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 1,1-dichloroethene 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 1,1-dichloroethene.

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.

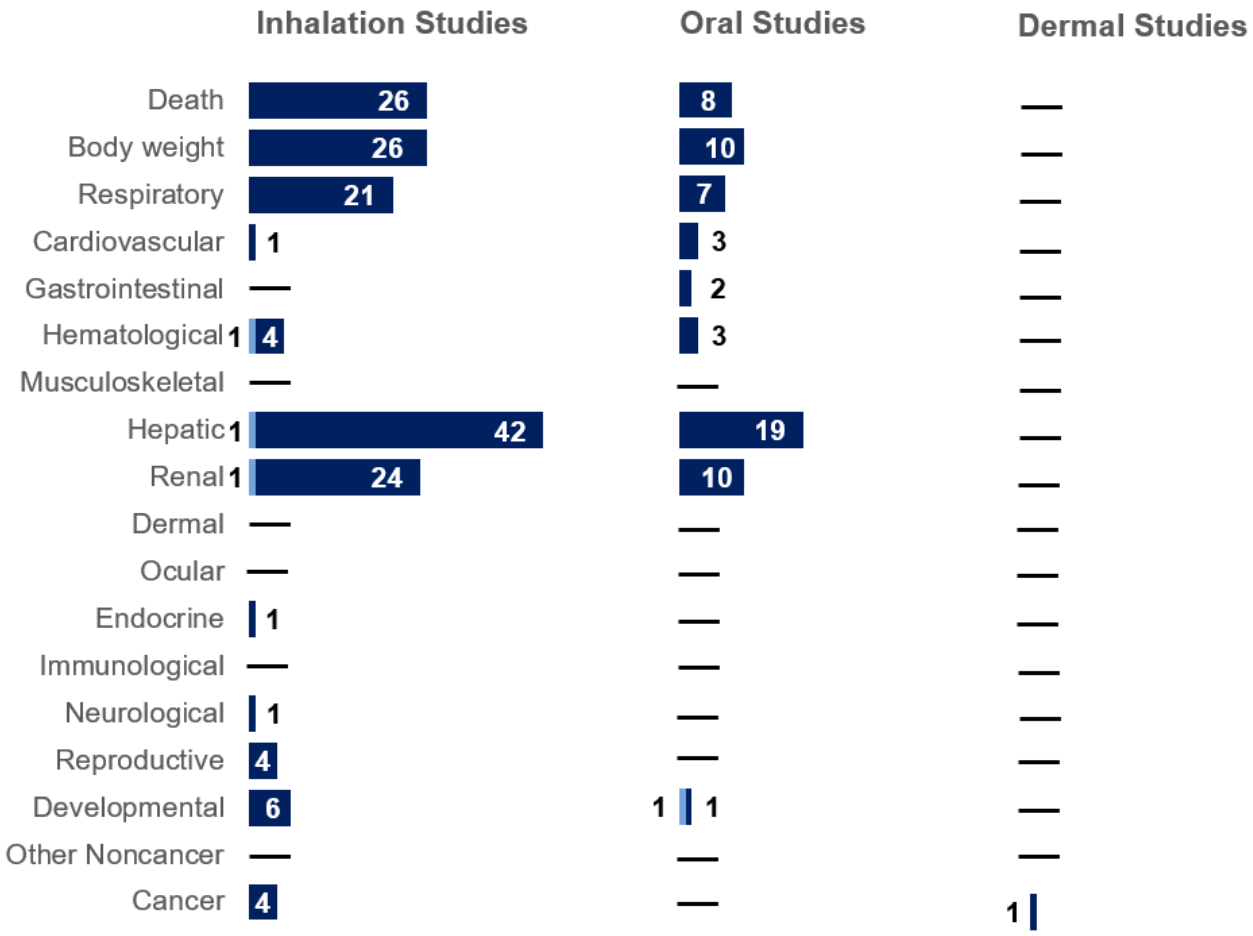
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethene 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 1,1-dichloroethene. 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.

There is little information available concerning the long-term health effects of 1,1-dichloroethene in humans following inhalation exposure. Most of the information concerning health effects in humans is reported in occupational studies that are difficult to interpret because of limitations in study design (e.g., exposure levels and duration cannot be quantified and concurrent exposure to other toxic substances cannot be ruled out). No information concerning oral or dermal exposure to 1,1-dichloroethene in humans was found in the reviewed literature.

Figure 6-1. Summary of Existing Health Effects Studies on 1,1-Dichloroethene By Route and Endpoint*

Potential hepatic, body weight, renal, and respiratory 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; most studies examined multiple endpoints.

The effects of 1,1-dichloroethene in animals following inhalation and oral exposure have been studied in a variety of species following acute, intermediate, and chronic exposure durations. One oral exposure study reported observations of the "appearance" and "demeanor" of test animals, but this was not considered an appropriate analysis of possible neurological or behavioral effects. Genetic effect endpoints were examined following inhalation exposure only. Carcinogenicity studies in animals following exposure by the oral, inhalation, and dermal routes are available.

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 available inhalation database was not considered adequate for derivation of an acute-duration inhalation MRL for 1,1-dichloroethene. No exposure-response human data are available. The lowest LOAEL for acute-duration inhalation exposure of laboratory animals is a serious LOAEL of 15 ppm for a study in which death and maternal body weight loss occurred in rats exposed to 1,1-dichloroethene vapor for 22–23 hours/day during GDs 6–16 (EPA 1977a).

The available oral database was not considered adequate for derivation of an acute-duration oral MRL for 1,1-dichloroethene. Some studies did not provide dose-response data because only a single dose level was used. Many of the available studies employed fasted animals which are known to be more sensitive than nonfasted rats to 1,1-dichloroethene-induced adverse effects following oral exposure. Among studies that employed multiple dose levels and nonfasted animals, the lowest LOAEL is 100 mg/kg/day for 11% depressed body weight in female rats administered 1,1-dichloroethene by gavage for 14 days (NTP 1982). Results from inhalation studies and longer-term oral studies identify the kidney as a sensitive target of 1,1-dichloroethene toxicity in mice. However, available acute-duration oral studies in mice do not include dose-response assessment of the kidney. Additional acute-duration inhalation and oral studies are needed to examine exposure-response relationships; such studies should evaluate comprehensive sets of endpoints, including the liver and kidney.

Intermediate-Duration MRLs. The database was considered adequate for derivation of an intermediate-duration inhalation MRL for 1,1-dichloroethene. The database was not considered adequate for derivation of an intermediate-duration oral MRL. No dose-response data are available for humans. Gavage studies of rats and mice treated for 90 days (NTP 1982) were the only available intermediate-duration oral studies in which treatment-related adverse effects were observed. Although the 90-day oral studies of NTP (1982) included histopathologic examination of multiple tissues and organs, the study report presented results only for the liver. The kidney is a known target of toxicity following inhalation exposure to 1,1-dichloroethene, particularly in mice (NTP 2015a). Additional intermediate-duration oral studies that employ exposure via drinking water or food should be designed to evaluate dose-response relationships; such studies should evaluate a comprehensive set of endpoints, including the liver and kidney.

Chronic-Duration MRLs. The database was considered adequate for derivation of a chronic-duration inhalation MRL for 1,1-dichloroethene based on histopathologic nasal lesions in mice (NTP 2015a). A similarly designed study of rats employed a higher range of exposure levels (25–100 ppm) than those employed in the study of mice (6.25–25 ppm). In the rat study, nasal lesions were observed at all exposure concentrations. The potential for 1,1-dichloroethene-induced nasal lesions in rats chronically exposed to 1,1-dichloroethene vapor at exposure concentrations <25 ppm represents a data gap. Relatively few chronic-duration oral studies are available for 1,1-dichloroethene. Most chronic-duration oral studies employed relatively low doses; for many evaluated endpoints, the highest dose level represented a NOAEL. Additional chronic-duration oral studies could be performed at higher dose levels to ensure that maximum tolerated dose levels are achieved. However, the database was considered sufficient to derive a chronic-duration oral MRL for 1,1-dichloroethene.

Health Effects.

Immunological. 1,1-Dichloroethene-induced effects on the immune system have not been studied in humans; limited animal data are available. Investigations including measures of immunocompetence and histopathological observations of animal organs and tissues involved in immunological response would provide valuable information. Additional dermal sensitization studies in animals might provide information on whether 1,1-dichloroethene is likely to cause an allergic response.

Genotoxic. No studies were identified that evaluated genotoxic effects of 1,1-dichloroethene in humans following any route of exposure. Several *in vitro* studies suggest that 1,1-dichloroethene, only in the presence of activating systems, is mutagenic in both prokaryotic and eukaryotic organisms. These results are consistent with the idea that a reactive metabolic intermediate(s), and not the parent compound, is (are) responsible for the genotoxic properties of 1,1-dichloroethene. Results from *in vivo* rodent assays that employed inhalation or oral exposure to 1,1-dichloroethene found no evidence for 1,1-dichloroethene-related effects on micronuclei in mouse peripheral blood erythrocytes (NTP 2015a), micronuclei in mouse bone marrow or fetal liver or blood (Sawada et al. 1987), chromosomal aberrations in rat bone marrow (Rampy et al. 1977), or dominant lethality in rats (Short et al. 1977c) or mice (Andersen et al. 1977). A weakly positive response was obtained for DNA damage in mouse kidney cells (Reitz et al. 1980). The genotoxic potential of 1,1-dichloroethene has been adequately assessed.

Epidemiological and Human Dosimetry Studies. Most of the available information on the adverse effects of 1,1-dichloroethene in humans comes from cases of acute poisoning occurring primarily in the workplace. Limitations inherent in these studies typically include unquantified exposure levels and durations, as well as concomitant exposure to other toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods, and/or brief exposure periods. Despite their inadequacies, studies in humans indicate that 1,1-dichloroethene can cause central nervous system effects and irritation of the mucous membranes (EPA 1979; Quast et al. 1986). Well-controlled epidemiological studies of people living near areas where 1,1-dichloroethene has been detected in surface water and groundwater, near industries releasing 1,1-dichloroethene, and near hazardous waste sites, as well as occupationally-exposed people could add to and clarify the existing limited database on 1,1-dichloroethene-induced human health effects.

Biomarkers of Exposure and Effect.

Exposure. Information regarding populations exposed specifically to 1,1-dichloroethene is not available; therefore, no known biomarker of exposure to 1,1-dichloroethene has been identified in humans. However, if 1,1-dichloroethene is metabolically disposed of by humans in a way similar to that observed in animals, 1,1-dichloroethene in expired air could be a biomarker of recent exposure to relatively high concentrations of 1,1-dichloroethene. Similarly, urinary excretion of metabolites such as thioglycolic acid could also be considered a biomarker of recent exposure. Such urinary metabolites would not be specific biomarkers for 1,1-dichloroethene exposure because other chemicals produce similar urinary

metabolites. Hence, the development of methods to detect alternative biomarkers specific to 1,1-dichloroethene exposure would be useful.

Effect. Information regarding populations exposed specifically to 1,1-dichloroethene is not available. Research leading to the identification of specific DNA adducts formed after 1,1-dichloroethene exposure would be valuable. This would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding the toxicokinetics of 1,1-dichloroethene in humans by inhalation, oral, or dermal routes. The animal data indicate that 1,1-dichloroethene is efficiently absorbed by the inhalation (Dallas et al. 1983; McKenna et al. 1978a) and oral routes (Jones and Hathway 1978a; McKenna et al. 1978b; Putcha et al. 1986). These studies have been conducted mostly in rats and mice. Dermal absorption data are lacking, but limited absorption by this route should be anticipated based on the physical and chemical properties of 1,1-dichloroethene and the fact that 1,1-dichloroethene was positive for initiation of papillomas in an initiation/promotion study of dermally-treated mice (Van Duuren et al. 1979). Furthermore, human and rodent studies of other halocarbons such as trichloroethylene have demonstrated that percutaneous absorption occurs (McDougal et al. 1990).

Animal data regarding inhalation exposure (Jaeger et al. 1977) and oral exposure (Jones and Hathway 1978c) to 1,1-dichloroethene demonstrate the distribution of 1,1-dichloroethene and/or its metabolites to the liver, kidney, and lung. Additional data on the distribution of 1,1-dichloroethene and its metabolites would be useful. Studies regarding distribution through the placenta were not available. However, another halocarbon, trichloroethylene, has been demonstrated to readily cross the placenta (Fisher et al. 1989).

The metabolism of 1,1-dichloroethene has been extensively studied in rats and mice following inhalation and oral exposure (Jones and Hathway 1978a, 1978c; McKenna et al. 1977, 1978b; Reichert et al. 1979). Experimental evidence indicates that the metabolism of 1,1-dichloroethene is a saturable process. Although information regarding metabolism following dermal exposure is lacking, there is no reason to believe that other pathways would operate following dermal exposure. Human toxicokinetic data are needed to evaluate the metabolic fate of 1,1-dichloroethene. The use of human cell systems and tissues in culture could serve as an alternative to studying the metabolic fate of 1,1-dichloroethene in humans.

Comparative Toxicokinetics. Limited *in vitro* data suggest that 1,1-dichloroethene toxicokinetic properties in humans may be similar to those observed in animals. Toxicokinetic studies in rats and mice suggest that no qualitative differences exist between these two species, although metabolism of 1,1-dichloroethene to toxic kidney metabolites are more prominent in mice than rats (Jones and Hathway 1978a, 1978c; McKenna et al. 1977, 1978b; Reichert et al. 1979). Experiments in animals (mostly rats and mice) indicate that the liver, kidney, and lungs are common target organs across species. Additional quantitative data on metabolic activation and inactivation of 1,1-dichloroethene in human liver, kidney, and lung could be used to evaluate the human relevance of mouse and rat cytotoxicity and carcinogenicity findings. The human data could be used to develop and validate a human PBPK/PD model for 1,1-dichloroethene.

Children's Susceptibility. No data were located to suggest significant age-related differences in susceptibility to 1,1-dichloroethene toxicity.

Physical and Chemical Properties. The physical and chemical properties of 1,1-dichloroethene have been adequately characterized (see Table 4-2). No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. 1,1-Dichloroethene is produced commercially. Information on production, uses, and releases of this chemical is available and have been discussed in Chapter 5. Additional information on the current criteria for land treatment or burial and on the amounts of 1,1-dichloroethene disposed of by incineration versus landfilling would be insightful.

Environmental Fate. Sufficient data exist to show that hydrolysis is not significant in determining the half-life in aqueous media. The available data suggest that 1,1-dichloroethene can undergo transformation by reaction with radical species in the atmosphere and biodegradation under certain conditions in water and soil/sediments as discussed in Section 5.4.2. The atmospheric half-life of 1,1-dichloroethene in air following hydroxyl radical reaction is estimated to be 4–20 hours, and the products of this reaction are highly toxic phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). The estimated half-life for hydrolysis of 1,1-dichloroethene at 25°C under neutral conditions is $1.2x10^8$ years (Jeffers et al. 1989). 1,1-Dichloroethene is reduced to vinyl chloride under various conditions in groundwater and sediment. In a methane-utilizing culture from lake sediment, 1,1-dichloroethene was degraded under aerobic conditions within 2 days; the end products, although unspecified, did not include vinyl chloride. Additional studies are needed to characterize aerobic and

anaerobic transformation processes in soils and water and to quantify degradation rates relevant to environmental conditions in these media.

Bioavailability from Environmental Media. The monitoring data available indicate that 1,1-dichloroethene is present in some samples of air, water, soil, and foodstuffs. Animal studies indicate that 1,1-dichloroethene is well absorbed following inhalation and oral exposure. 1,1-Dichloroethene and its metabolites can be measured in the breath, blood, urine, and adipose tissue of humans. While EPA's STORET database contains considerable water monitoring data, there are problems with the database that limit its usefulness. The detection limit is often recorded when no chemical is detected, with and without indication, so it is difficult to gain meaningful figures for surface water and groundwater concentrations representative of positive determinations to evaluate potential exposure scenarios. It would be helpful, when quantitative data cannot be obtained, if these monitoring data would indicate whether or not this chemical was qualitatively detected in the samples.

Food Chain Bioaccumulation. No information was found regarding the bioconcentration of 1,1-dichloroethene in plants, aquatic organisms, or animals. On the basis of the log octanol/water partition coefficient value of 2.13 (EPA 1982), bioconcentration of the compound to significant levels by terrestrial or aquatic organisms is not expected. No data were located regarding the biomagnification of 1,1-dichloroethene in terrestrial or aquatic food chains. Given the expected limited bioconcentration (CITI 1992) of the compound, the potential for biomagnification in terrestrial and aquatic food chains is very low. Additional experimental data to confirm this predicted limited food chain bioaccumulation of 1,1-dichloroethene would be helpful in evaluating the relative significance of this source of exposure.

Exposure Levels in Environmental Media. Data on the concentrations of 1,1-dichloroethene in surface water, soil, and food are limited. Continued monitoring would be beneficial in assessing the potential risk of environmental exposure. Reliable monitoring data for the levels of 1,1-dichloroethene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1-dichloroethene in the environment can be used in combination with the known body burden of 1,1-dichloroethene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. 1,1-Dichloroethene was included in NHANES for study years 2003–2004 and 2005–2006, where it was not found above the limit of detection. As a chemical used in the production of materials intended for food applications, continued biological monitoring of populations

would lend insight in assessing potential risk of deleterious effects from exposures. Additional information on potential exposures resulting from residence in the vicinity of hazardous waste sites would provide a more accurate characterization of human exposure in the United States.

Exposures of Children. Children may be exposed to 1,1-dichloroethene through the same routes as adults. Occupationally exposed workers are at greater risk of exposure to higher levels of this chemical than the general U.S. population.

6.3 ONGOING STUDIES

No ongoing studies were identified by the National Institutes of Health (NIH) (RePORTER 2020).