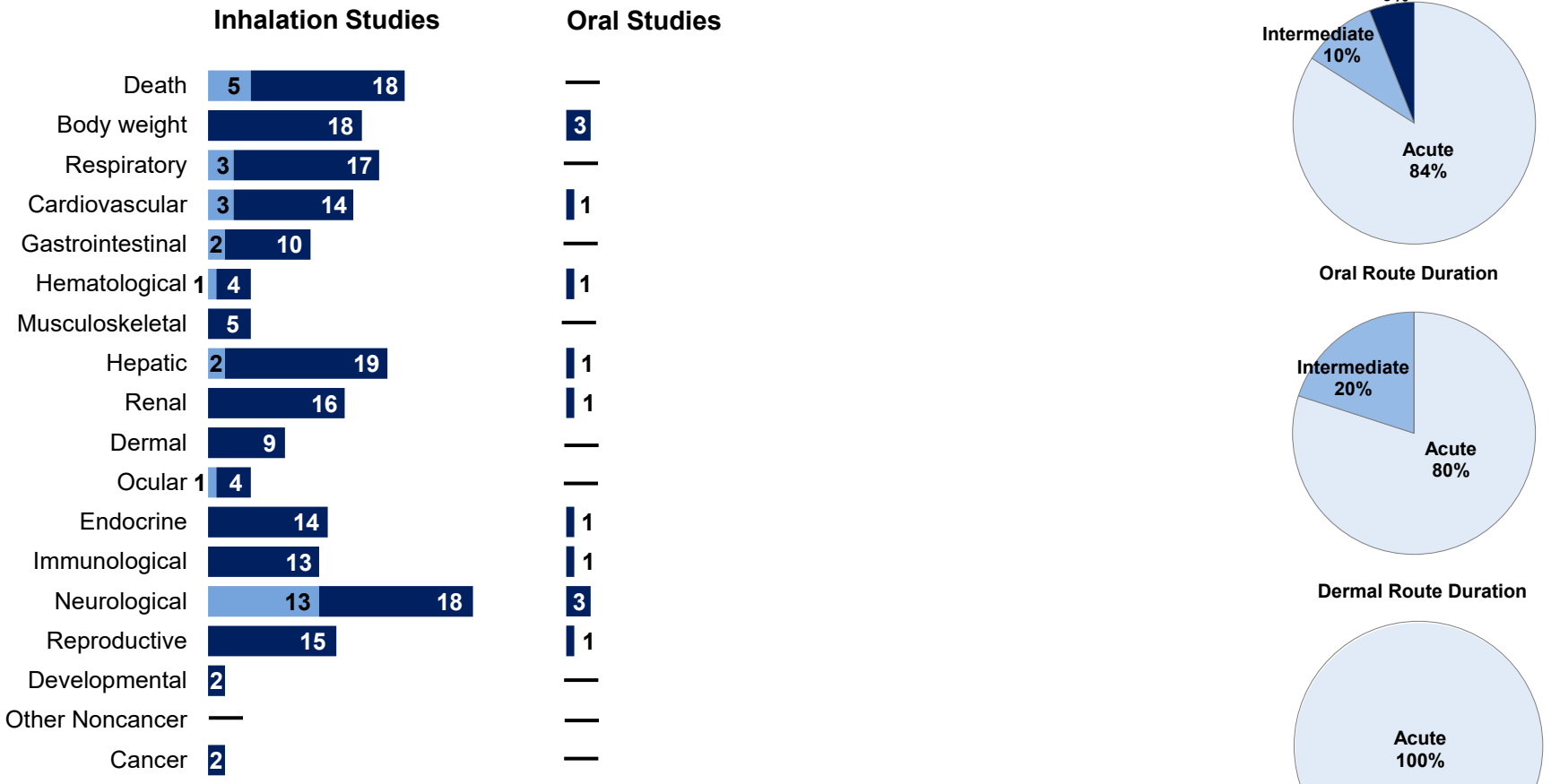
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chloroethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of chloroethane. The number of human 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 chloroethane come from inhalation exposure in humans and animals. In humans, the inhalation data are from a few volunteer exposure studies and several case reports of intentional solvent misuse. In animals, most inhalation studies are acute-duration studies and neurological effects are the most common health endpoints studied. No oral studies in humans were located, and only a couple of oral animal studies were identified. Dermal exposure studies were almost exclusively performed in humans and were related to the use of chloroethane for topical anesthesia.

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

Potential neurological, hepatic, and dermal effects were the most studied endpoints

The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint.

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. Although an acute-duration inhalation MRL was derived, additional studies that establish a dose-response relationship for neurological effects would be useful. The oral database is inadequate to derive an acute-duration oral MRL. Oral studies in animals are limited to two acute-duration gavage studies that did not include a control group and two drinking water studies that reported no health effects. Additional acute-duration oral studies examining a wide range of potential health endpoints are needed to identify the most sensitive targets of toxicity and to establish a dose-response relationship. However, since the predominant route expected for human exposure is inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. Although an intermediate-duration inhalation MRL was derived, additional studies that investigate a dose-response relationship for reproductive effects would be useful. In animals, intermediate-duration inhalation studies in rats, mice, and rabbits suggest that systemic effects are unlikely at high exposure concentrations (up to 19,000 ppm). However, neurological effects were not observed in these studies. Further investigation of neurological endpoints may be useful because neurological effects were noted in both acute- and chronic-duration inhalation studies. The oral database is inadequate to derive an intermediate-duration MRL. Only one poorly reported (and not listed in the LSE table), intermediate-duration oral study in animals was identified. Additional intermediate-duration oral studies are needed examining a wide range of potential endpoints to identify the most sensitive targets of toxicity and to establish a dose-response relationship. However, since the predominant route expected for human exposure is inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. The inhalation and oral databases are inadequate to derive chronic-duration MRLs. Available inhalation data in humans is limited to a case study and a poorly reported occupational

exposure study. In animals, additional inhalation studies are needed that investigate a dose-response relationship for health effects, particularly neurotoxicity. No chronic-duration oral studies were identified in either humans or animals. Chronic-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

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

Neurotoxicity. Studies of chloroethane inhalation in humans and animals have provided information on the neurological clinical signs resulting from acute-duration exposure to chloroethane and the levels at which they occur. It would be useful to have studies that quantify the neurobehavioral changes occurring during exposure, and that measure recovery times. Studies that evaluate specific neurobehavioral outcomes, such as learning and memory, may also be useful. Oral studies investigating neurological effects are limited to two gavage studies and a 14-day drinking water study. A control group was not included in the gavage studies. Reliable studies of neurotoxicity focusing on dose-related responses following oral exposure are needed. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on the neurological system.

Reproductive. No human studies evaluating reproductive toxicity were identified. Several animal inhalation studies identified reproductive effects including decreased uterine weight and GSH levels and increased estrous cycle duration. The relevance of uterine effects in animals to human chloroethane exposure is not known, and further studies to examine the mechanisms of uterine effects observed in chloroethane-exposed mice are needed. A multigeneration study to determine if uterine effects, estrous cycle effects, and effects on sperm motility impact reproductive performance is also needed. Available oral studies are not adequate for evaluating potential reproductive toxicity; therefore, additional oral studies evaluating this endpoint would be useful. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on the reproductive system.

Developmental. No studies were located on developmental effects of chloroethane in humans. Two prenatal inhalation studies were located for chloroethane and an increase in incidence of

DFFC of the skull bones (developmental delay of ossification of small centers of unossified bone of the skull) was seen in the fetuses of one study. The second study did not perform visceral or skeletal examinations. No significant treatment-related changes were observed on other developmental parameters in these studies. Additional developmental studies by inhalation and oral routes are needed. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on fetal development.

Epidemiology and Human Dosimetry Studies. Most of the human inhalation studies are case reports with no exposure level reported. Epidemiological studies of occupationally exposed workers or people living near industries releasing chloroethane or near hazardous waste sites are needed.

Biomarkers of Exposure and Effect. Although a couple of case studies reported the levels of chloroethane in blood and urine plus lung and brain tissue, these levels are not correlated with an exposure concentration. Other studies lacked environmental concentrations of chloroethane and levels of chloroethane in the breath, fluids, and body tissues. Studies examining the association between air and breath levels of chloroethane are needed. Although NHANES reported on concentration of chloroethane in the blood, these values were not correlated to exposure level (CDC 2017, 2018, 2020). Research is needed to ascertain whether there are biomarkers specific only for chloroethane exposure. Further research is required to determine if urinary excretion of GSH conjugates would serve as a useful biomarker following exposure of humans to chloroethane.

Unique biomarkers of effect have not been identified for exposure to chloroethane. Further research regarding the biochemical effects of chloroethane is needed to identify biomarkers of effect for chloroethane.

Absorption, Distribution, Metabolism, and Excretion. A single breath absorption study (Morgan et al. 1970) is the only quantitative study regarding the absorption, distribution, metabolism, and excretion of chloroethane in humans. Studies in rats and mice indicate that chloroethane is readily absorbed following inhalation exposure and is metabolized to acetaldehyde and GSH conjugates (Fedtke et al. 1994a, 1994b). Additional quantitative studies of the pharmacokinetics of chloroethane are needed.

Comparative Toxicokinetics. A study that compares the metabolism of chloroethane in rats and mice indicates that mice have a greater capacity to metabolize chloroethane than rats (Fedtke et al. 1994a, 1994b). An *in vitro* study using human liver preparations to study the metabolism of chloroethane is

needed to determine which species is the most appropriate model for the metabolism of chloroethane. It is currently unknown whether children differ from adults in their weight-adjusted intake of chloroethane. Changes in the skin surface area to body weight ratio as children grow may affect the tolerable dermal dose. This is demonstrated in model calculation of the Reasonable Maximum Exposure level (Table 5-8). Therefore, studies investigating this issue are needed.

Children's Susceptibility. No studies involving exposure of children or immature animals to chloroethane have provided quantitative dose-response information. There are several qualitative studies in children associated with the use of chloroethane as an anesthetic (Nibhanipudi 2015; Noble 1979; Ramsook et al. 2001; Soueid and Richard 2007). Studies with immature animals or children exposed to the compound are needed to investigate any differences in toxicokinetics and the presence and severity of effects. Current knowledge of differences in physiology and biochemistry between children and adults indicate that distribution and metabolism might differ between children and adults. Definitive studies do not exist evaluating whether chloroethane pharmacokinetic parameters are different in children as compared with adults, and no PBPK models exist on any age of children or immature animals. Changes in skin surface area to body weight ratios can help to model Reasonable Maximum Exposure levels; however, this model cannot predict difference in absorption that may occur. Studies evaluating qualitative and quantitative differences in these processes would greatly facilitate the understanding of adverse effects of chloroethane in the developing human.

Studies are needed to determine whether chloroethane or its metabolites cross the placenta, and no studies have evaluated placental or cord blood concentrations of chloroethane or its metabolites in humans or animals. Experiments evaluating these parameters are needed, as well as experiments to determine whether chloroethane significantly accumulates in breast milk. One study detected the compound in breast milk (Pellizzari et al. 1982), but the maternal exposure route and chloroethane concentration in the milk were not identified. In addition, studies determining whether chloroethane would be stored in maternal tissues would be informative, although the volatility of the compound, as well as data indicating its rapid clearance from the body following inhalation exposure (Morgan et al. 1970), indicate that tissue storage is not expected.

Adequate data do not exist on the effect, if any, that chloroethane exposure has on fetal development. Reliable studies of this type are needed in determining the fetotoxicity of chloroethane, as well as the potential of the compound for disrupting normal child development. Studies on postnatal exposures and their influence on development in immature animals would also be useful.

Physical and Chemical Properties. Data on the physical and chemical properties of chloroethane are available and provided in Table 4-2. No data needs are identified for these endpoints.

Production, Import/Export, Use, Release, and Disposal. Data are adequate for the production and disposal of chloroethane (IARC 1991; TRI23 2024). Information on the use pattern for chloroethane is not available after 1988. Information would have to be supplied by the chemical industry to establish the percentage breakdown of the current chloroethane uses. This type of information is needed to establish the sources of chloroethane release and the potential for general population and occupational exposure.

Environmental Fate. Conflicting data (days or years) are available concerning the hydrolytic half-life of chloroethane in water (Jeffers and Wolfe 1996; Laughton and Robertson 1959; Mabey and Mill 1978; Vogel and McCarty 1987). Experimental data obtained from a hydrolysis study carried out in distilled water under environmental conditions (at 25°C and pH 5–9) are needed to predict the half-life of chloroethane (Haider 1980; Kobayashi and Rittmann 1982) in natural water and moist soil. Available data regarding biodegradation of chloroethane are insufficient for predicting the importance of biodegradation as a removal process for chloroethane. Natural water grab sample biodegradation studies and soil metabolism studies carried out under both aerobic and anaerobic conditions are needed to estimate the biodegradation half-life of chloroethane.

Although volatilization from soil is expected to be an important fate process (Washington 1996), data pertaining to the rate of volatilization from soil surfaces were not located in the available literature. Studies involving the measurement of the volatilization rate of chloroethane from soil surfaces are needed to evaluate the persistence of this compound upon release to soil.

The dominant removal mechanism for chloroethane in air is expected to be reaction with photochemically-generated hydroxyl radicals (Atkinson 1985; Howard and Evenson 1976). However, no data are available concerning the products of this reaction. These data are needed to understand the mechanism by which this compound degrades in the atmosphere.

Bioavailability from Environmental Media. Chloroethane is readily absorbed following inhalation exposure, the major route of exposure (Konietzko 1984; Lehmann and Flury 1943; Torkelson and Rowe 1981). Data regarding the bioavailability of chloroethane from different media for other routes of

exposure were not identified. Studies examining the absorption of chloroethane from various media following oral and dermal exposure are needed to predict exposure to chloroethane at hazardous waste sites.

Food Chain Bioaccumulation. Based on bioconcentration factors of 7 and 5 estimated from log K_{ow} and water solubility (Bysshe 1982; Horvath 1982; NLM 2023), chloroethane is not expected to bioconcentrate significantly in aquatic organisms. Studies in which chloroethane is measured in biota and environmental media are needed to determine if this prediction is correct.

Exposure Levels in Environmental Media. Relatively large amounts of chloroethane are released to the environment on an annual basis (TRI23 2024). Levels in the ambient air are monitored throughout the United States and reported in the AQS database (EPA 2023b). The WQP, monitoring water-quality in the United States and beyond, indicates that chloroethane is not a common surface water pollutant (WQP 2023). Reliable monitoring data for the levels of chloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chloroethane in the environment can be used in combination with the known body burdens of chloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Available data indicate that the general population may be exposed to chloroethane by inhalation, ingestion of drinking water, and dermal contact. Maximum inhalation and dermal exposure levels were calculated with the ATSDR (2022b) SHOWER model using data from the WQP (2023) and EPA (2023b). Even though chloroethane is a fairly large volume commercial compound, limited data are available concerning occupational exposure. There are no quantitative data relating type of occupation to level and route of exposure. Monitoring of workplace air is needed to evaluate exposure to occupational workers. Continued monitoring of air and water levels are needed to ensure accurate estimation of exposure to the general population and occupational workers.

Exposures of Children. Children are exposed to chloroethane via many different exposure pathways. Cardiovascular effects were observed in children exposed to a mixture of gases including chloroethane (Bush et al. 1952). However, the study lacked specificity for the chloroethane dose, and the use of a gaseous mixture obscures the health effect finding. Reliable exposure and body burden studies in children are needed to relieve this data gap. In addition, because many older children may be exposed to chloroethane through sniffing the compound directly, there is a need to explore the prevalence of this behavior, the frequency of the misuse, and resulting exposure doses.

6.3 ONGOING STUDIES

No relevant ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database, which tracks projects funded by NIH.