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 1,2,3-trichloropropane 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 1,2,3-trichloropropane.

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 1,2,3-trichloropropane 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 1,2,3-trichloropropane. 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.

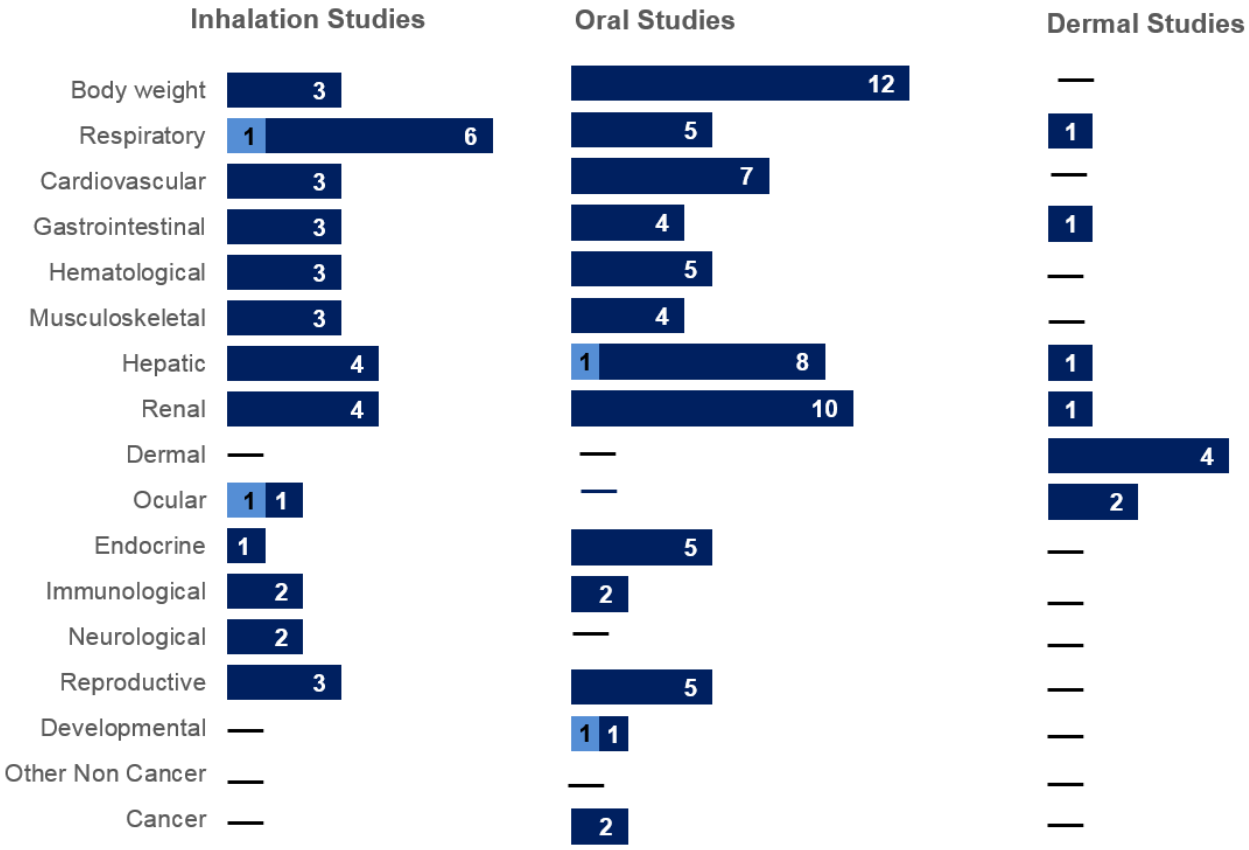
As illustrated in Figure 6-1, most of the data on the toxicity of 1,2,3-trichloropropane come from studies in experimental animals. The most commonly examined endpoints were liver, body weight, respiratory, and kidneys. Information of the toxicity of 1,2,3-trichloropropane in humans is limited to three studies, one being a case report. Approximately half of the experimental animal studies involved oral exposure; the remaining studies were equally split between inhalation and dermal/ocular exposure routes.

6.2 Identification of Data Needs

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

Figure 6-1. Summary of Existing Health Effects Studies on 1,2,3-Trichloropropane By Route and Endpoint*

Potential hepatic, respiratory, body weight, and renal 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. Studies may have examined more than one endpoint.

Acute-Duration MRLs. The available acute inhalation database was considered adequate for derivation of an MRL. Although several studies have evaluated the acute oral toxicity of 1,2,3-trichloropropane, the database was not considered adequate for derivation of an MRL. Several limitations were identified, including the lack of support for categorizing the increase in liver weight observed in the Merrick et al. (1991) study as adverse and lack of support for the observed cardiovascular lesions (Merrick et al. 1991). Additional studies that included examination of the liver and heart would provide valuable information for identifying critical effects and establishing dose-response relationships.

Intermediate-Duration MRLs. Several studies have evaluated the intermediate-duration toxicity of inhaled 1,2,3-trichloropropane in experimental animals (Johannsen et al. 1988); several adverse effects were identified including peribronchial hyperplasia, hepatocellular hypertrophy, and splenic extramedullary hematopoiesis. However, derivation of an MRL based on these endpoints resulted in a value that was about 10 times higher than the acute-duration inhalation MRL. One limitation of the intermediate-duration database is the lack of a study examining the nasal cavity, which was the most sensitive effect following acute exposure. Intermediate-duration studies examining a wide range of endpoints, particularly the nasal cavity, would be useful for identifying the most sensitive effect and derivation of an MRL. The oral exposure database was considered adequate for derivation of an oral MRL.

Chronic-Duration MRLs. No chronic-duration inhalation studies were identified for 1,2,3-trichloropropane, precluding the derivation of an MRL. Chronic-duration studies examining a wide range of endpoints, particularly the nasal cavity, which was the most sensitive target following acute-duration exposure, would be useful for identifying the most sensitive effect, establishing concentration-response relationships and derivation of an MRL. The chronic-duration oral database was considered adequate for deriving an MRL.

Health Effects.

Respiratory. Acute inhalation studies have identified the nasal olfactory epithelium as a sensitive target of 1,2,3-trichloropropane toxicity in rats and mice (Miller et al. 1986a, 1986b). Nasal effects have also been observed in following oral exposure (NTP 1993). However, nasal effects have not been examined in longer-term inhalation studies. Longer-term studies examining the nasal cavity would allow for a better understanding of the toxicity of inhaled 1,2,3-trichloropropane.

Cardiovascular. Inflammation, degeneration, and necrosis have been observed in rats following acute and intermediate oral exposure (Merrick et al. 1991). However, other investigators have not reported adverse effects in rats administered similar or higher doses. Additional studies are needed to support this finding.

Immune. Effects such as thymic and splenic lymphoid depletion and decreased weight of the spleen of rats and mice exposed orally and by inhalation to near-lethal levels of 1,2,3-trichloropropane for several weeks could have immunological significance (Johannsen et al. 1988; Merrick et al. 1991; NTP 1993). However, these effects could also be secondary to the observed decreases in body weight. Limited evidence from one study suggests that 1,2,3-trichloropropane may be a weak dermal sensitizer in guinea pigs (Clark 1977). Studies examining immune function are needed to evaluate the potential immunotoxicity of 1,2,3-trichloropropane.

Developmental. There were no effects on growth or viability of offspring of rats exposed by inhalation to low concentrations of 1,2,3-trichloropropane prior to mating and during gestation, (Johannsen et al. 1988). In a 2-generation study, decreases in reproductive function was observed in F1 rats (NTP 1990). Both studies were of limited scope. Given the genotoxicity of 1,2,3-trichloropropane, there is potential for developmental effects. Single and 2-generation studies examining a wide range of endpoints are needed; the developmental studies should also include neurological and cognitive endpoints.

Carcinogenicity. Although animal studies provide evidence of the carcinogenicity of 1,2,3-trichloropropane, very little information is available on the mechanisms of action for carcinogenicity and the causative agent. Mechanistic studies would provide valuable information to the understanding of the carcinogenic potential in humans.

Epidemiology and Human Dosimetry Studies. A small number of human studies have been examined the toxicity 1,2,3-trichloropropane (Brender et al. 2014; Han 2010; Silverman et al. 1946). Only one of these provided exposure data (Silverman et al. 1946), but only examined sensory responses. Studies of populations exposed to 1,2,3-trichloropropane could provide information on whether rodents are good models for human toxicity.

Biomarkers of Exposure and Effect. There are no established biomarkers of exposure for 1,2,3-trichloropropane in humans. Studies with rats suggest that respiratory or urinary excretion of 1,2,3-trichloropropane may be sufficient for monitoring purposes (Sipes et al. 1982). Additional studies could help determine the feasibility of using 1,2,3-trichloropropane in the breath or urine as a biomarker of exposure.

There are no known biomarkers of effects for 1,2,3-trichloropropane in humans. One study with rats (NTP 1993) suggests that anemia and alterations of serum enzymes (e.g., decreased serum pseudocholinesterase activity) might be sensitive biomarkers for hematologic and hepatic effects of 1,2,3-trichloropropane, respectively. Additional animal studies or examination of humans with known exposure to 1,2,3-trichloropropane are needed to identify potential biomarkers of effect, especially biomarkers specific to 1,2,3-trichloropropane that would be indicative of subclinical alterations.

Absorption, Distribution, Metabolism, and Excretion. There is limited information on absorption and excretion of single oral doses of 1,2,3-trichloropropane in rats (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984), but no data are available on the toxicokinetics of 1,2,3-trichloropropane in animals after inhalation or dermal exposure. Tissue distribution, metabolism, and excretion of intravenously injected 1,2,3-trichloropropane also have been investigated in rats (Volp et al. 1984). A PBPK model describing tissue distribution and excretion was developed using data from this intravenous study. A more complete oral study in animals, as well as animal studies using inhalation and dermal exposure, could provide necessary data (e.g., absorption kinetics) for expanding the model to include inhalation, oral, and dermal exposure and verifying the model. It might then be possible to use the model to predict the pharmacokinetics of 1,2,3-trichloropropane in humans exposed by these routes. Studies with several dose levels and exposure durations would allow more accurate comparison between routes (e.g., assessment of relative rates and extent of absorption, distribution, metabolism, and excretion) as well as detection of saturation effects.

Comparative Toxicokinetics. The toxicokinetics of 1,2,3-trichloropropane have been studied only in rats by the oral and intravenous routes (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). A PBPK model has been proposed based on the intravenous data. Studies in other species would be useful for verifying predictions made from the model about other species, including humans.

Children's Susceptibility. No information is available on children's susceptibility; additionally, there are limited developmental toxicity studies (see Health Effects section). Studies examining immature animals may provide valuable information on the potential increased sensitivity of children.

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Many of the physical and chemical properties of 1,2,3-trichloropropane are available (Table 4-2) (Hawley 1981; Mackay et al. 1982; McNeill 1979; Riddick et al. 1986; Ruth 1986; Weast 1985; Williams 1949). However, only estimated values are listed for the log K_{ow}, K_{oc}, and BCF (Lyman et al. 1982). Since the log K_{ow} was used to estimate the K_{oc} and BCF, an experimentally determined log K_{ow} would lead to less uncertainty in those estimated properties. Experimentally determined values would clarify the reliability of these data, although the techniques used for the estimations appear to be accurate.

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods for 1,2,3-trichloropropane are available (Baier et al. 1987; Hawley 1981; NIOSH 1981; NLM 2020; Williams 1949); however, data regarding current production, import, and export volumes, and use patterns are lacking. We do know that the chemical is currently produced, but not in what quantities or whether future production levels will increase. We do not know if the chemical is widely used in the home, environment, or workplace, but it does not appear that such widespread use is likely. It has not been found in food, although foods may not have been tested for its presence. Use, release, and disposal information is useful for determining where environmental exposure to 1,2,3-trichloropropane may be high, and may help in estimating whether exposure is likely, and may therefore help to determine whether further toxicological studies are warranted. General data are available regarding the methods of disposal of 1,2,3-trichloropropane (NLM 2020), but information concerning the efficiencies of these methods, as well as the amount disposed of by each method, is lacking. Specific disposal information, obtainable by polling industries or industry organizations, may be useful for determining environmental burden and potential concentrations where environmental exposures may be high. Rules and regulations governing land disposal of 1,2,3-trichloropropane are known (EPA 1988a).

Environmental Fate. The environmental fate of 1,2,3-trichloropropane remains unclear due to a lack of experimental data. We do not know where the chemical partitions in the environment. However, based upon estimated physical properties (Lyman et al. 1982), the chemical is expected to partition into the atmosphere and groundwater (Swann et al. 1983). It has been shown that the chemical leaches through soil (Cohen et al. 1986, 1987; EPA 1985b; Oki and Giambelluca 1987). It is estimated that it can

volatilize through near-surface soil and water to the atmosphere (EPA 1985a; Lyman et al. 1982). Nothing definitive is known about the biodegradability of the compound. The rate constant for reaction with hydroxyl radicals in the atmosphere is an estimated value (Atkinson 1987), as are significant partition coefficient values used in predicting the environmental fate of the compound (NLM 2020). Experimental data in these areas would aid in assessing the ultimate environmental fate of 1,2,3-trichloropropane, which would, in turn, aid in assessing its background levels in the environment and levels of human exposure.

Bioavailability from Environmental Media. Studies have shown that 1,2,3-trichloropropane is absorbed through the lungs, gastrointestinal tract, and skin of animals (Albert 1982; Clark 1977; Johannsen et al. 1988; Sipes et al. 1982; Union Carbide 1958; Volp et al. 1984). This indicates that it may be absorbed through the inhalation of contaminated air, ingestion of contaminated water, food, and soil, and through dermal contact. The amount of 1,2,3-trichloropropane that is bioavailable from each route is not well documented, and no data were found for humans. Data on the bioavailability of 1,2,3-trichloropropane would be helpful in assessing the importance of environmental exposure levels.

Food Chain Bioaccumulation. The estimated BCF for 1,2,3-trichloropropane (Lyman et al. 1982; NLM 2020) indicates that this compound would not significantly bioconcentrate in plants, aquatic organisms, or animals. No experimental data were found to support this conclusion. Information was unavailable on the biomagnification of 1,2,3-trichloropropane in food chains. Additional information on bioconcentration by plants, aquatic organisms, and animals and biomagnification in terrestrial and aquatic food chains could be helpful because it might help to indicate whether the chemical biomagnifies in food chains and thereby poses a potential for significant exposure. Biomagnification is not likely, however, based upon the estimated BCF.

Exposure Levels in Environmental Media. Limited data were available regarding the levels of 1,2,3-trichloropropane in the environment (Baier et al. 1987; Cohen et al. 1986, 1987; Dewalle and Chian 1978; EPA 1984, 1985b, 1987; Keith et al. 1976; Oki and Giambelluca 1987; Wakeham et al. 1983). Information on exposure to 1,2,3-trichloropropane from environmental media would be useful, especially from drinking water derived from groundwater downgradient from 1,2,3-trichloropropane-containing hazardous waste disposal sites and other contaminated surface waters, air near facilities that make or use products containing the compound, and soil at waste disposal sites. Data concerning the presence of 1,2,3-trichloropropane in foods would also be useful in assessing potential exposure.

Exposure Levels in Humans. No data have been found that indicate that 1,2,3-trichloropropane has been found in human samples of blood, urine, fat, or breast milk. Furthermore, no biomarkers of exposure or effect have been established. Data on both workplace exposure and ambient environmental exposure are sparse and outdated (NIOSH 1981, 1989). A detailed, recent database of environmental exposure levels would be helpful in determining the current exposure levels, thus allowing estimation of the average daily dose associated with various scenarios such as living near a hazardous waste disposal site, drinking contaminated drinking water, or working in a contaminated workplace. This database of environmental exposure levels may be very useful if current use patterns, for which information is not available, warrant it.

Exposures of Children. No monitoring data were identified for children. General population monitoring studies should include children to allow for an assessment of potential differences in exposure of children and adults.

Analytical Methods. Analytical methods for determining 1,2,3-trichloropropane in contaminated air, water, soil, liquid and solid waste, sewage sludge, and citrus fruits are available (EPA 1986a, 1986b; Ho 1989; Lopez-Avila et al. 1987; NIOSH 1987; Tonogai et al. 1986). No methods were found for the determination of 1,2,3-trichloropropane in sediments. Most of the methods used for environmental samples, however, did not report detection limits, recovery, accuracy, or precision for 1,2,3-trichloropropane. Knowledge of these factors, as well as the development of alternative methods of analysis, would help in estimating the potential for human exposure to 1,2,3-trichloropropane. No information was found regarding degradation products of 1,2,3-trichloropropane. Consequently, no comment regarding the availability of analytical methods for determining degradation products can be made.

There are methods for analyzing 1,2,3-trichloropropane in most of the biological matrices for the rat, although important information such as detection limits and recoveries was not reported (Sipes et al. 1982).

6.3 Ongoing Studies

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