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 1,2-dichloroethane 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 1,2-dichloroethane.

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

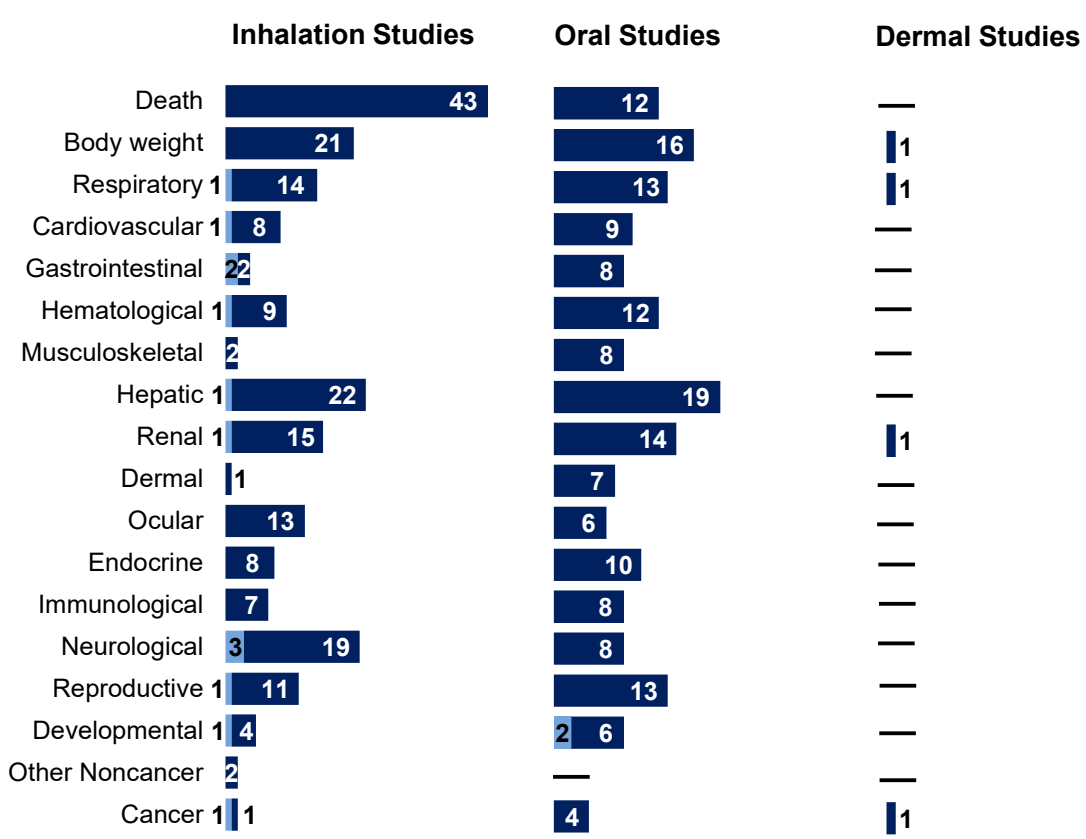
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloroethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,2-dichloroethane. The 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.

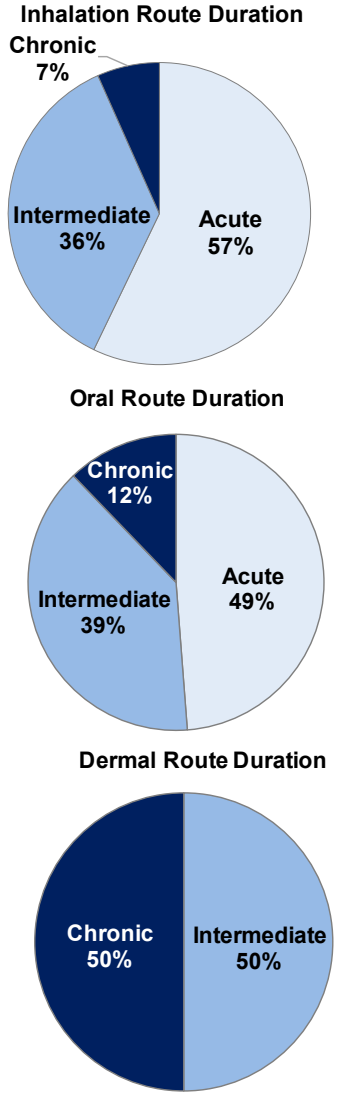
Figure 6-1 illustrates that a majority of toxicity data available for 1,2-dichloroethane comes from inhalation studies on laboratory animals. Respiratory, hepatic, neurological, and cancer endpoints were the most commonly studied endpoints. Studies on inhalation and oral exposure to humans primarily consisted of case studies. Dermal studies were limited to laboratory animals and were largely focused on cancer endpoints.

Figure 6-1. Summary of Existing Health Effects Studies on 1,2-Dichloroethane by Route and Endpoint*

Respiratory, hepatic, neurological, and cancer effects were the most studied endpoints

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





*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Some studies may have contributed information for 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 database of toxicity data on 1,2-dichloroethane was adequate to derive an acute-duration inhalation MRL. The available acute oral database was inadequate for deriving an MRL. Information on 1,2-dichloroethane toxicity in humans exposed orally is limited as it comes primarily from case reports of humans who died following acute-duration exposure to high levels of 1,2-dichloroethane by ingestion. Animal studies of acute-duration oral exposure used gavage administration, which is known to exacerbate toxicity of 1,2-dichloroethane (relative to drinking water administration), and thus is not a suitable model for human oral exposure to this chemical. The acute-duration study that identified the lowest LOAEL (Munson et al. 1982) observed immunosuppression in mice at a gavage dose of 4.9 mg/kg/day for 14 days; however, in a follow-up 90-day study reported in the same publication, no effect on immune response was seen in mice exposed to 189 mg/kg/day via drinking water. Additional studies are needed to characterize the effects of oral exposure to 1,2-dichloroethane via environmentally relevant modes of administration (e.g., drinking water or diet) to provide an appropriate basis for deriving an acute-duration oral MRL. Such data may lead to the development and use of PBPK models to extrapolate from gavage data to more environmentally relevant exposures.

Intermediate-Duration MRLs. The available intermediate inhalation database provided adequate data for deriving an intermediate-duration inhalation MRL. The most sensitive endpoint for deriving an intermediate-duration inhalation MRL is neurotoxicity, as demonstrated by alterations in open field tests following a 28-day exposure in mice. Additional studies evaluating neurotoxicity and male reproductive effects for longer intermediate exposure durations (e.g., >28–<365 days) may provide additional information for MRL derivation. The available intermediate oral database provided enough data to derive an intermediate-duration oral MRL for 1,2-dichloroethane.

Chronic-Duration MRLs. The available chronic-duration oral and inhalation databases were inadequate for deriving an MRL. The one reliable oral study on rats and mice was primarily designed to assess carcinogenicity, which is not applicable to MRL derivation. In addition, this study used gavage

administration, which is known to exacerbate toxicity of 1,2-dichloroethane (relative to drinking water administration), and thus is not a suitable model for human oral exposure to this compound. Chronic-duration oral toxicity studies are needed to identify noncancer target organs and enable derivation of a chronic-duration oral MRL. There were two chronic-duration inhalation studies of 1,2-dichloroethane. Both examined comprehensive endpoints but identified effect levels that were higher than the acute-duration inhalation point of departure (POD) (for nasal lesions) and a serious LOAEL (for sperm abnormalities) identified in an intermediate-duration inhalation study, precluding MRL derivation. One of the two chronic-duration studies (Cheever et al. 1990) identified a freestanding NOAEL for nasal lesions that was identical to the NOAEL in the acute-duration inhalation study (Hotchkiss et al. 2010) used for the acute-duration MRL. This finding suggests that 1,2-dichloroethane concentration may be a more important factor than exposure duration in the induction of nasal lesions. Studies to confirm this observation would be beneficial. Neither of the chronic-duration inhalation studies evaluated sperm parameters. The serious LOAEL for increased sperm abnormalities was identified in one 4-week inhalation study in mice (Zhang et al. 2017); no other studies have reported this effect. Additional studies are needed to provide confirmation for this effect and the exposure concentration at which it occurs.

Health Effects. Studies demonstrate that 1,2-dichloroethane readily absorbs dermally through human (Urusova 1953) and animal skin (Jakobson et al. 1982; Morgan et al. 1991). Dermal exposure to workers can occur in occupational settings (Bowler et al. 2003). Currently, there are no epidemiological or occupational studies examining health effects in humans exposed dermally and few studies examining animals exposed dermally. There is a need for dermal exposure studies examining a wide range of endpoints to identify possible toxicity endpoints from a variety of concentrations and exposure durations.

Toxicokinetic studies (see Section 3.1) have shown that the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) in rats (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980). Support for this finding comes from the studies by NTP (1991) that showed effects (including mortality) occurring at much lower doses in animals exposed to 1,2-dichloroethane via gavage compared with those exposed by drinking water. Gavage administration does not represent typical oral exposure in humans, which is most likely to occur via ingestion of contaminated drinking water in small doses spread out over the course of a day. Under these exposure conditions, biotransformation processes will probably not become saturated; thus, the risk for adverse effects is not as high as would be predicted from gavage administration of equivalent doses.

Nearly all of the acute- and chronic-duration animal studies of oral exposure to 1,2-dichloroethane used gavage administration, and the resulting LOAEL values are likely much lower than would be seen with drinking water administration. Additional studies using drinking water exposure are needed to determine effect levels for multiple endpoints that would be relevant to human exposures.

Respiratory. 1,2-Dichloroethane is readily absorbed through the lungs of humans and laboratory animals and is the most likely exposure route in humans. Two human studies (McNally and Fostvedt 1941; Nouchi et al. 1984) show adverse respiratory effects following inhalation of 1,2-dichloroethane, but the exposure concentrations were unknown in both cases. In animals, nasal olfactory degeneration/necrosis, respiratory tract irritation, and pulmonary congestion (Chan et al. 2002; Heppel et al. 1945; Hotchkiss et al. 2010) resulted from inhalation. There is an identified data need for epidemiological or occupational studies that evaluate effects on the respiratory system to humans exposed to 1,2-dichloroethane in air.

Immunological. A data need to conduct additional immunotoxicity studies via inhalation and oral exposure has been identified. Immunological effects reported in humans exposed to 1,2-dichloroethane are limited to splenic lesions in a single case of accidental ingestion (Hubbs and Prusmack 1955). In mice, this chemical had immunosuppressive effects following both acute-duration inhalation exposure and acute-duration oral exposure. A single 3-hour inhalation exposure to 5 or 11 ppm increased the susceptibility of female mice to bacterial infection, and exposure to 11 ppm decreased the bactericidal activity of the lungs. No change in bactericidal activity was seen in male rats after a single 5-hour inhalation exposure to 200 ppm or 12 5-hour exposures to 100 ppm (Sherwood et al. 1987). Other immune function endpoints studied in the rats were also negative. The relevance of the endpoint (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain. The streptococcal challenge test was used to evaluate potential immune effects of single exposures to 0, 2, 5, and 11 ppm 1,2 dichloroethane. A decreased immune response to challenge was observed at 11 ppm, with a NOAEL for immune effects of 5 ppm. However, substantial lethality was observed in both the 5- and 11-ppm exposure groups compared to controls. Therefore, the NOAEL for immunological effects cannot be used to derive an acute-duration inhalation MRL due to increased lethality. Gavage administration of 4.9 and 49 mg/kg/day of 1,2-dichloroethane to mice for 14 days reduced humoral (immunoglobulin response to sheep red blood cells) and cell-mediated (delayed-type hypersensitivity response to sheep erythrocytes) immunity. Only the humoral response was dose related. In addition, the

leukocyte number was decreased by 30% at the high dose (Munson et al. 1982). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and gavage routes in mice, as compared with endpoints in other studies in mice and in other species. The other studies, however, had limitations including wide spacing of the exposure concentrations, such that only NOAELs and serious LOAELs were identified. In contrast to the acute-duration oral study, higher doses of 1,2-dichloroethane (189 mg/kg/day) administered to mice in their drinking water for 90 days did not affect humoral and cell-mediated immunity (Munson et al. 1982), as assessed by some of the Tier I and Tier II procedures from the immunotoxicity testing battery (Luster et al. 1988). Immune function has not been evaluated in chronic-duration studies of 1,2-dichloroethane, but histopathological examinations failed to detect immune system lesions or immune-related changes in rats and mice exposed to 1,2-dichloroethane by inhalation or oral (gavage or drinking water) routes for intermediate or chronic durations (Cheever et al. 1990; Morgan et al. 1990; NCI 1978; NTP 1991). Leukocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats (Morgan et al. 1990; NTP 1991). The acute-duration data provide limited evidence that the immune system is a sensitive target of 1,2-dichloroethane in mice, but not rats. Because of the apparent interspecies differences in animal immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute-duration exposure by inhalation or ingestion.

Another possible explanation for the different outcomes of acute- and intermediate-duration oral exposure is that 1,2-dichloroethane may induce its own metabolism during the longer exposure period, thus reducing the dose to the immune cells. In addition to immune effects, induction of enzymes involved in 1,2-dichloroethane metabolism could also play a role across other outcomes.

The results of animal studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Clinical signs similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis, were observed after high-level, acute-duration vapor exposures (Heppel et al. 1945; Morgan et al. 1990; NTP 1991; Spencer et al. 1951). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks (Morgan et al. 1990; NTP 1991). No clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks (Morgan et al. 1990; NTP 1991), and no brain lesions were seen in rats intermittently

exposed to 50 ppm for 2 years (Cheever et al. 1990). No studies regarding the potential neurotoxicity of dermal exposure were located. The discrepancy in results between gavage and drinking water administration may be due to saturation of the detoxification/ excretion mechanism by the bolus gavage dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Intermediate-duration neurotoxicity studies in animals, using sensitive functional and neuropathological tests at inhalation and oral exposure levels significantly lower than those resulting in morbidity and death, would assist in the characterization of the neurotoxic potential of 1,2-dichloroethane.

Reproductive. A data need to conduct additional reproductive studies via dermal exposure has been identified. A single study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a decrease in duration of gestation (Zhao et al. 1989) but should be interpreted with caution since co-exposure to other chemicals occurred in most cases and the adequacy of the study design could not be evaluated because of reporting deficiencies. Results of animal studies indicate that this chemical is unlikely to cause female reproductive impairment at doses that are not maternally toxic. Although some inhalation studies found that exposure to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryo lethality in rats (Vozovaya 1974, 1977; Zhao et al. 1989), the methods used by these investigators were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed and reported study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study (Rao et al. 1980). In the absence of an apparent explanation for the discrepancy, greater credence should be given to the well-designed and reported study. One- and two-generation reproduction studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats (Alumot et al. 1976; Lane et al. 1982), but exposure to higher oral doses caused increases in non-surviving implants and resorptions in rats that also experienced maternal toxicity (30% decreased body weight gain) (Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results (Cheever et al. 1990; Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977), although reproductive performance was not evaluated in these studies. An inhalation study on male mice exposed to high concentrations revealed decreases in sperm concentration, motility, and progressive motility (Zhang et al. 2017).

The study was well designed, examining effects from a wide range of doses over acute and intermediate durations. While the study identified reproductive toxicity in male mice characterized by effects on sperm parameters and morphological abnormalities in spermatozoa, the effects across generations was not examined (Zhang et al. 2017).

Developmental. A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes. These studies found increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997). Increased ORs were seen for maternal residential proximity to industrial air emissions of 1,2-dichloroethane and birth defects, neural tube defects, and congenital heart defects (Brender et al. 2014). Primary routes of exposure in these epidemiologic studies were both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water). In these studies, the study populations were also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the studies, the associations with 1,2-dichloroethane are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryo and fetal lethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). The reliability of the reports of increased embryo and pup mortality following intermediate-duration inhalation of lower (not maternally toxic) concentrations of 1,2-dichloroethane (Vozovaya 1977; Zhao et al. 1989) is uncertain, due to the lack of statistical analysis, inadequate description of methods, and uncertainties in the reported results. The possibility of induction of cardiac malformations by 1,2-dichloroethane, as suggested by the epidemiologic data, was not adequately addressed in the animal studies because their conventional teratology protocols did not include detailed examinations of dissected hearts. Given the suggestive evidence of an association between exposure to 1,2-dichloroethane in drinking water and major cardiac defects in human offspring, and evidence of heart malformations in epidemiology and animal cardiac teratogenicity studies of dichloroethylene and

trichloroethylene (Dawson et al. 1993; Goldberg et al. 1990), which are metabolized to some of the same reactive intermediates as is 1,2-dichloroethane, it would be informative to have studies specifically designed to investigate the potential for induction of developmental heart malformations by 1,2-dichloroethane. In addition, neurodevelopmental effects need to be investigated since human case studies and laboratory animal data identified 1,2-dichloroethane as a neurotoxin in adult humans and adult animals.

Cancer. Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity of 1,2-dichloroethane in humans due to complicating co-exposures to various other chemicals, as discussed in the section on epidemiology. The carcinogenic potential of 1,2-dichloroethane has been examined in rats and mice following inhalation, oral, and dermal exposure.

The positive and suggestive carcinogenicity results from animal bioassays (Nagano et al. 2006; NCI 1978; Stoner 1991; Suguro et al. 2017; Theiss et al. 1977; Van Duuren et al. 1979), along with data indicating that 1,2-dichloroethane and certain metabolites are mutagenic and capable of forming DNA adducts as discussed in the preceding section, provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen.

Genotoxicity. A data need to conduct additional genotoxicity studies has been identified. Only one oral exposure study examined genotoxicity and no information regarding the genotoxicity of 1,2-dichloroethane in humans following oral, dermal, or parenteral exposure is available (Cheng et al. 2000). The study has several other limitations, such as not properly observing lifestyle factors, including alcohol consumption, and the small age range of subjects limited examination of an age-related response.

However, a great deal of data are available regarding the genotoxic effects of 1,2-dichloroethane in human cells *in vitro*; prokaryotic organisms, fungi, and nonhuman mammalian cells in vitro; and insects, rats, and mice *in vivo*.

Although genotoxicity in humans could be investigated directly by examining peripheral lymphocytes obtained from exposed workers for clastogenic effects, the utility of such studies is likely to be limited due to the workers' exposures to other chemicals. Additional *in vivo* studies

examining the importance of the route of administration on 1,2-dichloroethane-induced quantitative genotoxicity data (i.e., adducts) in animals are needed since the available information indicates route-dependent effects (inhalation doses are less potent than oral gavage) (Storer et al. 1984). DNA adduct and monoclonal antibody dosimetry work also are needed to provide quantitative genotoxicity data, and perhaps could be used as a biomarker of exposure to 1,2-dichloroethane.

Epidemiology and Human Dosimetry Studies. Most of the available information on the adverse noncancer effects of 1,2-dichloroethane in humans comes from cases of acute poisoning by inhalation or ingestion (Chen et al. 2015; Dang et al. 2019; Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Liu et al. 2010; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973; Zhan et al. 2011; Zhou et al. 2015) and epidemiological studies of exposure to drinking water contaminants, residence near hazardous waste sites, or employment in the chemical industry (discussed later in this section). Limitations inherent in the case studies include unquantified exposure and the high-dose nature of the exposures. Despite their inadequacies, the available human case studies indicate that 1,2-dichloroethane can cause neurotoxicity, nephrotoxicity, gastrointestinal toxicity, and hepatotoxic effects, and death due to cardiac arrhythmia. These observations are similar to those in high-dose animal studies, but other, more sensitive effects seen in animals at low levels of exposure have not been investigated in humans.

Epidemiologic investigations of adverse birth outcomes found an increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), an increased OR for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997), and an increased adjusted OR for maternal proximity to industrial facilities using 1,2-dichloroethane and neural tube defects and spina bifida (Brender et al. 2014). The study populations also were simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, and do not establish a cause-and-effect relationship. The animal data do not indicate that 1,2-dichloroethane is teratogenic, but conventional teratology protocols were used that do not include detailed examinations of dissected hearts. Increased rates of premature births were reported in workers exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). This study was generally deficient in reporting of study design and accounting for possible confounders, including other chemicals in the factory.

Epidemiological studies of workers in the chemical industry suggest that exposure to chemical manufacturing processes that involve 1,2-dichloroethane is associated with formation of cerebral edema (Chen et al. 2015; Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011; Zhou et al. 2015), an increased incidence of brain tumors (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), significant neuropsychological impairment (Bowler et al. 2003; Ruffalo et al. 2000), nonlymphatic leukemia (Ott et al. 1989), stomach cancer, and leukemia (Hogstedt et al. 1979), and with increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers (Benson and Teta 1993) among chemical plant workers. Increased risk of breast cancer was reported among men working at jobs associated with exposure to gasoline or gasoline combustion products containing 1,2-dichloroethane (Hansen 2000), and the risk of several cancer types was increased in residents living proximal to a Montreal municipal waste site that emitted volatile organic substances including 1,2-dichloroethane (Goldberg et al. 1995). These studies involved exposure to other chemicals and did not deal with 1,2-dichloroethane exposure exclusively. Isacson et al. (1985) reported an association between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon and rectal cancer in men aged ≥55 years old, but other organic chemicals were present in the drinking water. Studies in animals are adequate to support the determination that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen.

Well-controlled epidemiological studies of people living in areas where 1,2-dichloroethane has been detected in water or near industries or hazardous waste sites releasing 1,2-dichloroethane, and/or of people exposed in the workplace, could add to and clarify the existing database on 1,2-dichloroethane induced human health effects. Previous studies of 1,2-dichloroethane from hazardous waste sites or drinking water have not been able to establish anything more than a weak association between a health effect and 1,2-dichloroethane due to the presence of many other chemicals at the sites or in the water, small numbers of cases with the health effect, and difficulties in controlling for all of the variables that may confound the results for a general population study. At present, the only known health effects of 1,2-dichloroethane in humans, seen in cases of acute-duration high exposure, are neurotoxicity, nephrotoxicity, hepatotoxicity, and effects on the cardiovascular system. A particularly sensitive endpoint of acute-duration inhalation or gavage exposure to 1,2-dichloroethane in mice (but not rats) is immunological effects. No data regarding this endpoint are available for humans.

Biomarkers of Exposure and Effect. A data need has been identified for biomarkers of exposure. Proposed biomarkers for exposure to 1,2-dichloroethane include levels of parent compound in

the breath, blood, urine, and breast milk; levels of thioethers in the urine; and levels of thiodiglycolic acid in the urine (Igwe et al. 1988; Payan et al. 1993; Spreafico et al. 1980; Urusova 1953). However, use of the parent compound as a biomarker would only be possible at a known time since exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane. If epidemiological studies are conducted in which there is a correlation between 1,2-dichloroethane exposure time and time to specific adverse health effects, then it may be possible to correlate these health effects quantitatively with changes in tissue and/or body levels of 1,2-dichloroethane.

Biomarkers of effect for 1,2-dichloroethane include serum enzyme levels indicative of liver damage (ALT, AST, SDH), increased liver or kidney weight (size), and DNA adduct formation for liver and kidney effects (Brondeau et al. 1983; Inskeep et al. 1986; Nouchi et al. 1984; Prodi et al. 1986). Another potential biomarker would be tests for immunosuppression, but immune effects have been demonstrated only in mice in acute-duration exposure studies (Munson et al. 1982; Sherwood et al. 1987). Because they have not been seen in humans, rats, or even mice exposed for an intermediate duration, the relevance of these effects to humans is uncertain. None of these biomarkers are specific for 1,2-dichloroethane. These biomarkers are indicative of effects, but dosimetry has not been worked out for any of them. Because immunological effects of 1,2-dichloroethane have been seen only in mice, it is uncertain whether immunosuppression would occur in humans exposed to this chemical.

Absorption, Distribution, Metabolism, and Excretion. A data need to assess the toxicokinetics of 1,2-dichloroethane following inhalation, oral, and dermal exposure has been identified. Case reports of toxic effects subsequent to inhalation or oral exposure suggest that 1,2-dichloroethane is absorbed following exposure by these routes (Garrison and Leadingham 1954; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Inhalation exposure of lactating women in the workplace resulted in distribution of 1,2-dichloroethane to their milk (Urusova 1953). Animal studies were sufficient to characterize the rate and extent of absorption following inhalation, oral, and dermal exposure (Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Distribution, metabolism, and excretion have also been well studied in animals exposed by the inhalation or oral routes (D'Souza et al. 1987, 1988; Reitz et al. 1982; Spreafico et al. 1980; Sweeney et al. 2008) and are qualitatively similar across these routes. Metabolism is saturable in animals, but the precise levels at which saturation phenomena come into play have not been determined and appear to differ between gavage and inhalation exposures (Reitz et al. 1982). Additional studies investigating the saturation of CYP metabolism by inhaled and ingested 1,2-dichloroethane, as well as the roles of the oxidative and glutathione conjugation metabolic pathways in 1,2-dichloroethane toxicity and

mutagenicity/carcinogenicity, would enable better understanding of the metabolism of this compound. Based on the elimination of virtually all radiolabel from inhalation or gavage administration of 1,2-dichloroethane to rats within 48 hours, Reitz et al. (1982) concluded that the potential for 1,2-dichloroethane to accumulate with repeated exposure is minimal. The rate of elimination of the parent compound from adipose tissue was similar to that from blood following gavage administration to rats, but was slower following a single inhalation exposure or intravenous injection (Spreafico et al. 1980; Withey and Collins 1980), raising the possibility that 1,2-dichloroethane may accumulate to some extent in adipose tissue and in breast milk of nursing women. In the past, 1,2-dichloroethane has been detected in human milk (EPA 1980; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breastfeeding mothers. However, historic data likely reflect exposures from former use patterns that are no longer relevant today. Thus, the importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. More quantitative information on the presence of 1,2-dichloroethane in fat and breast milk would be useful to assess the ability of 1,2-dichloroethane to accumulate in fat and the potential hazard to nursing infants. Further study into the long-term fate of low-level 1,2-dichloroethane exposure in humans and animals and the potential for accumulation in humans would also provide valuable information.

Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics across species is limited as most studies have been performed in rats (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Only one set of studies included mice (D'Souza et al. 1987, 1988), and these studies were conducted to validate PBPK modeling, primarily for levels of the direct glutathione conjugate in selected tissues of concern for carcinogenicity (liver and lung). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure. The database with regard to comparative toxicokinetics across routes does include comparative toxicokinetics across acute-duration inhalation and gavage (oil) administration (Reitz et al. 1980; Spreafico et al. 1980). The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) reported that 1,2-dichloroethane is absorbed more rapidly by the gastrointestinal tract following gavage administration in water than in corn oil; the estimated area under the curve (based on data for up to 300 minutes post-dosing) was also much greater for the water than the corn oil vehicle. Information on toxicokinetics for repeated or longer-term continuous exposure is not available.

Comparative Toxicokinetics. Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics consists primarily of studies in rodents (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980; Sweeney et al. 2008). More information on the toxicokinetics of 1,2-dichloroethane in other animal species, including humans, would be useful for more fully assessing interspecies differences and the implications for human exposure.

Children's Susceptibility. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Physical and Chemical Properties. The physical and chemical properties of 1,2-dichloroethane are well characterized to permit estimation of its environmental fate (see Chapter 4). No additional studies are needed at this time.

Production, Import/Export, Use, Release, and Disposal. Production methods for 1,2-dichloroethane are known and there does not appear to be a need for further information. The use pattern of 1,2-dichloroethane is known. Detailed information on the uses of 1,2-dichloroethane in industry and consumer products is available from Chemical Data Reporting (EPA 2012a, 2016). Additional data on the uses of 1,2-dichloroethane are not needed. TRI contains data on releases to air, water, and soil from facilities that produce 1,2-dichloroethane. There does not appear to be a need for additional data on releases of 1,2-dichloroethane. More information regarding the amount of 1,2-dichloroethane that is disposed of at hazardous waste sites or abandoned would be useful. No current data are available on the amount of 1,2-dichloroethane disposed of annually. Methods for disposing of 1,2-dichloroethane are described in the literature.

Environmental Fate. The partitioning of 1,2-dichloroethane into air, water, and soil is well established (Brüggemann et al. 1991; Chiou et al. 1980; Dilling 1977; Dilling et al. 1975; EPA 1981, 1985; Jeng et al. 1992; Jury et al. 1990; Pearson and McConnell 1975; Wilson et al. 1981). 1,2-Dichloroethane is highly mobile in soil and is expected to leach into groundwater. Available laboratory data are sufficient to estimate its atmospheric lifetime, but information on degradation rates in soil and water are limited. Recent data indicate that 1,2-dichloroethane will biodegrade slowly in soil, water, and groundwater under both aerobic and anaerobic conditions. Additional data regarding the degradation rates of 1,2-dichloroethane in soil and water would be helpful in assessing its environmental fate.

Bioavailability from Environmental Media. 1,2-Dichloroethane has been measured in the breath, blood, urine, adipose tissue, and breast milk of humans (Barkley et al. 1980; EPA 1980, 1982; Wallace et al. 1984). Thus, it can be concluded that 1,2-dichloroethane is bioavailable from the environment. Good quantitative data that correlate varying levels in the environment with levels in the body and associated health effects are lacking. Data are lacking regarding the extent to which 1,2-dichloroethane can be absorbed from various media (e.g., soil).

The health effects observed in humans following exposure to 1,2-dichloroethane are those generally associated with exposure to chlorinated hydrocarbons. Therefore, it may not be possible to correlate the exact levels of 1,2-dichloroethane in the environment with observed health effects in humans. The methodology to predict exposure levels of 1,2-dichloroethane from observed health effects is lacking.

Food Chain Bioaccumulation. The limited experimental data on bioconcentration of 1,2-dichloro-ethane in aquatic organisms (Banerjee and Baughman 1991; Farrington 1991) and the physical and chemical properties of this compound indicate that bioconcentration and biomagnification are not likely to occur. However, experimental data on food chain biomagnification will aid in determining the potential for human exposure to 1,2-dichloroethane.

Exposure Levels in Environmental Media. 1,2-Dichloroethane has been detected at low levels (ppb) in ambient urban and rural air (Class and Ballschmiter 1986; Cohen et al. 1989; EPA 1988, 1991; Jüttner 1986; Kelly et al. 1994; Pellizzari et al. 1986; Singh et al. 1982, 1992), outdoor and indoor air samples of residences located near hazardous waste disposal sites (Andelman 1985; Barkley et al. 1980; Heavner et al. 1996; LaRegina et al. 1986), surface water (Brown et al. 1984; EPA 1977; Yamamoto et al. 1997), groundwater (Barbee 1994; Brown et al. 1984; Lesage et al. 1990; Plumb 1987; Westrick et al. 1984), drinking water (Barkley et al. 1980; Clark et al. 1986; Iowa DWAW 1985; Krill and Sonzogni 1986; Lam et al. 1994; Steichen et al. 1988; Suffet et al. 1980), sediment (Bianchi et al. 1991; Oliver and Pugsley 1986), and food stuffs (Gold 1980; Heikes and Hopper 1986, Heikes 1987; Miyahara et al. 1995; Rembold et al. 1989). Data on estimated human intake from all media have not been located.

Reliable monitoring data for the levels of 1,2-dichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on environmental levels of 1,2-dichloroethane can be used in combination with the known body burden of 1,2-dichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Recent estimates of the size of the population occupationally exposed to 1,2-dichloroethane are not available, and monitoring data on workplace exposure levels are 30–40 years old and generally inadequate. General population exposure estimates have been prepared by the EPA (1985) for inhalation of the compound in ambient air, which is believed to be the most important route of exposure. However, the general population may also be exposed to low concentrations of 1,2-dichloroethane through ingestion of contaminated water and/or food. The use of old consumer products that contained 1,2-dichloroethane represents a possible, but most likely inconsequential potential exposure route. Quantitative information about the size of the exposed populations and the levels of exposure are generally incomplete. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. There is no information available on the exposure of children to 1,2-dichloroethane under the age of 12 years. Children are most likely to be exposed to 1,2-dichloroethane via inhalation of ambient air. Ingestion of drinking water and food may also yield childhood exposures. Contact with older household products that contained 1,2-dichloroethane is possible but is unlikely to be a major source of exposure since 1,2-dichloroethane is no longer used in most consumer products. Children are unlikely to be exposed to 1,2-dichloroethane from pica. Accurate data on the levels of 1,2-dichloroethane in children are needed to identify ways to reduce the potential exposure risks.

6.3 ONGOING STUDIES

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